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Editors

Critical Care Toxicology

Diagnosis and Management of the
Critically Poisoned Patient

Second Edition

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With 675 Figures and 487 Tables

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Foreword

Critical Care Toxicology belongs in every critical care unit, emergency department, poison center, library, emergency response center, and on the most easily reached shelf for anyone interested in or who comes in contact with medical toxicology. This masterful compilation of information has many attributes, among which are:

- Evidence based well-referenced information
- Editors and authors who are experts in their fields
- Concise and clear presentation
- Tables that convey critical data
- Figures and diagrams that are clinically relevant
- Paragraph headers that allow focused access to information
- Calculations and formulas that are fully explained
- Lists of treatment materials to obtain in advance with contact information of unusual items
- Therapeutic dosages that are detailed enough to be utilized without additional references

In most cases, diagnostic and therapeutic information can be obtained in a few minutes given the book's careful organization. For those patients presenting with complicated or multiple exposures, the structure provides a straightforward method of rapidly developing and working through a differential diagnosis.

The quality of this book should come as no surprise after looking at the impressive listing of authors. The editors, each of whom I have known, worked with, and respected for many years, have selected an international group of experts whose credibility is unmatched. They represent the best of our profession of medical toxicology and have written a large percentage of the most important and groundbreaking publications in our field. The editors and authors are the most sought-after educators in our annual toxicology meetings around the world and provide clinical expertise as well as leadership and training for all of us who work in this wide and varied area.

In the preface to the first edition of *Critical Care Toxicology*, the word "passion" occurs in the very first sentence. For all of us who have ever written a scientific monograph, paper, chapter, book, or prepared a teaching session, the word passion certainly defines a major requirement for preparation of materials

that will communicate the knowledge that is intended. It takes time and effort to write something that will stand the test of time, and when written with passion it means that the author has not skipped over anything and left nothing of importance unaddressed. It requires thorough knowledge of the subject, real world experience, fully researched literature, and draft after draft until communication is assured. When reading this book, it is apparent that the editors and authors have achieved their goal.

Before writing this foreword, the editors provided me with some chapters from the second edition. In reviewing four of them – “Acid-base,” “Hypotension and Shock,” “Seizures,” and “Acute Respiratory Distress Syndrome” – it was readily apparent that this second edition is an improvement on an already excellent book. More current materials are included as expected, but using these chapters as examples the authors have dramatically improved this book. Acid-base in the critical care setting is a complicated and often difficult issue. To address that the authors have doubled the length of this chapter and substantially added information which will be valuable to all who utilize it. The chapters on hypotension and shock and acute respiratory distress syndrome have been broken out of their previous locations and addressed comprehensively to reflect their importance. The chapter on seizures has also been doubled in length and contains a considerable amount of new information that is clearly presented.

The authors have also added speed of access to this book through the use of a table of contents at the beginning of each chapter. This further enhances the ability of the reader to get to an answer under emergent circumstances.

The book also has another purpose than just providing critical information in a clinical setting. It provides a very readable and understandable educational experience for all those who are studying this area. This must include addressing controversial areas with which the reader may be familiar and if not familiar ought to be familiar, and this book engages all of this.

Even those of us who have been in this field for a long time stand to learn something from this book. The discussion of the strong anion gap in the acid-base chapter coupled with the very practical explanations of the other factors in this important area is the clearest I have ever read. An area in which I have little knowledge is malignant hyperthermia, and this chapter provides a clear explanation along with even a phone number and website to get additional updated information in what is apparently a rapidly evolving issue. The editors clearly want readers to get the right answers to their questions.

Critical Care Toxicology covers all of the areas in medical toxicology in a series of well-written chapters following the excellent chapters that provide an approach to the critically poisoned patient and an understanding of toxic syndromes. Images of various aspects of toxicological encounters provide visual reinforcement of the written materials.

The index is very well done and comprehensive. Unlike the 7th edition in 1959 of Nelson’s pediatric text where the editor’s daughter, who hated having to produce the index, entered under B “Birds, for the” and listed the entire book, the index of *Critical Care Toxicology* was obviously prepared by someone who had a passion for helping readers get to answers.

Critical Care Toxicology provides a very valuable contribution to all aspects of medical toxicology from education to, as the title states, critical care. It should be readily accessible to everyone who may face this issue from forming a differential diagnosis to rendering care.

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Barry H. Rumack
Director Emeritus

Preface to the Second Edition

Those readers who are familiar with the first edition of *Critical Care Toxicology* (CCT) know that it was about passion – our collective passion for caring for patients with the group of fascinating physiological derangements caused by exogenous chemical exposures. While our passion for the field of clinical toxicology remains unabated, an additional theme that characterizes the second edition of *Critical Care Toxicology* is scientific evidence.

In the 10 years since the publication of the first edition, a considerable body of new scientific evidence has emerged, new antidotes have become available, and systematic reviews and meta-analyses have become more commonplace in the field of clinical toxicology. Seizing upon the opportunity to provide a compendium of this accumulated evidence-based knowledge, we have worked with our chapter authors to assure that they have stayed true to the existing body of empirical data and, in the many places, where data gaps exist identify them so that the user of this book will understand the basis for the treatment recommendations we provide. In order for the user of CCT to quickly discern the veracity of the evidence supporting the treatment recommendations provided, we have adopted the US Public Health Service's rating of scientific evidence. These gradings allow the reader to instantly know the level of scientific support for various treatment recommendations and thus to be able to rely most heavily on well-supported therapeutic modalities.

We are highly cognizant of the reality that there are many areas where the evidence base relating to treatment decisions is insufficient. Nevertheless, the clinician treating the critically poisoned patient still requires guidance. Given that so many of our chapter authors represent the world's authority on their topic, we have also strongly encouraged them to give their highly informed opinions on how to proceed in the many areas where there are clear knowledge gaps. Where they have supplied these opinions they have been identified as such, and we have worked with them to also explain their thought processes underlying these opinions.

We are very proud of the group of chapter authors that have been brought together in CCT. Where possible we have endeavored to recruit a group of international experts in their respective subject matter who are also experienced clinicians, proficient in the intensive care of patients poisoned by the toxins and toxicants they have addressed. This quest for such a uniquely qualified group of chapter authors has required us to seek out scholars from many areas of the world. Being such highly respected individuals, our chapter

authors are for the most part very busy with their various academic and clinical pursuits. We are greatly indebted to them for the generous donation of the time they gave us to not only produce their excellent chapters but also to put up with our compulsively detailed editing and challenges to them for justification of the information contained in their chapters. In most instances, they have done so because they were dedicated to the idea of working with us to achieve the goals enumerated above.

Critical Care Toxicology is not a static textbook in the traditional sense. The online version is a living dynamic document that can, and will, be updated as needed and new chapters will be provided beyond the date of the original publication of the current edition. In this way, we will feel confident that you, the reader of CCT, will have the most up-to-date information available to you in your care of your critically poisoned patients.

Jeffrey Brent
Keith Burkhart
Paul Dargan
Benjamin Hatten
Bruno Megarbane
Robert Palmer
Julian White

Preface to the First Edition

To us, this book is about passion. It is the result of the passion we share for the clinical challenges we face every day in caring for critically poisoned patients and in understanding their unique and enchanting pathophysiology and its therapeutic implications. This is a passion we hope to elicit in all who venture into the world of clinical toxicology as they read this book. To the medical toxicologist, the care of the seriously poisoned patients merges the diverse worlds of critical care, emergency medicine, pharmacology, altered drug pharmacokinetics (hence the term “toxicokinetics”), diagnostic challenges, multisystem involvement in often otherwise healthy patients, and the use of specific and often esoteric treatment strategies and antidotes.

Before embarking on the extraordinarily labor-intensive activity of generating a book of this depth and complexity, we queried the importance of producing another clinical toxicology textbook. We are aware of several excellent general clinical toxicology textbooks on the market and appreciate their attempts to achieve a far greater breadth than the present work. However, toxicology is such a broad field that general textbooks encompassing all of clinical toxicology necessarily must limit the extent of their coverage of the intensive care unit management of major poisonings. Thus, the intensivist, and critically poisoned patients, deserve a reference that specifically addresses their needs. This need is made all the more important by the life-threatening nature of many of these poisonings. Stark evidence of the complexity of just these issues is that to cover them adequately required 160 chapters and 1633 pages.

Our goal was to have the most knowledgeable and experienced medical toxicologists author relevant chapters. In order to achieve this goal we drafted our colleagues with unique experience and expertise worldwide. As witnessed by our contributor list, all continents, except Antarctica, are represented. We proudly boast that our collective chapter authors represent a significant proportion of the most experienced critical care toxicologists in the world. Medical toxicologists interested in acute care tend to be domiciled at the bedside, in poison centers, or both. Because of the highly clinical nature of this book, we selected authors with a predominantly bedside care orientation.

With the ready access to facts and data via the Internet, the very nature of hard copy books has changed dramatically. No longer is it necessary for books to be compendia of facts. However, electronic databases cannot convey the reasoned clinical approaches and the synthesis of pathophysiology with

clinical effects and treatment that characterizes the pages that follow. Certainly, important physiologic and monitoring parameters as well as drug dosages are amply provided. The degree to which they are included represents our view of the best balance between those that are important to know and the desire to dedicate as much space as necessary to an elucidation of relevant concepts and a critical discussion of therapeutic controversies. We have embraced rather than glossed over controversies. The reader will find that this is not simply a “how to” handbook. Our aim is to provide the practitioner with the data needed to care for his or her individual patients. As an aid to those who choose to delve more deeply into the concepts, approaches, and controversies in this book, chapters are well referenced with primary source citations.

It is our hope and expectation that this book will evoke the same passion in the reader that the subject does for us.

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About the Editors



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A former President of the American Academy of Clinical Toxicology, Dr. Brent has also served on the board of directors of the American College of Medical Toxicology.

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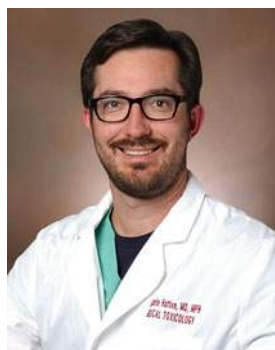


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Part I

General Management of the Critically Poisoned Patient

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Medical toxicology is a medical subspecialty focusing on the diagnosis, management, and prevention of poisoning and other adverse health effects due to medications, drug overdose, acute drug abuse problems, chemical exposures, occupational and environmental toxins, biological agents, and envenomations. Critical care is the specialized care of patients whose conditions are life-threatening and who require comprehensive care and constant monitoring, usually in intensive care units. The disciplines of critical care medicine and medical toxicology have been intertwined throughout medical history. Texts combining the principles of these closely related specialties may be traced to medieval times; Maimonides wrote his *Treatise on Poison and Their Antidotes* in 1198 [1]. In his *Treatise*, Maimonides outlined the classification, diagnosis, and antidotal therapy of poisonings and described some resuscitation methods of the age. He also, in undoubtedly what was among the first attempts to evaluate therapies critically, refuted many of the then-popular treatments. The need to continually reevaluate – and commonly refute – generally accepted therapies continues to this day. This book continues this tradition in the spirit

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established by Maimonides, except, of course, with a more data-driven approach.

Descriptions of the use of specific antidotal therapy dates back to Homer's *Odyssey*, in which Ulysses was advised to use "moly," likely a natural cholinesterase inhibitor, to treat poisoning from anticholinergic plants such as *Datura stramonium* [2]. Other publications from ancient times addressing the use of poisoning therapies include Nicander's *Alexipharmaca*, or "that which keeps off poisons"; Dioscorides' *Materia Medica*; and Galen's *DeAntidotis* and *De Theriaca ad Pisonem* [3, 4].

The identification, diagnosis, and therapy of poisons began in Greek and Roman times, with classifications by Dioscorides of poisonings by source and speed of action [3]. The Greek Nicander and King Mithridates of Pontus described the use of "theriacs" and "alexipharmacas" as universal antidotes and red clay ingestion or induction of emesis with feathers or oil to prevent toxin absorption [3]. In addition to his general description of poisons, Maimonides suggested emesis by ingesting oil, water, and honey [1]. Antimony salt, also known as tartar emetic, was widely used to induce stomach emptying and functioned as a sedative and cathartic in the nineteenth century, but it was replaced in the early twentieth century by saltwater emetics, mustard powder, mechanical throat stimulation, copper sulfate, and apomorphine [5, 6]. Ipecac syrup was first employed to induce emesis in the seventeenth century and became the emetic of choice in the twentieth century. Gastric lavage was first advocated by Munro in 1769 and supported by the physicians Physik of Philadelphia, Jukes of Britain, Dupuytren of France, and Bryce of Edinburgh [7]. In the sixteenth century, Paracelsus emphasized the fundamental importance – and to this day, the often overlooked – dose relationship of chemicals and drugs and the need for scientific study of toxins. Charcoal to adsorb toxins was described in the eighteenth century and employed in self-experiments by Bertrand and Touery, who publicly ingested toxins followed by a dose of charcoal [8]. The "universal antidote" of magnesium oxide, tannic acid, and activated charcoal was touted as the definitive adsorbent of toxins

throughout the twentieth century, until it was recognized to be inferior to activated charcoal alone [5]. Activated charcoal ultimately replaced other means of gastric decontamination beginning in the 1970s [8].

Textbooks establishing medical toxicology as a unique scientific specialty began to appear in the nineteenth century, with the publication of Orfila's *Traite des Poisons* in Paris in 1814, which emphasized experimental and forensic toxicology, followed by his student Christison's writing the first of several editions from Edinburgh of *Treatise on Poisons* in 1829 [9]. Christison reportedly first highlighted the lifesaving properties of artificial respiration in opium poisoning, showing the close relationship between medical toxicology and critical care medicine [7] (Fig. 1). Other texts of that era were Costill's *A Practical Treatise on Poisons* and Taylor's *On Poisons*, both published in 1848. Early texts of the twentieth century on clinical toxicology include Leschke's *Clinical Toxicology*; Driesbach's *Handbook of Poisoning*; Gleason, Gosselin, and Hodge's *Clinical Toxicology of Commercial Products*; and Jay Arena's *Poisoning*. Historical toxicology reference texts are listed in Table 1.

More specific therapies and antidotes to treat poisonings also date back in history. Beginning with Maimonides, some examples include the use of natural anticholinesterase inhibitors to treat anticholinergic poisoning, *Strychnos nuxvomica* (strychnine) as an arousal and emetic agent, and in the 1800s the use of rabbit brain to protect against *Amanita phalloides* mushroom poisoning [1, 6]. Physostigmine, an anticholinesterase inhibitor from the Calabar bean, reportedly was advocated for atropine poisoning by Christison's successor to the Chair of Medical Jurisprudence in Edinburgh, Thomas Fraser [7]. Arousal of the patient affected by opiate or sedative toxicity was popularized in the nineteenth and twentieth centuries, first by mechanical stimulation and later by the use of analeptics [7]. The latter included natural agents, such as caffeine, strychnine, cocaine, camphor, picrotoxin, and lobeline, and later synthetic agents, such as pentylenetetrazol, nikethamide, methylphenidate, and bemegride [10]. The use of analeptics eventually was

Fig. 1 Sir Robert Christison (Picture from Wikipedia under the Creative Commons license)

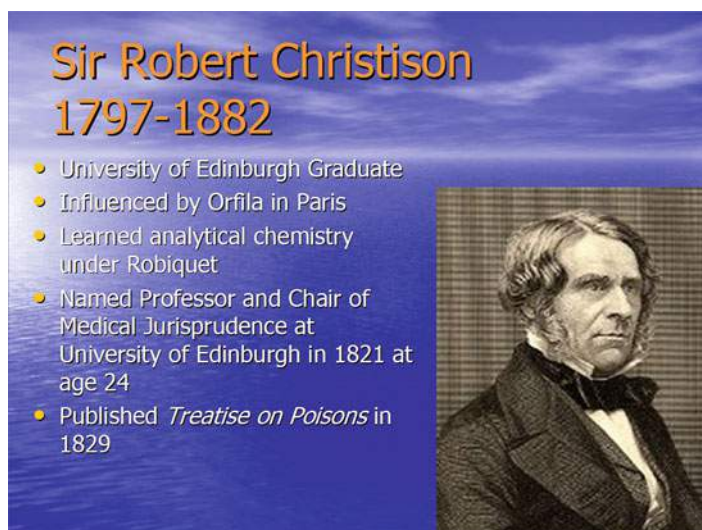


Table 1 Historical toxicology reference texts

Text	Author	Date	City
<i>A Treatise on Poisons</i>	M.C. Cooke	1770	London
<i>Traite des Toxicologie</i>	H.J.B. Orfila	1813	Paris
<i>A Treatise on Poisons</i>	Robert Christison	1829	Edinburgh
<i>On Poisons</i>	Alfred Taylor	1848	London
<i>A Practical Treatise on Poisons</i>	O.H. Costill	1848	Philadelphia
<i>Micro-Chemistry of Poisons</i>	Theodore Wormley	1869	New York
<i>What to Do in Cases of Poisoning</i>	William Murrell	1884	New York
<i>A Manual of Medical Jurisprudence, General Toxicology</i>	M.D. Ewell	1887	Boston
<i>A Manual of Medical Jurisprudence and Toxicology</i>	Henry Chapman	1896	Philadelphia
<i>Handbuch der Toxicologie</i>	A.K. Kunkel	1899	Jena
<i>Manual of Toxicology</i>	R.A. Witthaus	1911	New York
<i>Handbook of Poisoning</i>	R.H. Driesbach	1955	Los Altos, CA
<i>Clinical Toxicology</i>	C.H. Thienes	1955	Philadelphia, PA
<i>Clinical Toxicology of Commercial Products</i>	Gleason, Gosselin & Hodge	1957	Baltimore
<i>Poisoning</i>	J.M. Arena	1963	Springfield, IL
<i>Medical Toxicology</i>	Ellenhorn & Barceloux	1988	New York, NY

recognized to cause serious complications, such as hyperthermia, seizures, delirium, and increased mortality [10]. One of the most important advances in medical toxicology occurred in Scandinavia in the 1940s, when intensive supportive care with mechanical ventilation and cardiovascular support instead of analeptics was shown to reduce mortality from barbiturate poisoning from 20% to 2% [9, 10]. The overlap of critical care medicine and medical toxicology again was

reinforced. This overlap further included the advocacy for poisoned patients of close observation and monitoring; airway protection; frequent pulmonary toilet; and careful attention to fluid and electrolyte balance, cardiovascular status, and position changes.

Later advances in toxicology in the twentieth century included the discovery of the opiate antagonists/agonists nalorphine and levallorphan and the pure antagonist naloxone, the

development of highly specific and sensitive assays for drugs and chemicals, greater understanding of pharmacokinetic principles, refinement of the principles of urinary pH manipulation to enhance drug excretion, and implementation of extracorporeal removal techniques. In the twenty-first century, progress has been made in the application of immunotherapies as antidotes, the development of additional antidotes to reverse specific drug effects, the use of lipid infusion and hyperinsulinemia-euglycemia therapies, the wide availability of toxicology information via computer software and the Internet, and the early use of toxicogenetics to determine individual variations in responses to toxins and treatments. The most important advance has been the increasing number of medical toxicologists providing bedside care.

Epidemiology

Incidence

Poisonings has become an epidemic worldwide, and since 2008 has been the leading cause of injury death in the United States, exceeding those from motor vehicle deaths and falls (Figs. 1 and 2) [11].

Since 2000, the rate of deaths from drug overdoses has increased by 137%, including a 200% increase in the rate of deaths involving opioids [12]. In 1999, poisoning deaths numbered 12,986, increasing to 20,950 in 2004, 38,851 in 2013, and to an astonishing 47,055 in 2014 [11–13] (Table 2). This represents an incidence of poisoning deaths of 4.4 per 100,000 population in 1999, to 7.1 in 2004, and to 14.7 in 2014. Of the 47,055 drug overdose deaths in 2014, 28,647 (61%) involved some type of opioid, including heroin (Fig. 3) [12]. Most drug poisoning deaths occur in those between the ages of 25–64, with the highest rate in the 45–54 age group (Fig. 4) [14]. In the United Kingdom, there is a reported incidence of 310 poisonings per 100,000 population, or 170,000 annual hospital visits, much lower than the US rate [14, 15]. Overdoses account for one fourth of all suicide attempts in England [16].

Hospital Visits

Poisonings typically represent 1–3% of all emergency department visits and account for 10% of all admissions for injuries [17, 18]. Reports of emergency department (ED) visits for poisonings in the United States range from 1.1 to 2.5 million per year, depending on the source, data collection methods, and definitions [19, 20]. The peak age

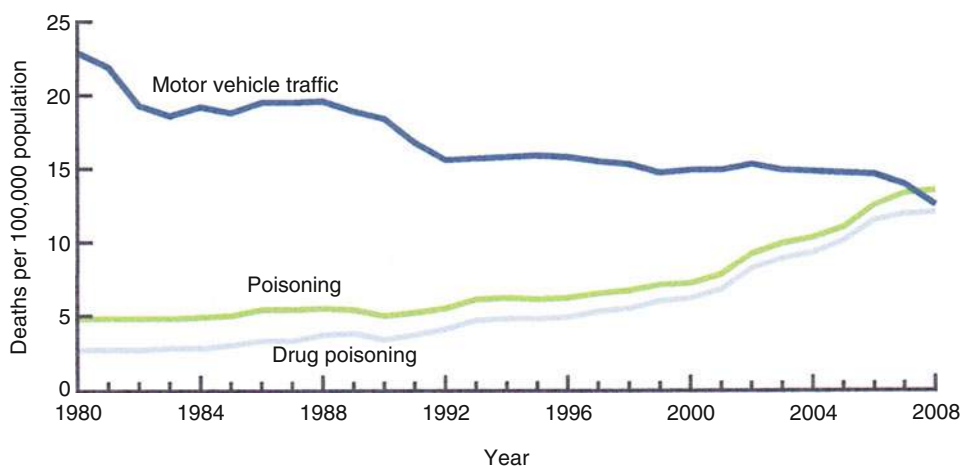


Fig. 2 Motor vehicle traffic, poisoning, and drug poisoning deaths rates: United States 1980–2008. From the US National Center for Health Statistics Data Brief. 81: December 2011

for ED visits for drug poisoning is 20–34 (Fig. 5). Hospital admissions for poisonings in the United States are about 130 per 100,000 population, or about 260,000 poisoning admissions in the United States each year [20, 21]. There are a reported 80,000 poisonings admissions each year in England, which result in about 400 deaths, or 0.5% of all such admissions [16]. According to another report, for all of the United Kingdom, the total admissions are about 170,000 annually [15]. It was reported in 2012 that drug-related

admissions in England alone increased by 58% from 2000 to 2001 [22].

Emergency department reporting of poisoning cases is highly variable. In one study, an academic tertiary care emergency department called its regional poison control center (PCC) on 26% of its cases [19]. In many poisoning cases, the exposure was highly reported to the PCC (e.g., 95% for cyclic antidepressants), in contrast to cases of drug abuse (e.g., 5% for cocaine or heroin poisoning), which are not often reported to poison control centers. A review of an entire state’s hospital admissions for poisoning indicated that the Oregon Poison Center was contacted for 54%, or 1,352, of 2,486 admissions in 1989 [23].

Drug overdoses typically account for approximately 2.5–5% of all intensive care unit (ICU) admissions in the United States, with an average length of stay (LOS) of 2.5–3.5 days [24, 25]. Poisonings have been reported to represent 11–14% of all ICU admissions in some countries [26–28]. In the 2014 annual report of the National Poison Data System of the AAPCC, 101,141 of the recorded 612,184 patients (16.5%) referred to a hospital were admitted to an ICU [29]. This number of annual US admissions to an ICU can be estimated to be only about one half of all ICU poisoning admissions, based on underreporting of cases to regional poison centers [19, 20]. Mortality

Table 2 Causes of death in the U.S. for 2013

Mortality 2013
All unintentional injury deaths
Number of deaths: 130,557
Deaths per 100,000 population: 41.3
Cause of death rank: 4
Unintentional fall deaths
Number of deaths: 30,208
Deaths per 100,000 population: 9.6
Motor vehicle traffic deaths
Number of deaths: 33,804
Deaths per 100,000 population: 10.7
Unintentional poisoning deaths
Number of deaths: 38,851
Deaths per 100,000 population: 12.3

From: Deaths: Final Data for 2013, Tables 9 and 18. <http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64>

Fig. 3 From Ref. [12]

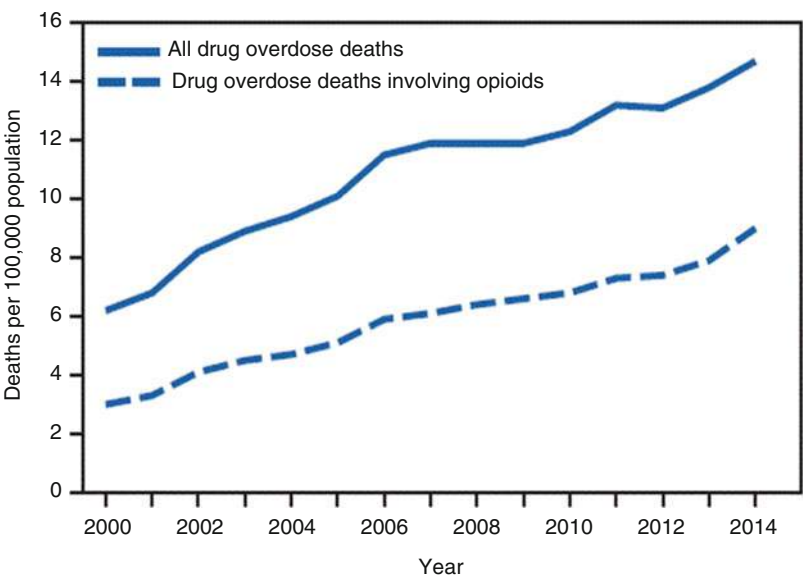


Fig. 4 Source US Centers for Disease Control and Prevention. National Center for Health Statistics, National Vital Statistics System, 2013

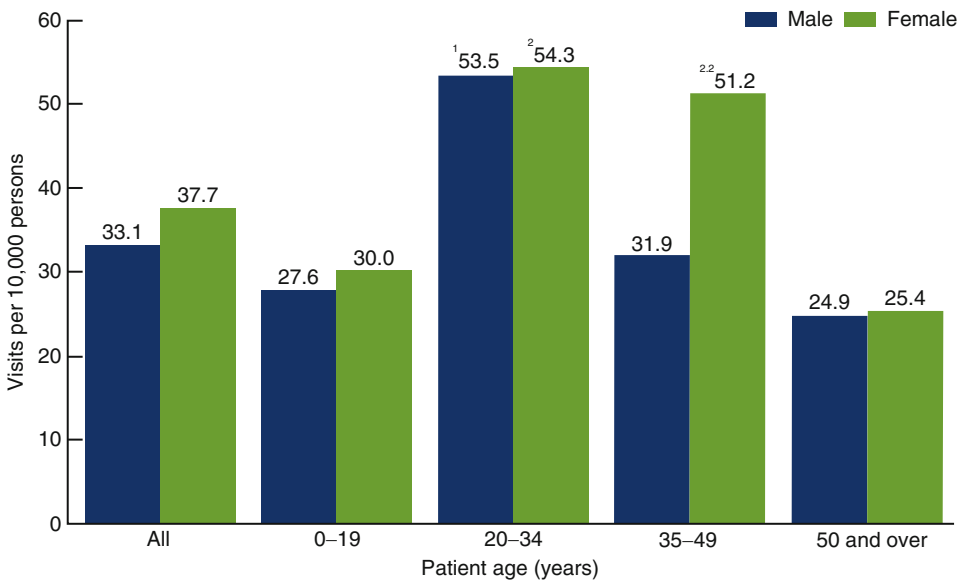
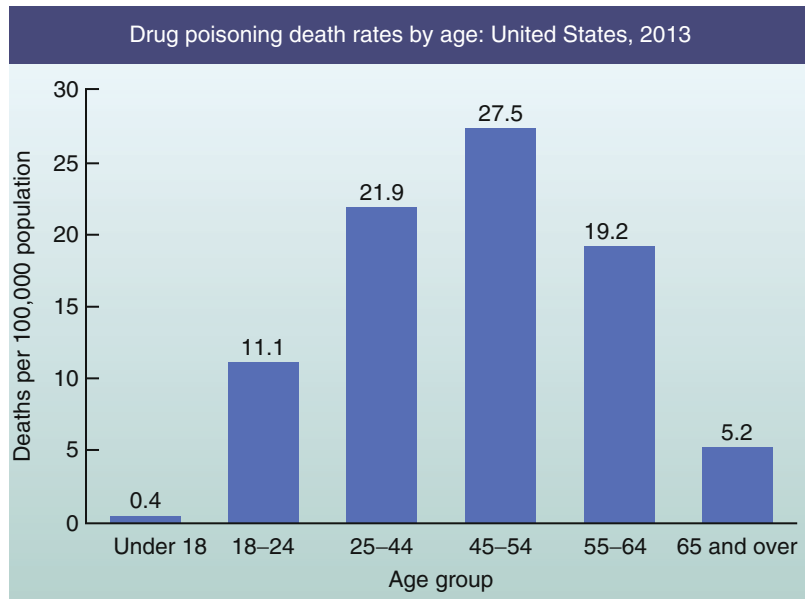


Fig. 5 Emergency Department visit rates for drug poisoning, by age and sex: United States, 2008–2011. From the US National Center for Health Statistics, Data Brief Number 196, April 2015

rates in the ICU for poisoning admissions range from 3 to 6% according to most reports [24–28].

Toxins

The history of drugs and toxins causing hospital admissions have evolved over the last several

decades. It is interesting to review historically these changing patterns. Reports from Edinburgh describe the changing patterns of admissions from the 1960s into the 1990s. In 1966, 60% of the admissions to the Royal Infirmary of Edinburgh were for barbiturate poisoning [30]. Only in the teenage group did aspirin surpass barbiturates as a cause of toxicity. In this time period, poisoning

accounted for 10% of hospital admissions. In 1968, 74% of the patients had a LOS of 2 days or less [31]. Proudfoot reported on the subsequent 20-year trend (1967 through 1986) at the same center [9]. During this period, barbiturate poisonings decreased from 30% of admissions in the 1970s to a rare occurrence. Methaqualone was initially responsible for 10% of admissions but by the mid-1970s was almost no longer seen. A predominance of benzodiazepine overdoses subsequently replaced barbiturates and methaqualone, their incidence increasing from 10% to approximately 40% of admissions in the 1970s. Throughout the 1970s, there was also a rapidly increasing admission percentage for paracetamol (acetaminophen), whereas there was a decreasing trend for salicylates.

Benzodiazepines were reported as the predominant ICU admission for poisonings in Stockholm, Sweden, from 1972 through 1985, increasing from 17% to 28% of the total number [32]. In 51% of these cases, a benzodiazepine was part of a polydrug overdose and in 21% of cases, benzodiazepines were the single ingestant. Benzodiazepine-alone admissions were intubated in 37% of cases, whereas the intubation rate was 47% if benzodiazepines were consumed with alcohol or as part of a polydrug overdose. Of the 702 ICU admissions, the complication rate was 9.8%. There were five fatalities related to respiratory insufficiency or aspiration pneumonia or both.

During the 1980s and 1990s, cyclic antidepressant poisoning was a predominant ICU admission diagnosis. In the Netherlands from 1994 through 1998, cyclic antidepressants constituted 33.3% of the total intoxication admissions and 2.4% of total admissions. The average LOS was 3.1 days. Of these patients, 40% were intubated and seven (2.7%) died [26].

In New Zealand in 1992, there was a similar experience [33]. Of all emergency department visits, 1.2% were poisoning related, yet these cases constituted 11% of ICU admissions. The incidence was 17 per 100,000 population. The most common agents ingested were cyclic antidepressants (19.6%), benzodiazepines (18%), acetaminophen (16.9%), and various antipsychotics [33]. The average LOS was 2.4 days. A 6-year review (1986 through 1991) of ICU admissions

for poisoning was published in Australia [27]. Poisonings accounted for 13.8% of all admissions. The most common agents were benzodiazepines, ethanol, tricyclic antidepressants, acetaminophen, phenothiazines, and antihistamines. The mean age was 32, the mortality rate was 2%, and 6 of the 14 fatalities were from nonmedicinal products [27].

The introduction of flumazenil, a benzodiazepine antagonist at the γ -aminobutyric acid receptor site, reportedly had an impact on ICU care and LOS in Israel. Leykin and colleagues described acute poisonings treated in the ICU from 1982 through 1984 [34]. The predominant intoxicants were benzodiazepines (51%), tricyclics (25%), barbiturates (21%), and narcotics (11%). Flumazenil was believed to have contributed to a decreased ventilator time and LOS (from 4.8 to 3.1 days). The introduction of the safer antidepressants, selective serotonin reuptake inhibitors, also markedly reduced the ICU admission rates, LOS, and cost of care [35].

In many countries, nonmedicinals such as plants and pesticides remain a significant cause for ICU admissions and fatalities. Over a 15-year period in Hong Kong during the 1980s and 1990s, rates of medicinal poisoning admissions per 100,000 population ranged from 57.3 to 80.9 [36]. In the more recent years of the report, admissions for nonmedicinal poisonings decreased from 53 to 22 per 100,000 population. Overall, poisoning fatality rates have ranged from 2 to 4 per 100,000 population, with an increasing rate into the 1990s.

The climate can have an impact on environmental exposures. In South Africa, 15.5% of toxicology consultations are for plant, spider, snake, scorpion, mushroom, and insect poisoning [37]. In addition, frequent consultations occur for household, agricultural, and industrial agents, including cholinesterase inhibitors and other pesticides, volatiles, corrosives, and soaps. The pattern of pharmaceutical exposures is similar to that in many other countries, however. Acetaminophen is the most common (14.6%), followed by benzodiazepines (13.1%), aspirin and nonsteroidal antiinflammatory drugs (9.4%), antidepressants (6.7%), and cardiovascular agents (5.5%) [37].

In a report from Ecuador, only 26% of the reported poisoning cases were drug related [38]. The leading drugs were benzodiazepines (24%), acetaminophen (23%), aspirin (22%), and carbamazepine (11%). Except for carbamazepine, this experience is not too different from that in many other countries. The top four categories of nonmedicinal substances were organophosphate pesticides, which constituted 18% of all poisonings, followed by phosphorus (14%), rat poison (10%), and solvents (6%). Pesticides are often a leading category of poisoning in some developed and many underdeveloped countries. In one hospital in Turkey, pesticides followed analgesics as the second most common poisoning [39].

A few reports have focused on pediatric poisoning admissions. In a study from Boston during 1981 and 1982, 90 acute poisonings (52 accidental and 38 suicidal) constituted 1.1% of the 8,296 total admissions [40], 64% were medical ICU admissions and 4.5% of the total medical ICU admissions. The average LOS was 2.2 days. There was one fatality due to diphenoxylate. The most frequent agents responsible were alcohol (11), barbiturates (9), cyclic antidepressants (9), theophylline (8), aspirin (8), and benzodiazepines (8). A review of pediatric hospitalizations from the same children's hospital approximately a decade later (over a 4-year period from 1992 to 1995) documented a 0.9% admission rate for poisoning [41]. Two thirds of the 638 admissions for poisonings were medication related. Toddlers, age 1–5 years, accounted for 42% of admissions, and adolescents older than 12 years accounted for 45% of admissions. In the toddlers, lead, caustic agents, and benzodiazepines were the most common agents, whereas acetaminophen predominated in the adolescents. Antidepressants, antihistamines, and salicylates also accounted for a significant number of admissions. The LOS over this period decreased from 5.85 to 3.45 days [41].

The US state of Washington reviewed all hospital pediatric discharges over an 11-year period [42]. The incidence was 45 per 100,000 children per year. Intoxication accounted for 0.6% of the hospitalizations. Children aged 12–18 accounted for 75% of the admissions, whereas toddlers (age ≤ 5 years) accounted for 20% of the admissions. The

fatality rate was 0.2%. The average LOS was 1 day (range 1–3 days). ICU issues related to pediatric poisoning are discussed in detail in Intensive Care of Pediatric Poisoning Patients.

Currently, the best source for identifying the poisons, toxins, and toxidromes likely to cause hospital admissions is the ToxIC (Toxicology Investigators Consortium) Registry of the ACMT (American College of Medical Toxicology). Although the cases collected are less than the National Poison Data System of the AAPCC (American Association of Poison Control Centers), they better reflect those patients requiring inpatient care by medical toxicologists and intensivists. In 2014, 9,712 cases were entered from 47 medical toxicology services, providing care at 77 clinical facilities [43]. They included 81% of the accredited US medical toxicology fellowship sites, thus capturing the great majority of patients seen at the busier academic medical toxicology facilities. There is likely a bias in this data towards the sickest poisoned patients based on the type of facility and the active presence of a medical toxicology program. The ToxIC Registry recorded the referral services leading to admissions or inpatient consultations and found that almost all (93.5%) came from the emergency department, the admitting inpatient service, or by transfer from another facility [43]. Of concern was that only 0.1% of cases accounted for referral from a poison control center to a medical toxicology service, demonstrating a current lack of collaboration between poison centers and medical toxicology services. This presents a heretofore underutilized opportunity to greatly improve patient care by coordinating initial phone consultations with bedside care by toxicologists.

Pharmaceutical products exposure, particularly intentional, was the most common reason for consultation by a medical toxicologist, accounting for 61.7% of all cases. Accidental exposures to pharmaceuticals or toxins followed with 13.4% and organ system dysfunction at 3.8% [43] (Table 3). Adverse drug reactions represented only five of the total cases for medical toxicology consults, yet are increasing events which could benefit from medical toxicologist consultation. This demonstrates the need for collaboration

Table 3 Reasons for medical toxicology encounter/consultation

	N	(%)
Intentional exposure – pharmaceutical	4,803	(52.4)
Intentional exposure – nonpharmaceutical	913	(10.0)
Unintentional exposure – pharmaceutical	853	(9.3)
Unintentional exposure – nonpharmaceutical	379	(4.1)
Organ system dysfunction	347	(3.8)
Not documented	297	(3.2)
Withdrawal – opioids	270	(2.9)
Envenomation – snake	234	(2.6)
Withdrawal – ethanol	227	(2.5)
Ethanol abuse	194	(2.1)

From Rhyee et al. [43], p. 392

Table 4 Agent classes involved in medical toxicology consultation 2014

	N	(%)
Analgesic (nonopioid)	1,599	(12.8)
Sedative-hypnotic/muscle relaxant	1,546	(12.4)
Opioid	1,311	(10.5)
Antidepressant	1,301	(10.4)
Ethanol	849	(6.8)
Anticholinergic/antihistamine	761	(6.1)
Cardiovascular	713	(5.7)
Antipsychotic	689	(5.5)
Sympathomimetic	684	(5.5)
Anticonvulsant	421	(3.4)
Psychoactive	312	(2.5)
Envenomation	282	(2.3)

From Rhyee et al. [43], p. 393

between the Institute for Safe Medication Practices and poison control centers, medical toxicologists, and emergency departments to decrease the incidence of these events through diagnosis, treatment, reporting, education, and development of prevention strategies [44].

Nonopioid analgesics, particularly acetaminophen, were the most common medication involved (12.8%), as has been the case for many years (Table 4). Sedative-hypnotics were a close second agent class seen in 12.4%, then opioids in 10.5%, and antidepressants in 10.4%. In the

Table 5 Antidotal therapy

	N	(%) ^a
<i>N</i> -acetylcysteine	921	(31.1)
Naloxone/nalmefene	605	(20.4)
Sodium bicarbonate	322	(10.9)
Physostigmine	156	(5.3)
Thiamine	119	(4.0)
Fomepizole	90	(3.0)
Flumazenil	81	(2.7)
Glucagon	80	(2.7)
Calcium	77	(2.6)
Folate	74	(2.5)

^aPercentages are of total antidotes administered
From Rhyee et al. [43], p. 406

category of individual psychoactive drugs of abuse, the rapid emergence of synthetic cannabinoid abuse accounted for 26% of these agents, second only to herbal marijuana (32.4%) in this class.

The treatment required by the patients in the 2014 ToxIC Registry clearly exemplify the intertwined relationship between medical toxicology and critical care medicine. Of the 9,172 patients, antidotes were administered 2,962 times, or 51.8% of all treatments reported [43]. *N*-Acetylcysteine for acetaminophen overdoses and naloxone or nalmefene for opioids accounted together for over one half (51.5%) of all antidotes administered. The only other antidote given that was more than 10% of the total was sodium bicarbonate, usually used for cardiac conduction abnormalities, arrhythmias, or hypotension in sodium-channel blocker toxicity (Table 5). Specific toxicologic care was administered in conjunction with supportive general pharmacologic and nonpharmacologic care, frequently directed by intensivists. General pharmacologic supportive care was given 2,843 times, with benzodiazepines, opioids, and vasopressors being the most common (Table 6). Intravenous fluid administration and mechanical ventilation were the most commonly employed forms of supportive care, used 2,733 times collectively in the 9,172 patients (Table 7). The provision of critical care and medical toxicology together, either by the medical toxicologist or in collaboration with the intensivist, is essential for the recovery of the poisoned patient.

Table 6 Supportive care – pharmacological

	N	(%) ^a
Benzodiazepines	1,624	(7.1)
Opioids	261	(9.2)
Vasopressors	239	(8.4)
Antipsychotics	186	(6.5)
Glucose (concentration > 5%)	165	(5.8)
Anticonvulsants	78	(2.7)
Neuromuscular blockers	66	(2.3)
Albuterol (or other bronchodilator)	63	(2.2)
Corticosteroids	49	(1.7)
Antiarrhythmics	42	(1.5)
Antihypertensives	35	(1.2)
Beta blockers	27	(0.9)
Vasodilators	8	(0.3)
Total	2,843	(100)

^aPercentages are of total number of treatments
From Rhyee et al. [43], p. 406

Table 7 Supportive care – nonpharmacological

	N	(%) ^a
IV fluid resuscitation	1,937	(67.6)
Intubation/ventilatory management	796	(27.8)
CPR	40	(1.4)
Hyperbaric oxygen	21	(0.7)
Transfusion	21	(0.7)
Pacemaker	15	(0.5)
Therapeutic hypothermia	13	(0.5)
Cardioversion	11	(0.4)
ECMO	7	(0.2)
Organ transplantation	4	(0.1)
Aortic balloon pump	1	(0.0)
Bypass	1	(0.0)
Total	2,867	(100)

CPR cardiopulmonary resuscitation, ECMO extracorporeal membrane oxygenation

^aPercentages are out of the total number of treatments administered

From Rhyee et al. [43], p. 406

Fatalities by Toxin

Carbon monoxide (CO) is the second most common toxin causing poisoning fatalities, with alcohol the leading cause [45]. Most CO fatalities do not present to health care facilities but rather are found deceased and are coroner cases. Historically, in the 1950s and 1960s in Scotland, England, and Wales, barbiturates were the second most common

cause. In 1962, there were 4,208 carbon monoxide deaths and 1987 barbiturate, sedative, and salicylate deaths combined [30]. In 1968, the fatality rate for all poisoning admissions at The Royal Infirmary of Edinburgh was 0.7% [31].

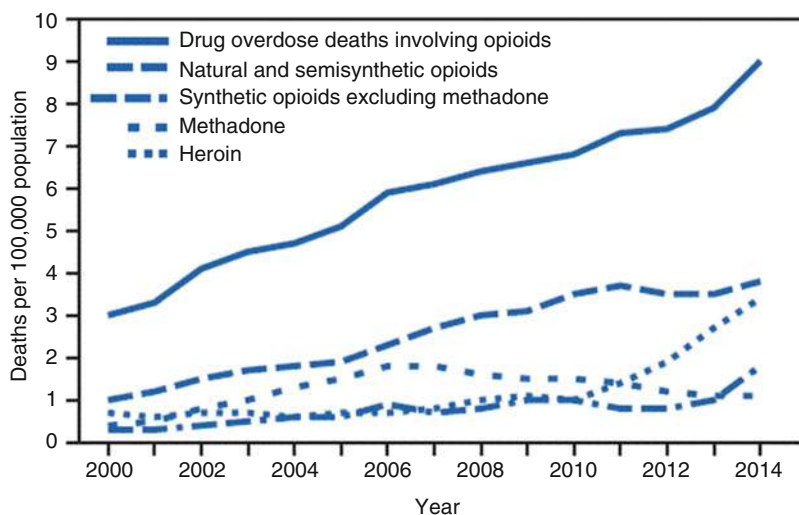
The Rhode Island Poison Center reviewed and compared its fatality reports with reports of the medical examiner for a 4-year period (1986 to 1989) [46]. Carbon monoxide was the most common cause of fatality, accounting for 98 of the 369 fatalities. After excluding cases of patients pronounced dead at the scene or dead on arrival, there were 112 cases in which the PCC could have been called; however, they were called on only 33 of these cases. In 10 of these cases, the poison center determined that they would have had additional recommendations that may have altered the outcome.

In Australia, deaths due to poisonings in 1989 and 1990 [47] had an average victim age of 36 years. Opiates primarily accounted for 40% of the cases, cyclic antidepressants accounted for 14%, and benzodiazepines accounted for 6.5%. Only 25 of the 231 patients reached the hospital alive. In a later Australian report, the Hunter Area Toxicology Service reported a 0.6% mortality rate from 1987 to 1995 [48].

Recent data show that most poisonings who are now admitted to a hospital have a low fatality rate. Hospital fatality rates in both the National Poison Data System of the AAPCC and the TOXIC Registry of the ACMT are about 1% in the years 2012–2014 [20, 43]. Currently, the most common causes of death in poisoned patients presenting to a hospital are pharmaceuticals, causing 83% of all deaths. Analgesics, and specifically opioids and acetaminophen, accounted for 39% of all deaths [20, 43]. Prescription opioids as a class were the most common, particularly methadone, followed closely by oxycodone and hydrocodone. However, illicit heroin was the single most common cause of death. From 2000 to 2014, there has been a 200% increase in opioid deaths, particularly heroin (Fig. 6).

Stimulants such as amphetamines and cocaine were the second most common cause of in-hospital deaths, followed by cardiovascular drugs, antidepressants, and sedative/hypnotic/antipsychotic agents [20].

Fig. 6 Opioid deaths by class, 2000–2014 From Ref. [12]



Aspiration syndrome after drug overdose is a common complication and reason for ICU admission. In a study from 1987 through 1995, 39% of all community-acquired aspiration syndromes admitted to the ICU were secondary to drug overdose [49]. The overall mortality rate was 22%, but it was unclear how many of these fatalities followed drug overdose.

The aforementioned reports show that poisoning fatalities, mostly suicidal, continue to be a leading cause of death, especially in young adults. In North America, most of these fatalities occur out of the hospital and are reported by coroners. In-hospital fatalities continue to occur, however. Although some deaths are unavoidable (e.g., post-cardiac arrest or hypoxic brain injury occurring before hospital arrival), avoidable deaths still occur. A validated assessment or predictive tool for poisoned patients does not exist. It is difficult to envision the development of such a tool because of the variability of each potential intoxicant and the diverse pharmacokinetic profiles of drugs and other chemical substances. The time of ingestion and dose taken can be used to predict the course of intoxication. This evaluation must be done individually in each case, however. The medical toxicologist and PCC are resources to help predict severity for each individual case and to provide specific information that may attenuate the severity.

The mental health and social issues that lead to poisoning fatalities need further studies and resources to help reduce poisoning fatality rates.

Stern and associates [45] followed 104 consecutive ICU admissions for poisonings [50]. Of these, 88 were followed for 5–24 months. The follow-up mortality rate was 6% by another overdose; 42% were readmitted for another overdose or psychiatric illness.

Ojehagen and colleagues [46] analyzed the repeat overdose patients and the nonrepeaters in a total of 79 patients admitted to a Swedish ICU over an 18-month period [51]. The predominant psychiatric diagnoses were adjustment disorder (31%), alcohol abuse (22%), major depression (19%), dysthymia (14%), and psychosis (9%). Of the patients, 66% were receiving psychiatric care. Repeaters were 58% of the sample and were less educated, had a higher rate of unemployment, and were more likely to be taking psychopharmacologic therapy. In many other series of patients from other countries or regions, the rates of repeaters have been much lower. The psychiatric care of critically poisoned patients is discussed in greater detail in ► [Chap. 6, “Psychiatric Issues in the Critically Poisoned Patient.”](#)

Medical Toxicology Training

Training of health care professionals in toxicology has lagged behind that of other disciplines around the world [52]. Academic toxicology programs are lacking in most countries, although veterinary and pharmacy students receive some background

in the field [52, 53]. It became apparent in recent years in the United States that the fields of emergency medicine, critical care medicine, internal medicine, pediatrics, pharmacology, and occupational medicine could collaborate their basic and clinical science curricula to train physicians in the subspecialty of medical toxicology [54]. Success has been limited so far, owing to inadequate resources in faculty, curriculum guidelines, and clinical training centers. Despite this, in the United States there is a clearly evolving trend of medical toxicology training for medical students, residents, and fellows, particularly at those institutions with medical toxicology attendings.

Medical Students

A 1990 survey of Canadian and US medical schools found that although 88% of US schools reported teaching medical toxicology, only 5% had formal toxicology courses [52]. In Canada and the United States, medical schools averaged only 5 h of didactic toxicology teaching. An MD or PhD toxicologist was on staff at only 51% of the schools. This report represented an improvement, however, from an earlier survey of undergraduate US education [55]. In Great Britain's 24 medical schools, 22 reported formal toxicology teaching for a median of 5 h (range 1–12 h) [56]. Many medical schools have moved away from traditional lecture-based curricula to problem-based, facilitator-guided learning formats. Toxicology is often covered in the neuroscience or pharmacology block in the second year [57].

Residency Training

The experience in medical toxicology obtained in residency programs is highly variable. The formalization of training in medical toxicology varies greatly among countries. In the United States, medical toxicology is a core content area for emergency medicine residencies, so these postgraduate programs provide the most training in the field. Nonetheless, only 26% of the programs in a 1990 survey of US emergency

medicine residencies had a board-certified medical toxicology faculty member and 19% offered no toxicology rotations at all [58]. Of the programs, 43% required toxicology training outside of the emergency department, but most of this was at poison information centers rather than bedside experiences. A 2,000 survey of emergency medicine residencies documented an increase in toxicology faculty to 63% of the programs [59]. A toxicology rotation was required at 76% and was an elective at 19%. The experience was widely variable, however, with most still receiving the training primarily at a PCC rather than inpatient care [59]. PCC training has been shown to modestly increase test scores in toxicology [60]. Poison information center experience, however, is limited in its ability to provide the skills necessary to treat critically poisoned patients.

In other US residency training programs, clinical toxicology education is usually lacking any meaningful experience. Only 4% of pediatric and psychiatry programs offer a clinical toxicology rotation, yet only 11% of the pediatric residency directors believed that their residents needed improvement in toxicologic management [61, 62]. Only 41% of psychiatry programs have didactics in toxicology, and only two programs had a toxicology elective [62]. Although internists in their roles as hospitalists, admitting physicians, or intensivists care for most poisoned inpatients, there is no toxicology required in internal medicine residency programs except substance abuse didactics.

Fellowship Training

In the United States, medical toxicology is a formally recognized subspecialty by the American Board of Medical Specialties, the regulatory authority for specialty and subspecialty certification. Postresidency fellowship training programs in medical toxicology emerged in the 1970s in the United States. In 1974, the American Board of Medical Toxicology (ABMT) was established by a subgroup of physician members of the American Academy of Clinical Toxicology (AACT) to set standards in care and training [54]. The primary

function of the ABMT was offering a certifying examination in medical toxicology to physicians, which began in 1975. Entrance to this exam required completion of a fellowship program or a practice pathway of 2 years of clinical experience. In 1989, the ABMT published guidelines for fellowship training in medical toxicology and continued to certify physicians until 1992, when the American Board of Medical Specialties officially recognized medical toxicology as a subspecialty [63]. This new subspecialty board was developed and sponsored by the American Boards of Emergency Medicine, Preventive Medicine, and Pediatrics [54].

Medical toxicology fellowship training requirements in the United States have been developed under the auspices of the American College of Graduate Medical Education (ACGME). Board certification or qualifications are required in a primary medical specialty, and subspecialty medical toxicology training requires 2 years of full-time fellowship in a program accredited by the ACGME. Medical toxicology program requirements are found at www.acgme.org. Fellowship programs grew from 21 in 1997 to 28 in 2016, with 70 fellows in training (www.acmt.net) [64]. The certification examination was first offered in 1994, and accreditation of training programs began in 1999 [64]. In 2000, the grandfather practice route to medical toxicology subboard certification closed. Qualifications to be entered into the ABMS subspecialty examination now require completion of an approved 2-year fellowship. Cognitive expertise examinations are also now required, and a recertification examination is required every 10 years. The core content of medical toxicology, which outlines the knowledge base essential for the practice of medical toxicology, fellowship training, and the framework of the certification and cognitive examinations, was updated in 2012 [64]. The core content includes principles of toxicology, toxins and toxicants, clinical assessment, therapeutics, population health, and analytical and forensic toxicology.

Clinical experience is still variable and often very limited in many programs, despite an ACGME requirement for providing bedside evaluation and management of toxicology patients for

a minimum of 12 months. Some programs offer little but the required experience in telephone consultations at a regional poison control center. Bedside experience, although often limited, usually includes consultations on adult and pediatric patients. A few programs have inpatient admitting referral services, but most are consult services. Limitations on bedside training at many fellowships continue to restrict expansion of the specialty and expertise of recent fellowship graduates. In the only study of fellowship training, it was reported that fellows spent only 19% of their time in inpatient encounters. The fellowship programs had a mean total exposure to only 204 (Range 5–1,000) inpatients per program annually [64]. Twenty-four percent of all fellows were required to work in the ED as a part of their fellowship, further diluting their inpatient toxicology experience [64]. Pediatric emergency medicine offers a combined fellowship with medical toxicology [66, 67]. In the United Kingdom, medical registrars receive training in medical toxicology at regional poison treatment centers, in preparation to be consultants in the specialty [9]. They receive extensive bedside experience in the diagnosis and treatment of the poisoned patient, typically well beyond that of fellows in US programs.

With the establishment of the medical toxicology subboard by the ABMS, the American Board of Medical Toxicology (whose primary purpose had been to provide the certifying examination) was no longer necessary and went out of existence, although the ABMT Certification remains a lifetime board certification. The ACMT was founded in 1993 to fill the void left by the dissolution of the ABMT and to provide a physician specialty society for medical toxicologists. Since that time, the College has continued to expand both in numbers and activities, including offering an annual scientific meeting and other educational seminars, publishing the *Journal of Medical Toxicology*, providing a voice in organized medicine for toxicologists, providing research and training grants, and sponsoring the Toxicology Investigators Consortium Case Registry (www.acmt.net). The College now represents the vast majority of physicians who are Board-Certified in Medical Toxicology. By 2016, there were over

500 members of the ACMT, who were certified by the ABMT or the ABMS subspecialty board. Of these, 221 ACMT members had been recognized as Fellows of the American College of Medical Toxicology (FACMT), meaning they were not only board-certified but also had made significant contributions to the specialty (www.acmt.net).

Medical Toxicologists

Medical toxicologists admit or consult on patients hospitalized or in the ED, staff outpatient occupational and environmental practices, perform research and education, serve industry or governmental agencies, participate in pharmacy and therapeutics committees, and serve as expert witnesses. Most often, however, they still practice by providing telephone consultation for a PCC [68]. There were 209 physician toxicologists certified by the ABMT between 1974 and 1992, having qualified by fellowship training, practice experience, or a combination of both, but by 1992 there were only 183 still practicing in this field [64, 68, 69]. Between 1994 and 2014, 498 medical toxicologists were certified by the ABMS subboard, although 60 certifications have since lapsed. In terms of professional practice, a survey of medical toxicology fellowship graduates in 1998 found that fewer than half spent more than 50% of their professional time in medical toxicology at that time, and one third spent less than 25% [64, 69]. In 2002, there were 315 medical toxicologists, representing 55 solo or group practices serving 125 hospitals in the United States [70]. The average number of in-hospital patients treated annually at that time was 228 per group practice, and 36 of these groups were affiliated with a poison control center. A later survey in 2007 showed that 88% of the respondents were clinically active in toxicology, but only 35% spent an equal or more time in toxicology as compared to their primary specialty [68]. Only 22% saw more than 200 acetaminophen-poisoned patients per year, the most common poisoning seen, and 46% saw less than 50 per year. Of the estimated 260,000 poisoning hospitalizations in the United States each year, only about 12,540 (<1%) are seen

by a medical toxicologist. [64, 69–71] Most critically poisoned patients are cared for not by medical toxicologists but by intensivists, hospitalists, or primary care physicians. A barrier to medical toxicology practice has been perceived to be inadequate financial reimbursement. In the early years of the specialty, this was indeed true for most toxicologists. In one study of a solo practice, charges and income were nominal [72]. As the specialty evolved, multiple practices nationally began to succeed in becoming economically feasible [73]. Some of the reasons were the increasing number of adolescents and adults requiring hospitalization due to drug abuse or intentional self-poisoning, increasing complexity and severity of cases, changes in practice methods from telephone consults to bedside care, the increased number of medical toxicologists available to form practice groups, and gradually increased knowledge of these groups in billing practices. Nevertheless, adequate compensation for medical toxicologists is a persistent problem because of the poison control center model of telephone consultations provided with little or no charge [74].

Other Health Care Professionals

Additional training in medical toxicology is needed for other health care professionals worldwide. Critical care and emergency department nurses scored only about 50% on a questionnaire about antidote dosing and indications [75]. Paramedic training programs in the United States devote only 2% of their time to toxicology, and only 11% have a designated experience at a poison center [76]. Poison centers and regional toxicology treatment centers are rich resources for continuing education for health care professionals. These centers have filled this role in industrialized nations and in developing countries, such as Zimbabwe [77]. The poison center may function as a multidisciplinary training site where medical, pharmacy, nursing, paramedic, and school of public health students work together with residents and toxicology fellows in the delivery of clinical advice [78]. Clinical pharmacology

has been combined with clinical toxicology in some institutions [79].

Medical Toxicology Practice Standards

The provision of poisoning treatment throughout the world generally is the responsibility of emergency physicians, pediatricians, internists, occupational physicians, and intensivists. They are supported by a relatively small group of trained clinical toxicologists, consisting of medical toxicologists and pharmacologists, who usually are located at large academic centers or poison centers. In such centers, a medical toxicologist often functions as the primary attending physician for poisoned patients. In the absence of locally available specialists in the field, physicians are forced to rely on telephone consultation, computerized data information systems, or standard texts. The now-disbanded World Federation of Associations of Clinical Toxicology Centers and Poison Control Centers in the 1960s advocated that poison information centers be available and provide the physician with advice tailored to the individual case, but this is not always practical [9]. The American College of Emergency Physicians (ACEP) has stated that poison treatment and information should include consultation with a medical toxicologist or PCC and that there should be regional centers for poison treatment for serious poisonings [80]. Many professional societies, such as the AACT, the European Association of Poison Centres and Clinical Toxicology (EAPCCT), the Society of Critical Care Medicine, the ACEP, and the American Heart Association, have published clinical guidelines for the treatment of poisonings, and these principles are outlined in chapters throughout this book [81–83].

There are multiple demonstrated weaknesses in providing poisoning care with the frequently employed model of care by generalists, such as lack of available medical toxicology care or consultation. Treatment recommended by emergency departments in simulated cases of drug overdoses was found to be correct in only 68% of cases. This included only 50% correct treatment of cases presenting to a teaching hospital and in only

22% of cases when the emergency physician was consulted [84]. A study of poisoning deaths in Massachusetts found that 29 of 60 deaths (48%) had errors in management as judged by an expert panel [85]. In two other studies, it was judged that 20–24% of in-hospital poisoning deaths could have been prevented if a medical toxicologist had been consulted [46, 87]. In England and in the United States, one fourth of all poisoning deaths occur after hospitalization, suggesting that better prehospital or in-hospital care might prevent some of them [85, 87]. An evaluation of the Acute Physiology and Chronic Health Evaluation (APACHE) III showed APACHE III to underpredict drug overdose mortality [88]. In this observational cohort study, APACHE III was used to predict mortality for 1,032 drug overdose admissions to 161 US hospitals. The predicted mortality from APACHE III was 7 (0.7%), but the actual mortality was 25 (2.4%) ($P < 0.0001$). This study suggests that in-hospital poisoning deaths are a greater risk than the APACHE III score can predict, or that there is need for improvement in toxicologic care.

A report from England showed significant variability in the management of poisoned patients. Thomas and coworkers reported this finding by comparing six hospitals in northeastern England over 12 weeks [17]. The catchment area included 1.52 million people. The admission rates for patients presenting to the accident and emergency wards varied from 50% to 87% (average 73%). The LOS varied from 0.8 to 2.1 days. Reasons for this variability were not presented. Only 12% of the patients had an LOS greater than two nights. Being elderly and ingesting benzodiazepines, acetaminophen, or antidepressants seemed to predict a longer LOS. Of the 690 admissions, there were three fatalities (0.4%) [17].

One study has now demonstrated that bedside care by medical toxicologists reduces lengths of stay, cost, and mortality of inpatients as compared to care by nontoxicologists. In this 2-year study of 3,581 patients, the LOS for the patients admitted to a large group's toxicology service were 0.3 days shorter than patients treated by nontoxicologists at both the same and different hospitals. This resulted in a median savings of 1,483 hospital days and

4,269 million dollars [89]. Most importantly, mortality rates were statistically significantly lower under the toxicologists' care, with a projected potential lives saved of 54.7 per 1,000 patients. Unfortunately, in 2014 there were only 42 reported medical toxicology services in the USA, serving 72 individual healthcare institutions [43].

Toxicology Resources

References for toxicology information in the mid-1900s were card files of individuals, poison centers, and the US National Clearinghouse for Poison Control Centers, followed by a computerized version of the Clearinghouse cards [78, 90]. In the 1970s, microfiche technology allowed for the storage and retrieval of larger toxicology databases, which eventually were replaced by computerized information database systems, such as the POISINDEX, which has become one of the standard references for clinicians and poison centers in the United States [78]. In the United Kingdom, the TOXBASE Internet database system is available to emergency departments and individual physicians at www.spib.axl.co.uk [9]. Both database systems contain extensive information on the features and management of pharmaceuticals and toxins.

Clinical toxicology textbooks are another resource for clinicians, although their reliability has been variable. To our knowledge, none before this book has comprehensively focused specifically on critically poisoned patients. The *Physician's Desk Reference* is a frequent source of drug overdose information for 50% of US physicians according to one survey, yet it was judged to include deficient treatment recommendations in 80% of the drugs reviewed, and in 35% of the drug outlines, contraindicated or potentially harmful advice was included [91].

It is often thought that contacting a PCC provides the local physician with reliable assistance in treating poisoned patients, avoiding transfer to a specialty center; some medical organizations even recommend that this be a standard of care [92, 93]. Contacting a PCC has been shown to be useful in cases of minor poisonings and drug or toxin identification, in which PCCs gave correct

information 75% of the time in one study [94]. Physicians contact a PCC in only 19–29% of serious cases, however, and even then the recommendations are followed less than half of the time [46, 85, 95, 96]. Although advice from PCCs regarding specific poisonings is generally excellent, the pharmacists or nurses giving most consultations from PCCs are not fully prepared to advise on issues related to the care of seriously ill patients. Contacts with PCCs are increased if a physician toxicologist is available, but experts are frequently not available or accessed for individual cases, and their advice is followed in less than two thirds of these cases [95, 97]. A study of recommendations by a PCC to use two advanced toxicology therapies, hyperinsulinemia euglycemia (HIE) and intravenous fat emulsion (IFE), showed that only 31 of 70 patients (42%) actually received HIE, and in only 10 of 30 cases (33%) did the physician follow the advice to give IFE [98]. Consultations by telephone have been known to be fraught with hazard, which may account for some of this reluctance, along with unfamiliarity with such treatments. Clinical data recorded at hospitals are often unavailable to PCCs or are significantly different from that provided, and the specialist at the bedside is often in a better position to assess and act on the patient's status than a telephone consultant [9, 99]. For this reason, the ACEP states, "Most medical conditions cannot be accurately diagnosed over the telephone." [93] The ACEP further recommends that "emergency departments do not attempt medical assessment or management over the telephone." [93] The assessment of the circumstantial, laboratory, and clinical evidence requires a high level of clinical and toxicologic expertise on the part of the consultant at the PCC, who is often a nonphysician [9]. Limitations of this model of poison care delivery are exemplified by a study in which treatment advice was sought from US PCCs in a simulated case of serious antidepressant poisoning. The advice was deemed to be correct from only 42% of all the PCCs contacted and from only 60% of the regional centers certified by the AAPCC [94]. In another study, 43% of recommendations by regional PCCs for the use of two antidotes, fomepizole and digoxin FAB fragments, were

improper [100]. Regrettably, most physicians and hospitals must rely on this model of toxicology care for inpatient care due to the relatively small number of medical toxicologists in the USA.

The lack of adequate resources also hampers hospitals in providing care to poisoned patients. Pharmacy stocking of emergency antidotes has been found to be adequate in a wide range of hospitals surveyed (2–98%), depending on the antidote, but only about 1% of hospitals have adequate supplies of all antidotes in amounts necessary to treat even one patient [101, 102]. Most health care facilities have on-site access to qualitative urine drug assays for only a few drugs of abuse and must rely on distant toxicology reference laboratories for more comprehensive drug screens and many necessary quantitative analyses [70]. Specialty poisoning treatment units are available in major cities in some countries, but this is not universally true.

Sites of Care

An ICU is usually recommended to be the most appropriate location for management of poisoned patients requiring hospital admission because of the availability of rapid diagnostic procedures, intense observation and monitoring, and complex treatment modalities [103]. Over 200,000 ICU admissions are due to drug- or toxin-related causes annually in the USA [29]. Caution must be employed in triaging patients with altered mental status to other sites. One study found that 69% of patients with unrecognized medical emergencies inappropriately admitted to a psychiatric unit had a drug overdose or intoxication, or severe drug/alcohol withdrawal [104].

The Society of Critical Care Medicine recommends that overdose patients be admitted to an ICU if they have cardiovascular instability, altered level of consciousness with airway compromise, or seizures [105]. One study found that ICU admission was necessary if in the emergency department the patient required mechanical ventilation or had seizures, coma, a partial pressure of carbon dioxide greater than 45 mmHg, arrhythmias, high atrioventricular block, a QRS greater

than 0.11 s, or systolic blood pressure less than 80 mmHg [106]. The Glasgow Coma Scale has been used to predict the need for ICU admission, with a score of less than 13, intubation, or the presence of infectious, cardiovascular, or electrocardiogram complications being sensitive and specific for needing ICU interventions in one study [107]. A smaller study suggested that nonintubated patients with a Glasgow Coma Scale score greater than 6 did not require ICU admission and could be handled on the general medical floors [22]. Intensive care for poisoned patients also may be delivered in an emergency department observation unit with respiratory care capabilities and can result in fewer complications and shorter LOS compared with admission to a general medical floor [108–110].

In severe cases, local resources may be inadequate to meet the patient's needs. Transfer of seriously ill patients to specialty centers is supported in policy statements of the ACEP, ACMT, and Society of Critical Care Medicine [111–113]. Transfer is often necessary to provide access to experienced medical toxicologists, antidotes, and analytic laboratory services not available elsewhere. Specialty poison treatment centers are available in a few cities around the world (see later section on “[Poison Centers](#)”).

Recommended Equipment and Resources

Care of the seriously poisoned patient requires medical and nursing expertise, an emergency department and critical care unit, analytic toxicology laboratory support, an adequate supply of antidotes, and psychosocial services [31, 114]. Available services should include hemodialysis, a clinical laboratory able to perform routine analyses, plus at least the emergency toxicology laboratory tests listed in the ACMT facility guidelines, a 24-h pharmacy, radiology, respiratory care, and psychiatric and social services [115].

The ACEP has published a clinical policy for the care of patients with toxic exposures, including recommended laboratory tests and common necessary emergency antidotes [83]. Although

intended for facilities serving as regional poison treatment centers, the guidelines of the ACMT also outline the resources deemed necessary in any hospital caring for poisoned patients [115]. The minimal qualitative urine drug assays recommended are listed in Table 8, and the quantitative tests necessary for immediate care are listed in Table 9. In addition to these drug assays, the hospital laboratory must be able to perform rapidly arterial blood gases, a comprehensive metabolic panel, coagulation studies, serum ammonia, serum osmolality, acetone, and lactate.

Table 8 Recommended analytes to be available on qualitative urine screening assays^a

Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine
Cyclic antidepressants
Opiates
Phencyclidine

^aThis is a recommended list for hospitals in the United States and Canada. It should be modified based on the regional drug use patterns in other locations

Table 9 Recommended analytes to be available for emergency quantitative drug assays (Available within 2 h)^a

Acetaminophen
Carbamazepine
Carboxyhemoglobin
Digoxin
Ethanol
Ethylene glycol
Iron
Isopropanol
Lithium
Methanol
Methemoglobin
Phenobarbital
Phenytoin
Salicylate
Theophylline
Valproic acid

^aThis is a recommended list for hospitals in the United States and Canada. It should be modified based on the regional epidemiology of poisoning

Antidote needs may vary based on geography and setting; the minimal required antidotes are listed in Table 10.

Poison Centers

The proliferation of accidental and intentional poisonings in the 1940s led to the development of centers for poison information dissemination and treatment around the world. The infancy of such centers was in Copenhagen, the Netherlands, Edinburgh, and Chicago. These specialty centers serve as resources for poison information, public and health professional education, poison prevention, research, and in some cases tertiary patient care. The increasing number of childhood accidental poisonings and deaths and physicians'

Table 10 Recommended emergency antidotes

Activated charcoal
Amyl nitrate
Antivenin, Crotalidae ^a
Calcium chloride
Calcium gluconate gel
Deferoxamine mesylate
Digoxin immune Fab
Ethanol
Folic acid
Fomepizole
Flumazenil
Glucagon
Leucovorin
Methylene blue 1%
N-Acetylcysteine
Naloxone
Physostigmine
Polyethylene glycol electrolyte solution
Pralidoxime hydrochloride
Protamine sulfate
Pyridoxine
Sodium bicarbonate
Sodium nitrite 3%
Sodium thiosulfate
Succimer
Thiamine hydrochloride
Vitamin K ₁

^aFor crotaline endemic areas

general lack of knowledge and resources about drug and chemical ingredients initially highlighted the need for poison centers.

Poison Information Centers

The first poison information service is thought to have been established in the Netherlands in 1949, followed in Europe by similar centers in Paris in 1959, London and Edinburgh in 1962, and Zurich in 1966 [9, 53]. The first information center, or PCC, in the United States was established in Chicago in 1953 and had been preceded by an informal information service in the pharmacy of St. Luke's Hospital [90]. The first PCC was intended to provide information to physicians on ingredient and toxicity information, and the database was a set of small cards. Subsequently a manual was developed outlining the ingredients of common household products and distributed to emergency departments. Similar centers began to appear across the United States, and by 1957, there were 17 PCCs, which now also were taking calls from the public [90]. An initial barrier was the lack of reliable data sources and data collection, so the US Surgeon General designated the National Clearinghouse for Poison Control Centers, which distributed index cards of poison information and collected poison data from centers [90]. There was an uncontrolled growth of PCCs in the United States during the 1960s and 1970s, resulting in 661 PCCs of variable quality [90]. The American Association of Poison Control Centers (AAPCC) was established in 1958 primarily by pediatricians to develop public and professional education programs, promote cooperation between centers, and set standards for operation. In 1978, the AAPCC published strict standards for PCCs, and as a result the number of PCCs declined to 91 in 1995, 73 in 1998, and 55 in 2015 [20, 116]. These centers are staffed around the clock by nurses and pharmacists and usually are directed by pharmacists with some medical direction provided mostly by part-time medical toxicologists [99]. Some centers do not have adequate medical toxicologist availability, and most cases do not involve physician

consultation [81, 99]. PCCs have been shown to reduce unnecessary hospital visits and health care expenses, however, and serve as a resource for education, research, poison prevention efforts, and data collection [99, 100]. They also have been shown to be a reliable source of first aid and triage advice for the public and hospitals in cases of nonlife-threatening toxic exposures [84, 94]. Poison center services in the United States to physicians caring for poisoned patients have evolved over the years. Initially, PCCs were primarily consulted for ingredient information. The lack of availability of medical toxicologists at most hospitals has rendered PCCs as the default source of treatment recommendations. Most of this advice comes from nonphysicians working in PCCs, however. The need for medical toxicology resources for information on the treatment of critically poisoned patients is evident.

Likewise, in Europe the EAPCCT was formed in 1964 to share knowledge and to identify toxic hazards. There are now approximately 80 - European PCCs [53]. Networks of multiple centers operate in France, Germany, Italy, and the United Kingdom [53]. In the United States, poison centers can be contacted by the public and health care professionals at 1-800-222-1222, and in the United Kingdom the National Poisons Information Service is available to health care professionals and emergency departments at 0870-600-6266. Health officers, medical toxicologists, and pharmacists staff the centers, and they are often affiliated with poison treatment centers, ICUs, or emergency departments [53]. It has been advocated that these centers be part of a larger toxicology center that includes an analytic laboratory, inpatient treatment center, outpatient services, adverse drug reaction and occupational exposure advice, research, an expanded medical staff, and training [114, 118].

In addition to the United States and Europe, there are poison information centers operating on every continent worldwide except Antarctica. Many of these centers are still in the early stages of development. The Japan Poison Information Center was established in 1986 to serve a population of 124 million and received only about 35,000 calls in 1994 [119]. This represents a

case volume of only 27 per 100,000 population, in contrast to the United States's call volume of 920 calls per 100,000 at that time [119]. Before its dissolution, the World Federation of Associations of Poison Centers and Clinical Toxicologists issued a directory (Yellowtox) of worldwide poison information centers and analytic toxicology services, which still can be found at www.intox.org/pagesource/yellowtox/yellowtoxhtm.

Poison Treatment Centers

Poison treatment centers are highly specialized inpatient units directed by medical toxicologists and are capable of caring for the most complex cases of poisonings. Strong centralized regional poison treatment centers have flourished in some countries and serve as specialty care centers and institutes for toxicologic research, treatment advances, and education. Their origin probably is based in Scotland, where a "delirium ward" was established at the Royal Infirmary of Edinburgh in 1879 (Fig. 7) [30]. This unit gradually evolved into the Regional Poisoning Treatment Centre of Edinburgh, and by 1964 it cared for more than 90% of overdose patients in the Edinburgh area [30]. Another formal treatment center in Europe was founded in 1949 in Copenhagen, followed by other centers in Paris and in Romford, Essex, in the late 1950s [9, 30, 31]. The impetus for further development of centers in the United Kingdom in Birmingham, Dublin, Belfast, Cardiff, and London was the Atkins Report of 1962 and the Hill Report of 1968, in which the United Kingdom Ministry of Health recommended the establishment of regional poisoning treatment centers with consultants in toxicology and associated psychiatric and chemical toxicology laboratory services [31]. Other such centers were developed in Europe and Russia in the 1960s and more recently in the United States and Australia [48, 70, 115, 120].

In 1993, the AACT published standards for toxicology treatment centers [121]. Subsequently the ACMT refined and promoted those standards [115]. The Center for Poison Treatment Facility Assessment Guidelines can be found at www.acmt.net. The rationale for the existence of these

treatment centers is cited as the need for a dedicated professional staff to develop expertise, to assess and manage more efficiently medical and psychiatric issues, to advance knowledge rapidly by concentrating patients at dedicated sites for education and research, to focus psychosocial support for the patients' special needs, and to make it efficient to provide analytic laboratory support on-site [30, 31, 48, 114]. These guidelines recommend a medical staff of physicians board-certified in medical toxicology and nurses with toxicology specialty training, adequate beds consistently available for the care of the poisoned patient, quality improvement and teaching programs, and other physician specialists and equipment typically found in university hospitals or regional medical centers. Further details can be found in these guidelines on the ACMT website. There is no mechanism currently to certify centers meeting these standards, but it is known that there are at least 54 medical toxicology services in the USA, most of which would meet these standards [43].

These centers have been found to improve care of the toxicology patient. It was reported that in the first year of operation, the Copenhagen center reduced poisoning mortality by half by centralizing care [30]. The average LOS also has been reported to decrease, compared with general ICU or hospital ward admissions. In Australia, there was a reduction of 2–3 days in hospital stays for complicated poisoning cases at two toxicology centers, but there was not a statistical reduction in mortality [48, 122]. Use of health care resources also has been shown to decrease at these centers without compromising patient care, and the coupling of a treatment center with an aviation medicine service allows for efficient access to therapies unavailable in rural regions [123, 124]. Transfer of such seriously ill patients to specialty centers is supported in a policy statement of the ACEP, which states, "Patients should be transferred to a health care facility that meets their needs." [111] Transfer is often necessary to provide access to experienced medical toxicologists, antidotes, and analytic laboratory services not available elsewhere.

Regional poison treatment centers care for a highly variable number of patients annually.

Fig. 7 Royal Infirmary of Edinburgh 1879



Admissions to the Edinburgh center peaked at about 2,200 admissions per year, then declined to about 1,500 annual admissions in 1986 [9]. Two centers in Australia admitted 736 and 192 patients in years reported in the mid-1990s [48, 122]. The center in St. Petersburg, Russia, serves about 7 million people and reported more than 5,500 admissions per year [120].

In the United States, centers in Pennsylvania, Colorado, Arizona, and Utah each had about 500 annual admissions in 2002 [70]. The 54 centers participating in the ACMT ToxIC Registry, representing the busiest toxicology services in the country, treated an average of only 195 patients annually in 2014 [43]. Despite poisonings now causing more deaths than motor vehicle accidents, unlike the proliferation of trauma centers in every state, there has been little growth in medical toxicology specialty services [43, 68]. Even most university hospitals and large regional teaching centers have no toxicologists on their medical staff. This failure of modern medicine to meet this healthcare responsibility is due to a lack of recognition of the need for specialty toxicology care, the relatively low number of medical toxicologists due to a lack of adequately supported fellowship programs, and unfortunately less

opportunity to generate profit from these patients for the healthcare system [74]. Despite these barriers, medical toxicology has grown significantly in numbers of board-certified practitioners, peer-reviewed journals, fellowship programs, research, professional society size and activities, and bedside care by an increasing number of clinical sites. Likewise, critical care medicine has established its place as the designated physicians staffing ICUs, developing standardized evidence-based treatment protocols for improved patient care, and published research. The interaction between these two specialties should continue to grow and establish the standard of care for responding to the epidemic of drug overdoses and other critically ill toxicology patients.

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A medical toxicologist must pay great attention to detail. Unlike other specialties, the toxicologist rarely has a gold-standard diagnostic test to confirm a poisoning or withdrawal condition. Instead, the medical toxicology evaluation requires a thorough history and physical examination and strategically ordered diagnostic testing. Then once all available information is gathered, the medical toxicologist must astutely interpret the findings within the appropriate clinical context. Therefore, the toxicologist can be nothing short of an astute diagnostician.

A key component of medical toxicology is separating the poisoned patient from alternative diagnoses. The Venn diagram of diagnoses for metabolic syndromes, traumatic injuries, infectious diseases, neurologic conditions, cardiac disease, pulmonary disorders, and toxicological illness has much overlap. Therefore, the diagnostic process in medical toxicology must rely heavily upon a detailed history, an astute physical examination, and contextually placed diagnostic testing in order to make the correct diagnosis.

Furthermore, the medical toxicologist must be prepared to exclude nontoxicological diagnoses. When the history is vague, the examination is equivocal, and the diagnostic tests are confusing, the medical toxicologist must have an open mind for alternative diagnoses. We have treated many patients who first present as an “overdose” but are later diagnosed with an ischemic stroke, encephalitis, or other medical condition. Certainly, we have witnessed the opposite scenario as well. Therefore,

This chapter is an update of the chapter on this topic written by Alex T. Proudfoot and J. Ward Donovan in the first edition of this text.

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constant review and re-review of a clinical picture are paramount to ensure all findings remain consistent with any suspected diagnosis.

History

A detailed history is the most important first step in the diagnostic process in medical toxicology. Therefore, it is critical to gather data from all possible sources. Often, family, friends, and first responders offer great diagnostic clues. Electronic media is a potentially great source of information, including text messages, emails, and social media posts. Electronic media is particularly valuable since it is time-stamped.

When gathering history, where and under what circumstances the patient was found is critically important. Since first responders are trained to “size-up” a scene, they tend to provide the best history. Family and friends may only recognize crucial details when a scene is evaluated on the second attempt after coaching from the medical team. When obtaining history, crucial questions may include:

- Where was the patient found?
- When was the patient last seen in their normal state of health?
- What were the circumstances surrounding the patient’s discovery?
- Were any pill bottles, empty wrappers, or chemicals closely available?
- Are any suicide notes, text messages, or social media posts available?
- Is there any history of past drug overdoses, other attempts at self-harm, or substance abuse/withdrawal?

All these questions, and certainly many more, help identify the substances involved with a poisoning. Moreover, the history assists in identifying those at risk for aspiration pneumonia, rhabdomyolysis, compartment syndrome, or concomitant traumatic injuries.

A careful evaluation of available pills is extremely important. When pill bottles are identified, have family, friends, and first responders

bring the bottles to the hospital. This will assist in clearly identifying any substances. However, counting pills and attempting to correlate how many are missing is often a fruitless endeavor. Patients may hoard or sell pills and fail to take them as prescribed. Pill counts, therefore, are often unreliable. The mere availability of a particular substance suggests it may have been ingested. When pill bottles are not identified, prescriptions or substances available in the home can provide helpful clues. Patients will often ingest what is most easily available. When obtaining the medication history, it is important to inquire about prescriptions, over-the-counter medications, supplements, herbal preparations, and illicit drugs.

One point of caution is reliability of the obtained history. Patients, family, and friends are easily confused by drug names. For example, patients may be confused when attempting to identify over-the-counter pain relievers, such as ibuprofen and acetaminophen. Therefore, obtaining the exact pill bottles from the scene is the most reliable way to obtain this portion of the history.

Equally important is identification of chemical containers. When a chemical is identified in a possible exposure, obtaining the container from the scene is as important as obtaining specific pill bottles. The only reliable means to identify a substance is a well-labeled container. Using a witness’ recall as a means to identify a substance may be helpful in narrowing down the potential chemicals. However, specific chemical products have extreme variability in chemical composition even within the same brand. Therefore, errors in chemical identification are more likely when containers are not obtained.

The history is often the only means to identify a poison as few hospitals have the ability to promptly test all exogenous substances in serum or urine. Most hospitals can quickly obtain serum ethanol, salicylate, and acetaminophen concentrations. Yet, obtaining timely quantification of drugs and chemicals in body fluids remains elusive for most other exposures. Therefore, obtaining a detailed history, where possible, is a critically important element of the diagnostic process when dealing with poisoned patients.

Physical Examination

In conjunction with the history, the examination can confirm or refute the suspected toxicological diagnosis. In the absence of any available history, the examination may be the only initial clue in formulating a differential diagnosis. Furthermore, there is no substitute for a thorough bedside evaluation by a medical toxicologist. Medical toxicologists tend to astutely recognize unique signs of specific chemical intoxications or toxidromes.

Certainly, the examination must be tailored to the particular circumstances and clinical picture. This section is not designed to be all-inclusive. However, we merely highlight clinical signs that are high yield in evaluating the poisoned patient.

Vital Signs

Vital signs are vital! They offer the first picture into a patient's illness severity and determine what immediate actions should occur. In addition, serial vital sign measurements provide valuable information concerning a patient's changing clinical condition or response to treatment. Therefore, vital signs should be monitored closely and frequently.

Since many toxicants, drugs, and withdrawal states affect heart rate, the pulse is extremely important. Even a normal heart rate can suggest specific clinical conditions. In some cases, the heart rate is reflexively altered in a poisoning. For example, a toxicant exposure that results in hyper- or hypotension may result in reflexive brady- or tachycardia, respectively.

Blood pressure is also of utmost importance, and like heart rate, many toxicological diagnoses affect blood pressure. Yet more important than the actual blood pressure is the body's ability to adequately perfuse vital organs. When blood pressure measurements suggest the potential for inadequate perfusion (e.g., mean blood pressures ≤ 65 mmHg), we evaluate perfusion by alternative means. In these circumstances, we have borrowed knowledge gained in the treatment of sepsis. Along with the blood pressure, we will often use

serum lactate concentrations and mixed venous oxygen saturations [1]. This topic is discussed in greater detail in ► [Chap. 14, "The Assessment and Management of Hypotension and Shock in the Poisoned Patient."](#)

Respirations are effected by the patient's acid-base status or drugs/toxicants directly. However, merely looking at respiratory rate is often insufficient. One must astutely assess the depth of respirations as well as the rate of breathing. Many toxicants, drugs, and metabolic conditions may alter the minute ventilation without affecting the respiratory rate. In other words, the respiratory rate may remain normal while the patient is experiencing hyperpnea or hypopnea. These changes in minute ventilation are often revealed during a careful physical examination.

Body temperature measurements are often forgotten in the initial evaluation of the poison patient. Yet, the body temperature evaluation may be critically important. Alterations in body temperature can suggest a specific drug ingestion, chemical exposure, or withdrawal condition. For example, electron transport uncouplers, like salicylate, may cause hyperthermia. In other circumstances, the body temperature is merely a marker of the patient's environmental exposure. If a patient has an altered mental status after a poisoning, the patient is at the mercy of the environment. If left exposed to extreme temperatures, patients often present with hypo- or hyperthermia not from the toxicity, but merely from inability to seek shelter. Therefore, body temperature measurements need careful interpretation.

However, an elevated temperature is most strongly associated with mortality in sympathomimetic poisoning [2]. Therefore, body temperature measurements should not go unnoticed. Moreover, when extremes in body temperature are identified, efforts should be made to make the patient eutermic. Certainly, hyperthermia is a more immediate threat to life than hypothermia. Yet, hypothermia may lead to slower or unpredictable drug metabolism. Therefore, extremely high or low body temperatures are a concern and may offer diagnostic clues in the poisoned patient.

Clinical Signs

There are a number of clinical signs unique to the poisoned patient. One of the first signs encountered in the poisoned patient is odors. Odors are the result of malodorous chemicals, drugs, and drug metabolites. An obvious example is the detection of an ethanol odor, which may assist in identifying an intoxicated patient (See Table 1).

A thorough visual inspection of the patient's skin may be informative. This inspection should include a review of the skin color, dryness, and signs of traumatic injury. The actual poison may affect skin color as seen in the yellow staining after dinitrophenol poisoning. In other cases, the drug may cause a physiologic change resulting in skin coloration as in the flushed reddened appearance from antimuscarinic drugs. Cyanosis to a medical toxicologist does not merely suggest hypoxia but may also indicate methemoglobinemia or sulfhemoglobinemia. Some exposures lead to excessive histamine release, and patients may present with erythroderma such as with scombroid poisoning or the anaphylactoid reactions associated with vancomycin. Skin dryness may help differentiate between toxic syndromes. An old adage in medical toxicology is the toxicologist's handshake, which includes placing the clinician's hand in the armpit. Since antimuscarinic toxicity can result in facial diaphoresis, a dry armpit will more clearly differentiate antimuscarinic from sympathomimetic toxicity. Signs of skin trauma can provide contextual history about a patient.

Bruising may suggest concomitant traumatic injuries or the presence of a coagulopathy from liver disease or anticoagulant toxicity. Needle marks also tell much about a patient's social history. Skin necrosis or skin necrosis blisters are helpful diagnostic clues. Skin necrosis lesions are erythematous patches of various shapes that develop after prolonged immobility. One can often recreate the exact positioning of the patient by a careful evaluation of these skin lesions. With more prolonged contact, blisters may develop. These blisters have been called pressure necrosis blisters or even "barb blisters" since they were first noted in the era of barbiturate-associated overdoses. Nonetheless, skin necrosis and skin necrosis blisters inform the clinician that the patient suffered prolonged immobility and is at risk for aspiration pneumonia, skin breakdown, rhabdomyolysis, and compartment syndrome. Therefore, a simple inspection of the skin can provide much information about a patient.

A neurologic examination is of high clinical yield in the poisoned, or potentially poisoned, patient. This includes detection of any focal deficits, level of consciousness, speech, pupil size, muscle tone, and deep tendon reflexes. The importance of a detailed neurologic examination not only helps identify the correct toxicological diagnosis but can often identify alternative diagnoses, such as an ischemic stroke. Identification of any focal deficits should suggest the evaluation for nontoxicological diagnoses.

A patient's level of consciousness may suggest how much and, possibly, what type of poisoning is

Table 1 Odors of drugs and toxicants

Odor	Toxicant	Odor	Toxicant
Acetone	Alcoholic ketoacidosis	Mothballs	Camphor
	Isopropyl alcohol		Naphthalene
Acrid (pearlike)	Paraldehyde	Solvent/glue	Paradichlorobenzene
	Chloral hydrate		Toluene
Bitter almonds	Cyanide		Xylene
Disinfectant	Phenol		Trichloroethane
Garlic	Arsenical insecticides	Smoke	Tetrachloroethylene
	Organophosphate insecticides		Carbon monoxide
	Selenium		Cyanide
	Thallium		Clomethiazole
	Phosphorus	Wintergreen	Methyl salicylate
		Rotten eggs	Hydrogen sulfide

present. In clinical practice, the terms alert, lethargic, obtunded, stupor, and coma are helpful in describing a patients' mental status. Alert patients are awake and conversant. Lethargic patients require a loud verbal command for arousal. Obtundation requires shaking a patient as if awakening from sleep. Stupor requires a painful stimulus for arousal. Finally, a comatose patient is completely unarousable to multiple painful stimuli. Often the first step in a neurological examination, level of consciousness, also quickly determines who may need a more urgent intervention. This topic is discussed in greater detail in ► Chap. 19, "Toxicant-Induced Alterations in Consciousness."

The character of speech is quite telling. Fluency, articulation, and the ability to have an attentive conversation are important factors to review. For example, antimuscarinic patients have a characteristic mumbled and difficult to comprehend speech which, once recognized, helps identify this toxic syndrome. As medical toxicologists, we are often consulted for delirium. One characteristic finding of delirium is the inability to remain attentive. A conversation with a patient filled with distraction can suggest delirium. Therefore, the speech character and the conversation quality assist in the toxicological evaluation of potentially delirious patients.

Pupil size is one of the most commonly utilized neurologic examination findings for toxic patients. Most clinicians examine pupils to assess miosis in case of opioid toxicity. However, large pupils can suggest antimuscarinic or sympathomimetic toxicity. Yet, as a point of caution, the pupillary evaluation can be extremely misleading. For example, meperidine, an opioid, often presents with mid-sized pupils due to competing mechanisms from muscarinic antagonism and opioid agonism [3]. Therefore, interpret the pupil exam with much caution, but when utilized correctly, can provide a wealth of information.

The medical toxicologist must distinctly differentiate neuroleptic malignant syndrome (NMS) from serotonin syndrome. Muscle tone and reflexes are an important part of the neurologic examination. Except for the neurologist, most other specialists fail to include this as part of their

standard examination. Since the defining features of many toxic syndromes require an evaluation of tone and reflexes, these should become a routine part of the medical toxicologist's evaluation. The details of differentiating these two syndromes are found in ► Chaps. 31, "Neuroleptic Malignant Syndrome" and ► 24, "Serotonin Syndrome."

Toxidromes

After exposure to an unknown poison, any single sign, symptom, or laboratory abnormality will rarely permit the medical toxicologist to reach a definitive diagnosis. Rather, pattern recognition, the presence or absence of physical examination findings, and detailed historical evidence, together, will lead to speedy and accurate diagnoses.

In 1974, Mofenson and Greensher coined the term "toxidrome" to describe constellations of signs and symptoms that consistently result from particular classes of toxicants [4]. In clinical practice, however, it is more common to encounter partial toxidromes or mixed toxidromes. For example, toxicity from diphenhydramine, a first-generation antihistamine, often results in profound antimuscarinic findings. However, it is also sedating (due to antihistamine effects) and may not result in significant mydriasis due to both the antimuscarinic properties and alpha-adrenergic antagonism. Furthermore, diphenhydramine is a sodium channel antagonist and can cause QRS and QT prolongation and ventricular dysrhythmias, which are not typically caused by purely antimuscarinic agents such as the plant-derived alkaloids in belladonna. Moreover, many intentional drug overdoses involve more than one agent. Thus, patients commonly present with mixed findings. At times, the toxicities of each agent have additive effects as seen in the coingestion of a benzodiazepine and an opioid. In other cases, an agent may mask findings expected of another. As an example, the sympatholytic effects of clonidine may blunt the expected tachycardia and CNS excitation expected after a significant bupropion overdose [5]. Nevertheless, knowledge of the classic toxidromes provides a sound framework around which to

initiate appropriate evaluation, stabilization, and treatment of the critically poisoned patient. Table 2 provides a summary of the classic toxidromes.

Opioid Toxidrome

The toxidrome associated with opiate or opioid intoxication includes the classic triad of coma, miotic pupils, and respiratory depression. Depending on severity of illness, the clinician may also note modest bradycardia and/or hypotension. This toxidrome is not pathognomonic for opioid toxicity, and a similar presentation may suggest an α_2 -adrenergic agonist (e.g., clonidine, guanfacine, and tizanidine) toxicity, barbiturate toxicity, intracranial hemorrhage, and brain stem stroke.

In the proper historical setting, the triad of coma, miosis, and respiratory depression often prompts the use of naloxone. Naloxone has anecdotally been reported to reverse some cases of clonidine toxicity and yet should have no effect in the setting of intracranial hemorrhage, stroke, or barbiturate toxicity. Thus, naloxone is both diagnostic and therapeutic.

Opioid toxicity is discussed in greater detail in ► Chap. 62, “Opioids.”

Sedative-Hypnotic

A wide variety of pharmaceuticals characterize this toxidrome and generally stimulate central nervous system GABA-A chloride channels. Among the most commonly prescribed agents associated with the sedative-hypnotic toxidrome are benzodiazepines. Others such as ethanol, barbiturates, gabapentin, pregabalin, and zolpidem present with similar findings. Typically, the toxidrome is best described as “coma with preserved vital signs.” Though many sedative-hypnotic agents reduce blood pressure, heart rate, and body temperature, the reductions are often mild to modest depending on the severity of the ingestion or the specific drug involved. For example, barbiturate toxicity is more likely to cause significant respiratory depression, hypotension, and hypothermia

than other sedative-hypnotic agents. In general, patients appear deeply sedate and pupils are generally mid-sized, although they may be disconjugate. Contrary to popular belief, patients generally do not exhibit respiratory depression in the setting of isolated oral benzodiazepine ingestions [6]. Hypoxia with respiratory depression more commonly develops after intravenous administration or secondarily from upper airway obstruction in the setting of obesity or impaired chest wall excursion. Overall, the sedative-hypnotic toxidrome is the hardest to characterize due to the wide variety of drugs involved and the nonspecific presentation.

Toxicity from these agents is discussed in great detail in ► Chap. 45, “Anxiolytics, Sedatives, and Hypnotics.”

Antimuscarinic Toxidrome

The antimuscarinic toxidrome, also referred to as the anticholinergic syndrome, in full or in part, is commonly evident in intentional drug overdoses or adverse drug reactions owing the ubiquitous nature of xenobiotics that affect muscarinic neurotransmission. Examples of drug classes that frequently exhibit antimuscarinic properties include first-generation antihistamines, antipsychotics, and class 1A antidysrhythmics. Additionally, alkaloids (atropine, scopolamine, and hyoscyamine) derived from many plants in the Solanaceae family – e.g., Jimson Weed (*Datura stramonium*), Angel’s Trumpet (*Brugmansia sp.*), Deadly Nightshade (*Atropa belladonna*) – are abused by teens and used in religious ceremonies throughout the Americas.

The effects of antimuscarinic drugs are indicative of competitive antagonism of muscarinic acetylcholine receptors [7]. The constellation of tachycardia, mild hypertension, mild hyperthermia, skin flushing, xerostomia and anhidrosis, mydriasis, urinary retention, delirium, carphologia (picking behavior), and muffled or garbled speech suggests antimuscarinic poisoning. Patients will commonly experience visual or tactile hallucinations too. In clinical practice, rarely do patients present with all these signs as

Table 2 Summary of the classic toxidromes

	Heart rate	Blood pressure	Respirations	Temperature	Pupils	Skin	CNS	Distinctive feature(s)
Opioid	↓	↓	↓↓	↓	Miosis	No change	↓ LOC	Coma, miosis, hypoventilation
Sedative-hypnotic	↓	↓	↓	↓	No change	No change	↓ LOC	Coma with normal vitals
Antimuscarinic	↑↑	↑	↑	↑	Mydriasis	Anhidrosis (except face)	Agitated delirium	Carphologia, mumbling speech
Cholinergic	↓↓	↓↓	↑	No change	Miosis	Diaphoretic	↓ LOC, seizures	Bradycardia, bronchorrhea, bronchospasm
Sympathomimetic	↑↑	↑↑	↑	↑	Mydriasis	Diaphoretic	Agitated delirium, seizures	Mydriasis, agitation, tachycardia, hypertension
Serotonin syndrome	↑↑	↑	↑	↑	Mydriasis	Mild diaphoresis	Agitated delirium, seizures	Lower extremity hyperreflexia
Neuroleptic malignant syndrome	↑	↑↑	↑	↑↑	Varies	Varies	Varies – agitated delirium to coma	Cogwheel rigidity with hyporeflexia

many agents that precipitate antimuscarinic findings have other competing pharmacologic effects. For example, antipsychotics exhibit varying degrees of α 1-adrenergic antagonism and thus may cause vasodilatory hypotension and pupillary miosis in the context of an otherwise antimuscarinic-appearing patient. The antimuscarinic syndrome is discussed in greater detail in ► [Chap. 23, “Anticholinergic Syndrome.”](#)

The antidote for antimuscarinic toxicity is physostigmine – a reversible acetylcholinesterase inhibitor that crosses the blood brain barrier. Physostigmine is both a diagnostic and therapeutic tool, but caution should be undertaken owing to the rare risk of precipitating self-limited cholinergic effects including seizures. In doses of 1–2 mg administered at 1 mg/min, physostigmine should reverse antimuscarinic signs. Physostigmine is especially useful when the antimuscarinic diagnosis may prevent a costly and invasive workup such as computerized tomographic (CT) or magnetic resonance imaging of the brain or lumbar punctures. More information on the clinical pharmacology and use of physostigmine is available in ► [Chap. 161, “Physostigmine.”](#)

Cholinergic Syndrome

The cholinergic toxidrome is seen less frequently in the USA or Western Europe than in other parts of the world due to regulation and limited availability of organophosphate pesticides. However, the increased popularity of electronic cigarettes has resulted in a rise of cholinergic toxicity due to the availability of concentrated liquid nicotine [8]. Furthermore, some chemical weapons, namely nerve agents, are highly potent cholinergic toxicants. Thus, rapid recognition of this syndrome is critical for prehospital, emergency medicine, and critical care providers. The classic cholinergic toxidrome includes diarrhea, urinary incontinence, miosis, salivation, vomiting, diaphoresis, and, most critically, bronchorrhea, bronchospasm, and bradycardia. These symptoms often present in conjunction with neuromuscular fasciculations, which may lead to skeletal muscle paralysis and respiratory

insufficiency. Seizures are also common due to elevated cerebral acetylcholine levels [9]. Additional information is available in ► [Chaps. 92, “Organophosphate and Carbamate Insecticide”](#) and ► [135, “Nerve Agents.”](#)

Some cholinergic toxicants are direct muscarinic acetylcholine receptor agonists and present with classic muscarinic findings described above. Notably, *Clitocybe* sp. and *Inocybe* sp. mushrooms contain significant concentrations of muscarine, a direct muscarinic receptor agonist. Other agents exert cholinergic effects by direct agonism of either nicotinic or muscarinic acetylcholine receptors. In particular, nicotinic agonists paradoxically lead to a constellation of cholinergic and sympathomimetic findings since nicotinic receptors are located on postganglionic nerves in both the sympathetic and parasympathetic nervous systems. In turn, nicotine often demonstrates a predominance of sympathomimetic findings early and parasympathetic findings later. Nicotine toxicity in toddlers classically starts with gastrointestinal distress, tachycardia, hypertension, agitated delirium and seizures followed by hypotension, bradycardia, and neuromuscular paralysis [10]. Therefore, some cholinergic toxicants may present with a constellation of findings that appear inconsistent with the ‘classic’ cholinergic toxidrome.

Sympathomimetic Toxidrome

Clinically, the sympathomimetic toxidrome is difficult to differentiate from antimuscarinic poisoning or alcohol withdrawal. There is a wide array of poisonings that result in sympathomimesis; however, the unifying characteristic is inappropriate adrenergic tone. Cocaine, amphetamines (including cathinone derivatives), and methylxanthines all produce findings of sympathomimetic toxicity. The toxicity is exemplified by tachycardia, hypertension, diaphoresis, mydriasis, and hyperthermia. Patients may have preserved mental status; however, in severe cases, agitated delirium and seizures may develop. In cases of hyperactivity or agitation, hyperthermia may result from excess skeletal muscle activity or altered serotonin and dopamine neurotransmission [11]. Further

details regarding this syndrome is available in ► [Chap. 25, “Sympathomimetic Syndrome.”](#)

Serotonin Syndrome

The constellation of autonomic instability (typically manifest as tachycardia and mild hypertension), altered mental status, and rigidity – particularly involving the lower extremities – is suggestive of serotonin syndrome. Normally, reflexes are diminished in rigidity; however, the sine quae non of serotonin syndrome is hyperreflexia despite rigidity. This toxidrome exists on a spectrum. Mild findings present with tachycardia and lower extremity hyperreflexia, while severe disease includes hyperthermia and hypertonic rigidity. Serotonin syndrome can occur in the setting of therapeutic use of serotonergic drugs such as selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, and tricyclic antidepressants [12]. Unlike the oft-confused neuroleptic malignant syndrome, serotonin syndrome develops abruptly over hours and resolves quickly over the course of 24–48 h in most scenarios. Neuroleptic malignant syndrome does not present with hyperreflexia. See ► [Chap. 24, “Serotonin Syndrome”](#) for further details.

Neuroleptic Malignant Syndrome

The sine quae non of the neuroleptic malignant syndrome is skeletal muscle rigidity and hyporeflexia in the context of antipsychotic use or dopaminergic withdrawal. In the absence of antipsychotic use or dopaminergic drug withdrawal, the diagnosis is not NMS. Classically, NMS begins insidiously and worsens over the course of days. The same triad as serotonin syndrome (autonomic instability, altered mental status, and rigidity) exemplifies the syndrome; however, diminished reflexes chiefly differentiate it from serotonin syndrome. See ► [Chap. 31, “Neuroleptic Malignant Syndrome”](#) for further details.

Technically, every xenobiotic has its own specific toxidrome. For example, salicylate-

poisoning presents with tachycardia, nausea and vomiting, diaphoresis, a high-anion gap metabolic acidosis, and respiratory alkalosis, while iron toxicity presents with severe GI distress, shock, leukocytosis, and lactate-associated metabolic acidosis followed by acute liver injury. In later chapters, the reader will appreciate nuances of varying presentations for each specific poison that will aid in expeditious diagnoses allowing providers to render timely and appropriate treatment.

Diagnostic Testing

As a rule, ancillary testing of poisoned patients is often directed by the history and physical examination. However, some tests are particularly valuable when evaluating the critically ill poisoned patient. This is especially important when attempting to determine the severity of illness. This section is not intended to be all-inclusive but merely a framework to provide context for the use of these diagnostic modalities as described in other sections of this book.

EKG

A 12-lead EKG and continuous cardiac monitoring are important tools in the initial diagnostic workup of the poisoned patient. This is particularly important because cardiac dysrhythmia is a common cause of death in the poisoned patient. Early identification of cardiac dysrhythmias and QRS or QT interval abnormalities is paramount and will dictate further treatment. A normal EKG can also suggest lack of significant exposure in certain cases, such as after tricyclic antidepressant overdose.

Poisonings often manifest changes in the EKG. Depending upon the exact exposure, the EKG may demonstrate tachycardia, bradycardia, ventricular dysrhythmias, QRS and/or QT prolongation, among others. Since the EKG is quickly obtained and often completed prior to other tests, the EKG is typically the first evaluation of a toxidrome. Hence, we discuss this diagnostic test first.

Most often, the medical toxicologist uses the EKG to evaluate intervals. Not only does QRS or QT prolongation suggest ingestion, the length of prolongation is often dose-related. This is particularly evident in tricyclic antidepressant overdose wherein the degree of QRS elongation is suggestive of more clinically significant ingestions and predictive of more severe pathology [13]. Serial EKGs (much like an EKG in the evaluation of an acute coronary syndrome) may help determine effectiveness of treatment and progression of poisoning. This strategy is most important for the tricyclic antidepressant overdose patient receiving IV sodium bicarbonate therapy for a prolonged QRS. Therefore, an EKG is a great diagnostic test during the initial evaluation of a poisoned patient and can help determine severity of illness. Please refer to ► [Chap. 21, “Cardiac Conduction and Rate Disturbances”](#) for a further discussion of this topic.

Arterial Blood Gases

Arterial blood gases (ABGs) add valuable information when evaluating the critically ill poisoned patient. Like an EKG, the ABG provides rapid results and can help determine the severity of the patient's illness in short order. The ABG provides a quick assessment of a patient's acid-base status (pH), oxygenation (PO_2), and ventilation (PCO_2). Since an ABG is quickly obtained, one can immediately use the information to correct an acid-base disturbance, oxygenation, and/or ventilation. Additionally, serial ABGs are a helpful resource when judging a patient's changing condition or response to treatment. Regardless of the type of exposure, an ABG is a helpful screening tool for an undifferentiated toxicology patient. Notably, however, measurement of the pH and PCO_2 are accurately assessed with a venous blood gas. Unless the P_aO_2 is specifically required, a venous blood gas is sufficient and preferable due to ease and decreased risk since there is no arterial puncture.

Characterization of any acid-base disturbance is often of value in diagnosing a particular

poisoning. The patient's acid-base status is then useful in guiding therapeutic interventions. An elevated anion gap metabolic acidosis is the most common acid-base disturbance seen in poisoned patients. Mnemonics used in formulating a differential diagnosis for an anion gap acidosis are riddled with a disproportionately large number of drugs or chemicals; ► [Chap. 15, “Acid–Base Balance in the Poisoned Patient”](#) this is discussed further elsewhere. Normal anion gap metabolic acidosis is less commonly identified in poisoned patients but is seen after exposure to carbonic anhydrase inhibitors and toluene.

When assessing the patient's respiratory status, the ABG will provide helpful information not relayed by pulse oximeters. Since many poisoned patients suffer from respiratory depression, the ABG will not only relay information regarding oxygenation, but also ventilation. Many poisoned patients present with altered mental status and adequate oxygenation but instead have hypercarbia discovered later.

Biochemical Analysis

In many poisoned patients, a complete blood count and electrolytes are reflexively ordered. Unless a particular toxicant is known to cause hematologic derangements such as hemolysis, the complete blood cell count is usually unhelpful. Nonspecific leukocytosis is common in overdose and likely due to demargination from acute stress reaction. We have seen white blood cell counts in excess of 40,000 cell/ μ L in sympathomimetic overdoses without concomitant infection. Acute anemia may provide evidence of an acute hemolytic process. Macrocytosis may suggest chronic ethanol use or acquired functional vitamin B12 deficiency from nitrous oxide abuse.

Electrolyte abnormalities, particularly those associated with acid-base disorders, are telling in the undifferentiated poisoned patient. The toxicological differential diagnosis for an anion gap metabolic acidosis is much broader than suggested by the frequently employed “MUDPILES” mnemonic. Certainly, high-anion

gap metabolic acidosis in the absence of hyperglycemia or shock is highly suggestive of a toxicological cause. Additionally, lactate elevation in the absence of shock, hepatic failure, sepsis, or abdominal catastrophes also suggests a toxicologic cause such as carbon monoxide, cyanide, or methanol poisoning.

Derangements in sodium homeostasis may suggest the syndrome of inappropriate antidiuretic hormone in the case of SSRI toxicity or diabetes insipidus in the case of lithium poisoning. Hyperchloremic nonanion gap acidosis may suggest topiramate toxicity. Profound hypokalemia occurs with barium, toluene, and methylxanthines. Therefore, the astute clinician can use electrolytes to evaluate exposures and compare to a known list of possible exposures.

Creatinine and blood urea nitrogen (BUN), as markers of renal function, are important in the evaluation of the critically poisoned patient. Many toxicants are renally eliminated, and the presence of renal failure may prompt initiation of extracorporeal removal in select cases. Furthermore, many toxicants, such as ethylene glycol, are themselves nephrotoxic, and thus a baseline evaluation and trending of renal function is crucial.

Elevations in aspartate and alanine transaminases occur in the setting of liver injury but also with rhabdomyolysis. One of the most common toxicological causes of acute liver injury is acetaminophen poisoning. In the undifferentiated patient, elevation of transaminases prompts consideration for empiric N-acetylcysteine treatment due to the prevalence of acetaminophen toxicity. Otherwise, there is a litany of hepatotoxins (including plants, essential oils, herbal supplements, over-the-counter and prescribed medications, some halogenated hydrocarbons, etc.), and only a careful history will allow the clinician to differentiate causes in the absence of other signs or symptoms. As important as transaminases may be for acetaminophen poisoning, the PT/INR is equally important. While transaminases provide evidence for hepatocyte injury, derangements in the PT/INR reflect hepatic synthetic dysfunction.

Toxicology Testing

Urine screens for drugs of abuse are rarely useful in the diagnosis or management of acutely poisoned patients. Most urine drug screens are enzyme-multiplied immunoassays and as such are limited by false-positive and false-negative results. On one hand, a patient who abuses fentanyl may present with the classic opioid toxidrome of coma, miosis, and respiratory depression, but their urine opiate screen could remain negative. On the other hand, a positive urinary result does not automatically suggest the patient is actually toxic from the detected substance. Since the bladder is a reservoir and urine drug testing often evaluates for the presence of metabolites, a positive urinary drug test does not provide confidence that a substance is the current cause of the patient's presentation. The clinical picture is most important. Any interpretation of urine drug testing must consider the context of a clinical examination and limitations of the test. We, therefore, place little weight on this test.

In direct opposition to urine drug testing, serum quantitative testing is particularly valuable. Quantitative measurements provide valuable information about the severity of exposure in real time. Routine serum measurement of salicylate, acetaminophen, and ethanol are encouraged since exposures are commonplace. Importantly, toxicity from any one of these drugs has a specific treatment. Many hospitals can also obtain serum concentrations of lithium and antiepileptics. If the patient has access to any of these drugs, serum quantitation may reveal the cause of the toxicity. We do not routinely encourage measuring drug levels if there is a delay in obtaining the results. This rarely offers real-time results and rarely affects patient care. However, if in-house testing is available for a specific drug in question, serum quantitation is frequently extremely helpful.

Osmolal Gap

Most hospitals are unable to obtain toxic alcohol (methanol, ethylene glycol, isopropanol)

Fig. 1 Calculation of the osmolality gap (where glucose, BUN, and ethanol reported in mg/dL)

$$2x [Na] + \frac{[Glucose]}{18} + \frac{[BUN]}{2.8} + \frac{[Etanol]}{4.6} = \text{Measured Osmolality}$$

$$\text{Osmolality Gap} = (\text{Measured Osmolality}) - (\text{Calculated Osmolality})$$

Fig. 2 Conversion of mg/dL to mmol/L

$$\frac{\text{mmol}}{L} = \frac{\left[\frac{\text{mg}}{\text{dL}} \right]}{\left[\frac{\text{gm}}{\text{mol}} \times \frac{1000 \text{ mg}}{\text{gm}} \times \frac{\text{mol}}{1000 \text{ mmol}} \right]} \times \frac{10 \text{ dL}}{L}$$

concentrations in clinically meaningful timeframes; thus, the clinical use of serum osmolality in an attempt to estimate toxic alcohol concentrations becomes an important discussion. Indications for obtaining a serum osmolality include historical information suggesting a toxic alcohol ingestion or an elevated gap metabolic acidosis of unknown etiology.

The osmol gap is the difference between measured osmolality and calculated osmolality (Fig. 1). Osmol gap elevations (typically >10 mosm/L) are generally considered abnormal. However, an osmolality gap ≥ 20 mosm/L exceeds 2 standard deviations of the population-based mean and represents a more clearly abnormal result. Therefore, interpreting gaps <20 mosm/L are less clear.

Calculation of the osmol gap requires simultaneous measurement of serum sodium, glucose, BUN, and ethanol concentrations, plus a serum osmolality. There are two general methods of osmolality calculation – boiling point elevation and freezing point depression. The latter is preferred because alcohols are volatile and may be lost in boiling point assessments. In the USA, unlike many other countries, calculation of the osmol gap requires conversion of glucose, BUN, and ethanol levels (all usually reported in mg/dL) to SI units (mmol/L) (Fig. 2). Once calculated, an osmol gap can also estimate a toxic alcohol concentration by multiplying the gap by one-tenth the molecular weight of the suspected toxic alcohol. For example, if the osmol gap is 100, the estimated serum ethylene glycol concentration is 621 mg/dL.

Patients with severe alcohol intoxication (e.g., levels in excess of 300 mg/dL [65 mmol/L]) typically have an elevation of osmol gap even when

one accounts for the serum ethanol concentration. The identity of the unmeasured osmols is unclear but likely the result of elevated lactate, acetaldehyde and/or acetate levels.

Imaging

Imaging for diagnostic purposes in poisoned patients is generally of limited value. Rare exceptions include ingestion of selected heavy metals, such as iron and lead. For example, the presence of iron tablets in the gastrointestinal tract on radiography may prompt initiation of whole bowel irrigation. In cases of body packing, a CT scan of the abdomen and pelvis may reveal the body burden of packaged drug, hollow visceral perforation, or obstruction. CT imaging of the chest, abdomen, and pelvis is becoming increasingly useful in predicting injury severity after caustic ingestion [14]. Occasionally, CT imaging of the head may reveal pathognomonic findings (e.g., bilateral basal ganglia infarction), suggestive of toxicity from an electron transport chain inhibitor (e.g., cyanide, methanol, carbon monoxide). However, in general, imaging provides useful information in limited cases.

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Aggressive supportive care is the mainstay of treatment provided to patients in the intensive care unit (ICU). Basic aspects of care must be reevaluated or adjusted to account for unique aspects in the pathophysiology of the critically ill poisoned patient. This may include the use of gastrointestinal (GI) decontamination or the administration of antidotes. This chapter discusses the initial management and resuscitation of the critically ill poisoned patient. Subsequent chapters describe therapeutic decisions unique to particular drugs and xenobiotics and discuss specific antidotes in greater detail.

General Approach to Patient Data for the Poisoned Patient

The organization of data may be problem based (e.g., phenytoin overdose or hydrocarbon aspiration) or system based (i.e., pulmonary, cardiovascular, renal, or hematologic). The system-based approach, typically used for critical care patients, better organizes large quantities of data (e.g., liver failure following acetaminophen ingestion causing coagulopathy, increased intracranial pressure, and hepatopulmonary syndrome). For the toxicology patient, substance-specific problems and therapies should also be noted. The system-based approach prevents important therapeutic and organizational issues from being overlooked (Table 1). The system-based approach clearly identifies the number of organ system failures, a

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Table 1 System-based approach to the poisoned intensive care unit patient

General
Vital signs: current HR, BP, RR, temperature
Avoid giving vital sign ranges (e.g., “systolic BP ranging from 50–180”), as this can be misleading and counterinformative
State vital signs that are “abnormal” (e.g., fever spikes, hypotension)
Input and outputs; weight
Cardiovascular
Cardiac biomarkers and ECG
Inotropes and vasopressors: dopamine, dobutamine, norepinephrine, epinephrine, phenylephrine, glucagon, high-dose insulin euglycemia
Advanced monitoring: CVP, PAP, PCWP, CO, SVR, SvO ₂ , stroke volume, IVC diameter and collapse, carotid velocity time integral
Echocardiogram, MRI, CT
Pulmonary
Ventilator settings
Mode and rate, V _T (tidal volume), PEEP, FiO ₂
Pressure support, if added to SIMV or CPAP modes
Report the patient’s actual RR, V _T , and V _E (minute volume)
Airway peak and plateau pressures, auto-PEEP
Arterial blood gases: pH, PCO ₂ , PO ₂ , SaO ₂
Liberation parameters: NIF (MIP), rapid shallow breathing index
Chest x-ray and CT findings
Gastrointestinal
Liver function tests, amylase and lipase, albumin
Abdominal ultrasound and CT findings
Bowel function/elimination
Renal
Electrolytes, BUN, creatinine, anion gap, osmolar gap
Infectious diseases
Maximum temperature (minimum temperature when low), antibiotics (day number), positive cultures, cultures outstanding
WBC and bands
Neurologic
Sedation and paralysis; analgesia
Electroencephalographic findings
Hematologic
Coagulation studies, platelet count, DIC information
Endocrine
Blood glucose
Corticosteroid levels and results of stimulation tests
ICU housekeeping
Stress ulcer and DVT prophylaxis
Nutritional support (tube feedings or TPN)

(continued)

Table 1 (continued)

Central venous and arterial catheters, intraosseous lines
Peripheral intravenous access
Toxicology
Toxin or drug exposed to and route of exposure
Ongoing diagnostic testing (e.g., follow-up renal function, ECG)
Current gastrointestinal decontamination (e.g., whole bowel irrigation)
Specific therapies or antidotes
<i>BP</i> blood pressure, <i>BUN</i> blood urea nitrogen, <i>CO</i> cardiac output, <i>CPAP</i> continuous positive airway pressure, <i>CT</i> computerized tomography, <i>CVP</i> central venous pressure, <i>DIC</i> disseminated intravascular coagulation, <i>DVT</i> deep venous thrombosis, <i>ECG</i> electrocardiogram, <i>FiO₂</i> fraction of inspired oxygen, <i>HR</i> heart rate, <i>ICU</i> intensive care unit, <i>IVC</i> inferior vena cava, <i>MIP</i> maximum inspiratory pressure, <i>MRI</i> magnetic resonance imaging, <i>NIF</i> negative inspiratory force, <i>PAP</i> pulmonary artery pressure, <i>PCO₂</i> partial pressure of carbon dioxide, <i>PCWP</i> pulmonary capillary wedge pressure, <i>PEEP</i> positive end-expiratory pressure, <i>PO₂</i> partial pressure of oxygen, <i>RR</i> respiratory rate, <i>SaO₂</i> oxygen saturation in arterial blood, <i>SIMV</i> synchronized intermittent mandatory ventilation, <i>SvO₂</i> mixed venous oxygen saturation, <i>SVR</i> systemic vascular resistance, <i>TPN</i> total parenteral nutrition, <i>WBC</i> white blood cell count

criterion used to determine the need for ICU admission and to predict ICU mortality [1].

Patients with Toxicologic Exposures Admitted to an Intensive Care Unit

The American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) reported 101,141 exposure-related ICU admissions (3.5% of all toxicant exposures and 16.5% of all exposures managed in a health-care facility) in 2014 [2]. Of all the patients included in the NPDS, 7% had medical outcomes classified as “moderate” and 1% were classified as “major.” For patients 20 years of age or older, 15% had medical outcomes classified as “moderate” and 2% as “major.” Presumably patients with moderate or major effects were more likely to require admissions to the ICU. Moderate effect is defined by AAPCC as the patient exhibiting signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more

systemic in nature than minor symptoms. Examples include acid–base disturbances, high fever, disorientation, hypotension responsive to treatment, and isolated brief seizures. Major effect is defined by AAPCC as the patient exhibiting signs or symptoms that were life-threatening or resulted in significant residual disability or disfigurement. Examples include repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia, hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation. Patients experienced major effects for less than 24 h 29% of the time, between 24 h and 3 days 34% of the time, and between 3 days and 1 week 19% of the time. Since 2000, cases with more serious outcomes increased by 4.29% (95% CI 3.87–4.72%) per year. Some patients with less pronounced effects were also admitted to the ICU due to hospital requirements to admit all suicidal patients to the ICU in order for them to be closely monitored.

Initial Assessment

As with any unstable or critically ill patient, the ABCs (airway, breathing, circulation) of basic life support take priority (Level III recommendation). In the poisoned patient, therapeutic interventions and diagnostic evaluation often are initiated simultaneously (see ► [Chap. 2, “The Diagnostic Process in Medical Toxicology”](#)). Findings on physical examination often guide the initial therapy. Airway patency and ventilatory drive frequently are compromised in patients with decreased mental status and may need immediate intervention. The decision to administer certain antidotes such as thiamine, glucose, naloxone, flumazenil, and physostigmine is made early in the diagnostic stage, generally before the patient is admitted to the ICU. Although naloxone and flumazenil may obviate the need for intubation in selected patients, flumazenil should only be cautiously administered to patients who may have long-term benzodiazepine use or to patients who have co-ingested a benzodiazepine and drugs that lower the seizure threshold. The risk of a

flumazenil-induced seizure must be weighed against complications occurring during intubation (Level I recommendation). Further discussions of benzodiazepine poisoning and the use of flumazenil are found in ► [Chaps. 45, “Anxiolytics, Sedatives, and Hypnotics,”](#) and ► [148, “Flumazenil.”](#) For further discussion about the role of physostigmine, see ► [Chaps. 23, “Anticholinergic Syndrome,”](#) and ► [161, “Physostigmine”](#). Decisions regarding GI decontamination, if any, which may include administration of single-dose activated charcoal (AC) and whole bowel irrigation (WBI) are also made early in the patient’s course, likely before the patient arrives in the ICU. Currently, there is no role for gastric lavage. Diagnostic tests often need to be repeated to follow the ongoing effects of the toxicant (e.g., acid–base status in ethylene glycol ingestion) or to determine effectiveness of treatment (e.g., electrocardiogram after administration of sodium bicarbonate in patients with signs of sodium channel blockade, such as after overdose of tricyclic antidepressants [TCAs] or Type 1a or 1c antiarrhythmics, or trending of transaminases following toxic ingestions of acetaminophen [paracetamol]). Various types of toxicology laboratory screening or quantitative testing often are performed, and proper interpretation of the results is essential to making appropriate therapeutic decisions. Further information related to this aspect of the care of poisoned patients can be found in ► [Chap. 2, “The Diagnostic Process in Medical Toxicology.”](#) Although GI decontamination if used should be initiated in the emergency department, the decision to continue GI decontamination in the ICU is usually toxicant specific and discussed later in this chapter.

Supportive Care Decisions

Airway Maintenance

The loss of airway-protective reflexes and concern for aspiration or the presence of respiratory failure dictates the need to secure the airway. Securing the airway should be accomplished by tracheal intubation as noninvasive ventilation is relatively

contraindicated in patients with hemodynamic instability, patients with inability to protect their airway, and patients with a full stomach (including pregnancy and obesity) [3]. Orotracheal intubation, if possible, is preferred over nasotracheal intubation for many reasons. Nasotracheal intubation causes a statistically significant increase in sinusitis [4–7], purulent and serous otitis [8], ventilator-associated pneumonia [9], and sepsis [10] and is technically more difficult compared with orotracheal intubation. Typically only a 6.0- or 6.5-mm endotracheal tube is used for nasotracheal intubation. These narrow tubes have increased airflow resistance compared with the larger diameter tubes used for orotracheal intubation. Airflow resistance increases after several days of intubation as secretions harden inside the tube and decrease the tube's diameter [11]. Increased airflow resistance can increase respiratory workload significantly. Should bronchoscopy be required (e.g., new infiltrates on chest x-ray, mucus plugging, lung collapse), the narrower, longer nasotracheal tube makes it more difficult, if not impossible, to pass a flexible bronchoscope.

An exception may be in patients with significant caustic injuries and swelling where nasotracheal intubation may be more practical than orotracheal intubation. In addition in patients with anticipated difficult airways, either nasotracheal intubation or an “awake orotracheal intubation” should be considered (Level III recommendation). Ingestion of caustic agents, with concomitant injury to the respiratory tract and oropharynx, requires special consideration in airway maintenance. Although airway obstruction is rare in patients who ingest caustic agents [12], airway patency is more at risk with the ingestion of solid rather than liquid caustic agents [13]. Only 11 of 33 children (33%) with either acid or alkali ingestions required intubation [14]. Seven children required immediate intubation for respiratory distress or airway obstruction, and the other four had minimal or no respiratory symptoms but were intubated after endoscopic findings of supraglottic edema. Most intubations after caustic ingestion can be done under direct visualization using standard direct laryngoscopic

techniques. The equipment for alternative methods of securing the airway (e.g., cricothyrotomy) should be in place before any paralytic or induction agent is given, however, in case the normal visual landmarks are obscured and orotracheal intubation cannot be accomplished. In the 11 intubated pediatric patients described above, no adverse consequences occurred as a result of orotracheal intubation [14].

Most patients are successfully intubated using a rapid sequence intubation (RSI) strategy which includes a period of preoxygenation. Preoxygenation prior to intubation assists in avoiding hypoxemia during the apneic period of RSI and decreases peri-intubation morbidity and mortality [15] (Level II-3 recommendation). However either due to an inability to adequately preoxygenate the patient or concerns that the patient may be difficult to intubate, strategies aside from RSI should be considered (Level III recommendation). While these strategies are well described, they have not been studied in the poisoned patient.

Delayed sequence intubation (DSI) temporarily separates the administration of the induction agent from the muscle relaxant in order to allow adequate preintubation preparation and preoxygenation [16, 17]. In DSI, patients are sedated with ketamine which causes dissociation and sedation while allowing for adequate preoxygenation before the administration of a muscle relaxant. This strategy is particularly useful in the delirious or agitated patient that cannot otherwise be preoxygenated. In one observational study, patients were induced with ketamine (starting dose of 1 mg/kg titrated to adequate sedation) and then preoxygenated for 3 min with either a non-rebreather or positive pressure ventilation (NIPPV) prior to the administration of a muscle relaxant [16]. Saturations increased from 89.9% prior to DSI to 98.8% afterward with an average increase of 8.9% (95% CI 6.4–10.9%). There were no complications and all patients were successfully intubated, aside from two patients that significantly improved and no longer required intubation.

Another potential strategy is an “awake intubation,” where the patient is given a light sedative

such as ketamine but is mainly anesthetized with local anesthetics prior to intubation [18, 19]. An awake intubation can be attempted via direct visualization or with the assistance of a fiberoptic scope. This intubation strategy can be considered in patients requiring urgent intubation, but that may have a contraindication to receiving a sedative and muscle relaxant that impairs their ability to breathe. Patients with caustic injuries requiring intubation due to concerns of airway deterioration may be candidates for an awake intubation (Level III recommendation).

Apneic oxygenation is used to extend the safe apnea period beyond the time which can be achieved with preoxygenation and should be considered regardless of the method of intubation [17, 20] (Level II-3 recommendation). Even without respiratory effort, the pharynx can be filled with oxygen using a high-flow nasal cannula and acts as a reservoir [21]. During intubation, the aveoli will continue to take up oxygen that then diffuses into the bloodstream and prevents hypoxia. Patients were preoxygenated, paralyzed, intubated, and placed on a ventilator in one study [22]. They continued to be oxygenated at 1.0 FiO₂ but were not given any ventilation; no patients developed saturations less than 98% despite being paralyzed and not ventilated.

Respiratory Function

Adequacy of respiratory function must be assessed immediately after the airway is secured. The causes of respiratory failure can be divided into four groups (Table 2), as follows [23]:

1. Hypoxemic (type I) respiratory failure arises from the flooding or collapse of alveoli, resulting in intrapulmonary shunting. Patients are hypoxic but have a low or normal CO₂ concentration.
2. Hypercapnic (type II) respiratory failure is caused by inadequate alveolar ventilation from either decreased respiratory drive or an imbalance between respiratory load and respiratory muscle strength. Patients will have elevated CO₂ concentrations and may be hypoxic.

3. Postoperative (type III) respiratory failure is caused by pain leading to shallow breathing, atelectasis, hypoxemia, and narcotic administration to control pain, which further decreases respiratory drive and worsens atelectasis.
4. Shock-related (type IV) respiratory failure is caused by a combination of inadequate oxygen delivery to respiratory muscles and increased total-body metabolic demands.

Type I respiratory failure in the overdose patient typically is caused by aspiration or agents that cause the acute respiratory distress syndrome (ARDS) (e.g., salicylates). Type II respiratory failure can be caused by ingestion of drugs that decrease respiratory drive (e.g., narcotic or other sedative overdose) or cause respiratory muscle weakness (e.g., botulism). Type IV respiratory failure can be associated with any drug ingestion that causes myocardial depression or shock, such as calcium channel antagonists. Type III respiratory failure is not applicable to the overdose patient. The type of respiratory failure may change during a patient's hospitalization. For instance, patients may initially present with type IV respiratory failure from cardiogenic shock. As the patient's hemodynamics improve, they may be difficult to wean from the ventilator due to the development of type II respiratory failure from the accumulation of sedatives and analgesics administered in the ICU.

The therapeutic approach to each type of respiratory failure is determined by the underlying pathophysiology. Type I respiratory failure is treated with a high fraction of inspired oxygen (FiO₂) and the judicious use of positive end-expiratory pressure (PEEP). Some focal lung lesions, such as lesions from hydrocarbon aspiration, may not be PEEP responsive, however. In these situations, high levels of PEEP (>10 cm H₂O) may worsen the patient's condition by decreasing venous return (preload) and causing hypotension. If patients have high FiO₂ and PEEP requirements and are developing ARDS, the use of high-frequency oscillatory ventilation (HFOV), while controversial, may be considered [24, 25]. HFOV is a mode of ventilation that delivers small tidal volumes at high frequencies in order to

Table 2 Classification of respiratory failure

	Type I: acute hypoxemic respiratory failure	Type II: hypercapnic	Type III: postoperative	Type IV: shock
Pathophysiology	Alveolar flooding Alveolar collapse	Decreased respiratory drive Increased respiratory workload Decreased respiratory muscle strength	Atelectasis (pain) Decreased respiratory drive from analgesics (narcotics)	Inadequate respiratory muscle perfusion with increased metabolic demands
Therapy	High FiO_2 PEEP Decrease pulmonary edema Treat pneumonia	Wake up/allow drugs to wear off Bronchodilators and suctioning Increase respiratory muscle endurance Correct metabolic abnormalities Intubation or NIPPV	Pain control Chest physical therapy Elevate head of bed	Treat underlying cause of the shock state Ventilator support
Overdose scenarios	Hydrocarbon aspiration, salicylates	Sedative overdose including narcotic or benzodiazepine overdose Bronchospasm Botulism	Not applicable	BB or CCA overdose Sepsis Mitochondrial inhibition

BB β -adrenergic blocking agents, CCA calcium channel antagonists, FiO_2 fraction of inspired oxygen, NIPPV noninvasive positive pressure ventilation, PEEP positive end-expiratory pressure

maintain alveolar recruitment while avoiding injury from barotrauma [26]. Further details regarding the pathophysiology and management of ARDS can be found in ► [Chap. 16, “Treatment of Acute Respiratory Distress Syndrome in the Poisoned Patient”](#).

When type II (hypercapnic) respiratory failure is caused by decreased respiratory drive, minute volume (V_E) provided by the ventilator must be sufficient to maintain alveolar ventilation. Respiratory load and respiratory muscle strength are connected inseparably. Bronchoconstriction and increased secretions increase respiratory load. Impaired neuromuscular transmission or respiratory muscle problems (e.g., botulism, myopathy, or overuse fatigue) decrease respiratory muscle strength. If respiratory load increases or strength decreases to the point at which load is greater than strength, type II respiratory failure ensues. Treatment of increased respiratory load includes the

use of bronchodilators and frequent suctioning. Muscle strength can be increased by treatment of underlying causes and ventilator support until respiratory muscle strength has returned. Therapy for type IV respiratory failure is to provide ventilatory assistance while treating the shock state.

The ventilator mode to be used is dictated by the type of respiratory failure. In general, patients with type I (hypoxemic) or type IV (shock) respiratory failure should be managed with an assist/control (A/C) or continuous mandatory ventilation (CMV) mode, which decreases the patient's work of breathing (Level III recommendation). Use of A/C or CMV decreases but does not eliminate respiratory muscle work and decreases the patient's oxygen and metabolic requirements. The decreased oxygen requirement is particularly important when oxygen transfer from the airways to the blood is impaired (aspiration) or there is inadequate oxygen delivery (shock). Type II

(hypercapnic) respiratory failure typically is seen with drug-induced coma or paralysis and is managed with either a CMV or a synchronized intermittent mandatory ventilation (SIMV) mode (Level III recommendation). If the drug-induced coma or respiratory depression is from narcotics or benzodiazepines, administration of naloxone or flumazenil, respectively, will improve the patient's ventilatory function and can prevent the need for intubation (Level II-3 recommendation). The risks and benefits of administering naloxone or flumazenil should be carefully weighed when administering them to patients with chronic use of either opioids or benzodiazepines. If the patient is already intubated, naloxone or flumazenil should generally be avoided. However in patients that were intubated but known to have ingested opioids or benzodiazepines, reversal agents may allow the patient to be extubated sooner. In addition, these agents may be useful to reverse iatrogenic sedation that prolongs the time that the patient is intubated. Decreasing the duration of time that the patient is intubated may decrease ventilator-associated complications.

Patient workload in a patient-triggered SIMV mode has been shown to range from 49% to 118% of the workload expected from a spontaneously breathing subject [27, 28]. This is important because if the patient's type II (hypercapnic) respiratory failure is from muscular weakness, the use of the SIMV mode can exacerbate the muscular weakness and prolong time on the ventilator. If there is increased respiratory load from bronchoconstriction, care must be taken to avoid air trapping within the lung. Commonly called *auto-PEEP*, this dynamic hyperinflation of the lung occurs when a breath is delivered to the patient before the previous breath is completely exhaled. Adverse effects of *auto-PEEP* include hypotension, pulmonary barotrauma (e.g., pneumothorax), and ARDS. *Auto-PEEP* can be minimized by decreasing inspiratory time and maximizing expiratory time (i.e., decreasing the I:E ratio) and use of small tidal volumes (V_T), slow respiratory rates, and increased flow rates. If the provider is concerned about air trapping and *auto-PEEP*, they should check the plateau pressure or the alveolar pressure; it should be below

30 cm H_2O . If air trapping is present, the patient should be immediately removed from the ventilator and have their chest manually decompressed before being placed back on the ventilator with new settings.

When the patient has been intubated and initial ventilator settings chosen, further information may be obtained from serial arterial blood gas measurements, bedside observations, and patient-ventilator interactions. Arterial blood gases (ABGs) assess the patient's acid-base status, arterial oxygenation, and ventilation. Venous blood gases (VBGs) can also assess the acid-base status and ventilation but not oxygenation. Initiation of mechanical ventilation may cause rapid deterioration in some poisoned patients if appropriate V_E , $PaCO_2$, and pH are not maintained. Intoxicants such as salicylates, methanol, and ethylene glycol produce severe, life-threatening acidosis for which the patient naturally compensates with a respiratory alkalosis. If the patient is well sedated, paralyzed, or fatigued, he or she may not be able to increase V_E to compensate for a metabolic acidosis. When the amount of V_E set on the ventilator is less than the V_E the patient was maintaining before intubation, significant acid-base changes may occur and precipitate disastrous events. Loss of compensatory respiratory alkalosis in salicylate intoxication causes acidemia and further movement of salicylate into the central nervous system that may precipitate seizures and death. While intubation may still be indicated, the physician must be vigilant in adjusting the ventilator settings to maintain appropriate ventilation. In the setting of salicylate intoxication, for instance, the rate should be set to match the patient's peak respiratory rate. It is important to monitor ABGs and make appropriate ventilator changes to keep pH, $PaCO_2$, and PaO_2 in the desired ranges.

When determining the ventilator settings, a lung protective strategy should be employed [29, 30]. Lung protective strategies prevent the development of ARDS from barotrauma and oxygen toxicity (Level II-2 recommendation). While these strategies are commonly used in the ICU, they have not been studied in the poisoned patient. Many intoxicated patients are intubated for

reasons other than for an acute lung injury (e.g., respiratory depression, altered mental status, delirium). In these situations, the FiO_2 should be titrated down as long as the PaO_2 remains greater than 90 mmHg. The patient's initial V_T should be set to 6 ml/kg and titrated based on their ABG and oxygen saturation in order to avoid barotrauma and toxicity from hyperoxygenation.

Frequent physical examination is necessary to evaluate the patient's comfort and interactions with the ventilator. If the patient is not synchronizing well with the ventilator, the cause of the patient's discomfort should be investigated. Ventilator settings must be adjusted to stabilize and comfort the patient rather than reflexively increasing sedation or paralyzing the patient. In addition, it should be ensured that the patient is receiving adequate analgesia. The endotracheal tube and ventilator are painful and most sedatives do not control pain. With adequate analgesia, most patients remain lightly sedated and synchronize well with the ventilator. In addition to improving patient comfort, proper administration of analgesics can decrease the patient's sedative requirement, preventing delirium and other complications. Much information can be obtained by observing the patient's pattern of breathing. Most ventilators display airway pressure versus time and flow versus time waveforms. Careful analysis of these waveforms yields important clues as to the cause of the patient's discomfort [31]. Waveform analysis is beyond the scope of this chapter and can be achieved best with the help of an experienced intensivist. Some maneuvers that can make the patient more comfortable on the ventilator include increasing V_E (by increasing V_T , respiratory rate, or both), decreasing triggering sensitivity or switching to flow triggering, and increasing flow rates [28]. Other maneuvers include treating pain, anxiety, and derangements of gas exchange or respiratory mechanics [31]. When these changes fail to match the ventilator to the patient, judicious use of sedation is required. Paralysis in poisoned patients usually is only reserved for specific indications (discussed later).

Circulation and Hemodynamics

After establishing an airway and supporting respiratory function, the next priority is assessment of circulatory status. In the poisoned patient, cardiovascular abnormalities commonly seen are hypertension, hypotension, cardiac arrhythmias, or conduction disturbances.

Hypertension

Elevated blood pressure in the poisoned patient may or may not be the result of exposure to any one of many substances (Table 3). Other causes of elevated blood pressure should be considered and include [1] withdrawal (i.e., benzodiazepine or ethanol withdrawal); [2] the discontinuation of a therapeutically prescribed medication, such as clonidine or minoxidil, causing rebound hypertension; and [3] inadequately treated or untreated underlying hypertension.

Treatment of hypertension is determined by its underlying cause. When hypertension is caused by overdoses of drugs with direct adrenergic activity, such as amphetamines, ephedrine, or pseudoephedrine, direct vasodilators, such as phentolamine or nitroprusside [32], may be required (Level III recommendation). Other commonly used agents include short-acting dihydropyridine calcium channel antagonists, such as nifedipine and clevidipine. When hypertension is caused by drugs with indirect adrenergic activity or by drug-of-abuse withdrawal, sedation with benzodiazepines [33, 34] may be the treatment of choice (Level II-2 recommendation). Pharmaceutical drug withdrawal can be treated by the reinstitution of the causative agent or use of another agent that attenuates the signs and symptoms. The physiology and treatment of withdrawal states are described in detail in ► Chap. 27, "Withdrawal Syndromes". Combining direct vasodilators, such as oral nifedipine or parenteral nitroprusside, and sedatives may be necessary in cases of severe hypertension resulting from any cause. For sympathomimetic-induced hypertension, such as seen with

Table 3 Common examples of toxicants causing hypertension

Direct adrenergic agonists
Albuterol
Epinephrine
Ergotamines
Methoxamine
Midodrine
Phenylephrine
Indirect adrenergic agonists
Amphetamine and derivatives
Cocaine
Fenfluramine
Ketamine
LSD
Methylphenidate
Monoamine oxidase inhibitors
Phencyclidine
Serotonergic agonists
Mixed direct and indirect adrenergic agonists
α -2 agonists (initially and only temporarily)
Ephedrine
Ergotamine derivatives
Oxymetazoline
Phenylpropanolamine
Pseudoephedrine
Tetrahydrozoline
Anticholinergic agents
Atropine and derivatives
First-generation antihistamines
Tricyclic antidepressants
Other agents
Nicotine
Scorpion venom
Drug-of-abuse withdrawal
Benzodiazepines
Ethanol
Other sedatives or hypnotics
Pharmaceutical drug withdrawal
Clonidine (and other α -2 agonists)
Minoxidil
Propranolol
Metoprolol
Methyldopa
Benzodiazepines

LSD lysergic acid diethylamide, PCP phenylcyclohexyl piperidine

cocaine or amphetamines, administration of a β -adrenergic blocker alone may cause unopposed α -adrenergic stimulation and worsen hypertension (Level III recommendation). Large ingestions of α -2 agonists can initially cause hypertension. However, this is temporary and the patient is at risk of becoming hypotensive. If hypertension from α -2 agonists is treated, only short-acting agents that can be rapidly removed (e.g., nicardipine, nitroglycerin) should be administered (Level III recommendation).

Hypotension and Shock

Shock is the inability to deliver oxygen at a cellular level where the consumption of oxygen (VO_2) is greater than the delivery of oxygen (DO_2) [35]. Clinically, it appears as the constellation of hypotension, tachycardia, decreased or altered mentation, and oliguria or anuria. Laboratory values consistent with dysfunction of aerobic metabolism include hyperlactatemia and metabolic acidosis. Of patients who receive fluid resuscitation for shock, 85% have inadequate oxygen delivery to the tissues despite normalization of vital signs and urine output, referred to as cryptogenic shock [36]. Cryptogenic shock is diagnosed by biomarkers such as serial lactic acid concentrations and either ABGs or VBGs. The goal of circulatory resuscitation is to return VO_2 and DO_2 to normal and not simply to “fix the vital signs.”

The initial assessment of the poisoned patient in shock is to determine the physiologic cause of the inadequate DO_2 . DO_2 is the product of arterial oxygen content (CaO_2) and cardiac output (Q_T):

$$\text{DO}_2 = \text{CaO}_2 \times Q_T$$

CaO_2 is determined primarily by hemoglobin concentration and saturation:

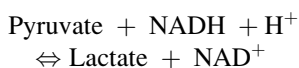
$$\begin{aligned} \text{CaO}_2 = & (1.39 \text{ mL O}_2/\text{g hemoglobin} \\ & \times \text{g hemoglobin/dL} \times \text{SaO}_2) \\ & + (0.0031 \text{ mL/dL/mmHg} \times \text{PaO}_2) \end{aligned}$$

Cardiac output (Q_T) is the product of heart rate (HR) and stroke volume (SV):

$$Q_T = \text{HR}(\text{beats/min}) \times \text{SV}(\text{mL/beat})$$

SV is determined by left ventricular preload, contractility, and afterload. Physiologic causes of inadequate DO_2 in the poisoned patient may be the result of decreased hemoglobin concentration or saturation, decreased left ventricular preload (hypovolemia), decreased afterload (vasodilation), or impaired cardiac contractility.

Interruption of oxygen use at the molecular level is another cause of inadequate DO_2 in the poisoned patient. Specifically, abnormal hemoglobins (i.e., methemoglobin, sulfhemoglobin, or carboxyhemoglobin [37–39]) and toxins that disrupt the mitochondrial electron transport chain (e.g., cyanide, hydrogen sulfide, or sodium azide [40–42]) prevent the use of oxygen at the molecular level. Ineffective oxygen use may also occur from the disruption of metabolic processes, such as the uncoupling of oxidative phosphorylation (e.g., salicylate and dinitrophenol ingestions). In addition, impairment of the redox potential (NAD:NADH) disrupts oxidative processes as can occur from ethanol. Elevated plasma lactate concentration accompanying a metabolic acidosis is often a marker of these toxicities. It is a by-product of anaerobic metabolism of glucose when pyruvate is shunted to lactic acid [43].



Lactic acidosis develops from an inequality between the production and breakdown of lactate, which is normally cleared by the liver and kidneys [44]. There are two forms of lactic acidosis as classified by Cohen and Woods in 1976 (Table 4) [45]. Type A lactic acidosis occurs from inadequate oxygen delivery [46]. While more common than Type B, both can be present at the same time. Carbon monoxide is an example of a toxicant producing a Type A lactic acidosis. Type B lactic acidosis occurs without evidence of poor tissue perfusion or oxygenation and is classified into 3 subtypes [47, 48]. Subtype B1 occurs with systemic disease (e.g., malignancy, ketoacidosis); type B2 is from medications, drugs, or toxicants; and type B3 is from inborn errors of metabolism.

Table 4 Causes of lactic acidosis

Hypoxic (Type A)	Non-hypoxic (Type B)
Ischemia (e.g., cardiac arrest)	Delayed clearance (e.g., hepatic dysfunction)
Global hypoxia (e.g., carbon monoxide)	Pyruvate dehydrogenase dysfunction (e.g., thiamine depletion)
Respiratory failure (e.g., asthma)	Uncoupling of oxidative dysfunction (e.g., salicylates)
Regional hypoperfusion (e.g., mesenteric ischemia)	Accelerated aerobic glycolysis (e.g., seizures)

Examples of toxicants that produce a type B lactic acidosis include uncouplers (e.g., salicylates, dinitrophenol), biguanides such as metformin, and methanol. The normal plasma lactate concentration is 0.5–1 mmol/L (4.5–9 mg/dl). Hyperlactatemia is defined as a concentration between 2 and 4 mmol/L (18–36 mg/dl) without a metabolic acidosis, while lactic acidosis is defined as a concentration greater than 5 mmol/L (45 mg/dl) with a metabolic acidosis [47]. Mortality is increased nearly threefold when lactic acidosis accompanies low-flow states with higher lactate concentrations associated with worse outcomes [49, 50]. A case-control study evaluated serum lactate concentration in drug overdoses at two urban teaching hospitals that were affiliated with a regional poison center [51]. Controls included consecutive drug overdoses admitted over a 1-year period surviving until hospital discharge. Cases were patients admitted over a 7-year period who died. The study consisted of 50 cases and 100 controls. The mean lactate concentration was 9.88 ± 6.7 mmol/L (89 mg/dl) for cases and 2.76 ± 2.9 mmol/L (25 mg/dl) for controls ($p < 0.001$). A lactate concentration of 3.0 mmol/L (27 mg/dl) conferred a 15.8-fold increase in odds of fatality ($p < 0.001$). Serum lactate concentrations were also evaluated in an 8-year retrospective review of all 110 β -adrenergic antagonist overdoses admitted to an ICU [52]. Serum lactate concentration (median 1.79 mmol/L; 10–90% percentiles 0.8–5.6) (19 mg/dl [7.2–50.5]) was the most significantly different parameter on admission between

survivors and fatalities ($p = 0.0008$). Six patients who presented with lactate concentrations >6 mmol/L (45 mg/dl) had prolonged prehospital cardiac arrests. Four patients died in the ICU despite lactate concentrations under 3.0 mmol/L (27 mg/dl). While a lactate >3 mmol/L (27 mg/dl) was associated with a 5.4-fold increased odd of mortality (OR 5.4, 95% CI 1.3–22.0), it only had a sensitivity of 55%, specificity of 80%, positive predictive value of 21%, negative predictive value of 95%, and an accuracy of 78%. The authors concluded that while serum lactate concentrations are useful, caution should be applied when using them to predict final outcome.

Decreased hemoglobin concentration may be the result of GI bleeding (e.g., gastric erosions from iron or nonsteroidal anti-inflammatory drug ingestion), intravascular hemolysis (e.g., arsine gas exposure), decreased production (e.g., benzene), or various chronic medical conditions (e.g., renal failure or cancer). Hemoglobin concentration is easily measured, and the administration of blood products may be indicated while the cause of the anemia is investigated. In acute bleeds, hemoglobin concentrations can be initially falsely elevated. While not studied in poisoned patients, recent studies advocate for conservative transfusion strategies in patients not in shock [53, 54]. When patients on anticoagulants are hemorrhaging, they should be reversed. Vitamin K antagonists (e.g., warfarin) can be reversed with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). Advantages of PCC include smaller volume and faster reversal. Unfortunately, it is more expensive and is associated with thrombotic complications [55]. Patients on newer oral anticoagulants are more difficult to treat as it is unclear if they can be reversed. Dabigatran-related hemorrhage can be reversed with idarucizumab [56, 57]. Other potential reversal modalities include PCC and hemodialysis [58, 59]. While not currently approved, andexanet alfa is being studied to reverse hemorrhage from factor Xa inhibitors (e.g., apixaban and rivaroxaban) [60]. A full discussion of the management of significant bleeding from oral anticoagulants can be found in ► Chap. 68, “Oral Anticoagulants.” Causes and treatment of decreased hemoglobin

saturation were addressed previously in the discussion of type I respiratory failure (see Table 2).

Hypovolemia in the poisoned patient may be caused by GI losses (e.g., organophosphates, cathartics, bleeding), renal losses (e.g., lithium or diuretics), redistribution (e.g., caustic burns or snake envenomations), or increased insensible losses (e.g., fever from sympathomimetics or salicylates). Signs of hypovolemia include dry mucous membranes, narrow pulse pressure, decreased urine output, and low cardiac output. Certain vasodilated shock states, such as liver failure from either acetaminophen overdose or *Amanita* mushroom poisoning or thyroid storm following thyroxine overdose, present with a clinical picture more consistent with sepsis: hypotension, warm extremities, a wide pulse pressure, and increased cardiac output.

Cardiac Dysrhythmias and Conduction Abnormalities

Cardiac depression, dysrhythmias, cardiac conduction abnormalities, or a combination of all three may cause shock from *impaired cardiac contractility*. Impaired cardiac contractility may be caused by β -adrenergic blocking agents or cocaine-induced myocardial ischemia and manifests as hypotension, narrow pulse pressure, low cardiac output, jugular venous distention, a gallop rhythm, and crackles in the lungs. Crackles are not present on examination with patients in right heart failure with preserved left ventricular function.

An electrocardiogram should be obtained in poisoned patients to assess for dysrhythmias, cardiac conduction defects, heart rate, and wave intervals (PR, QRS, QT), which may give clues as to the poison, the severity of the poisoning, and the treatment (Level III recommendation). The relationships between heart rate, QRS duration, and possible causes are listed in Table 5. Specific therapies are reviewed in ► Chaps. 21, “Cardiac Conduction and Rate Disturbances”, and ► 22, “Toxicant-Induced Torsade de Pointes”, and in chapters dealing with individual toxicants.

Torsades de Pointes, a form of ventricular tachycardia associated with a long QT interval, also may impair cardiac output. Although other causes such as electrolyte abnormalities exist,

Table 5 Examples of xenobiotic association between heart rate and QRS duration

Heart rate	Narrow QRS complex	Wide QRS complex
Tachycardia	α -Adrenergic agonists	Aberrant conduction
	Amphetamines	Antihistamines
	Anticholinergic agents	Cocaine
	Theophylline	Propoxyphene Sodium channel blockers Thioridazine Tricyclic antidepressants
Bradycardia	α -Adrenergic lytic agents	β -Adrenergic blocking agents
	β -Adrenergic blocking agents	Calcium channel antagonists
	Calcium channel antagonists	Hyperkalemia
	Cardiac glycosides	
	Ciguatoxin	
	Class Ia antiarrhythmics	
	Sodium channel blockers (open)	
	Tetrodotoxin	

torsades des pointes is often drug related. Medications that cause torsades des pointes, its pathophysiology, and its treatment are reviewed in ► Chap. 22, “Toxicant-Induced Torsade de Pointes” and in Table 6.

Fluid Resuscitation

Fluid resuscitation of the poisoned patient must be individualized. Many patients, especially patients found in coma many hours after their ingestion, are volume depleted (e.g., GI losses, fever, insensible losses). Volume depletion usually is not the acute cause of shock in poisoned patients but may be a contributing cause. Shock may be caused by vasodilation, myocardial depression, chemically induced hemoglobinopathy, or a combination of these. The usual approach of administering fluids until clinical improvement (e.g., improved blood pressure, mentation, adequate urine output) or development of a complication (i.e., pulmonary edema or worsening gas exchange) should be

Table 6 Examples of toxic causes of torsades des pointes

Antiarrhythmics
Amiodarone
Flecainide
Ibutilide
Moricizine
Procainamide
Quinidine
Sotalol
Antibiotics/antifungals
Azithromycin
Ciprofloxacin
Erythromycin
Fluconazole
Gemifloxacin
Itraconazole
Ketoconazole
Levofloxacin
Moxifloxacin
Antipsychotics
Chlorpromazine
Haloperidol
Olanzapine
Paliperidone
Perphenazine
Prochlorperazine
Promethazine
Quetiapine
Thioridazine
Thiothixene
Trifluoperazine
Ziprasidone
Cyclic antidepressants
Amitriptyline
Amoxapine
Desipramine
Doxepin
Imipramine
Nortriptyline
Serotonin reuptake inhibitors
Citalopram
Escitalopram
Fluoxetine
Mirtazapine
Paroxetine
Sertraline
Venlafaxine
Miscellaneous
Arsenic
Astemizole

(continued)

Table 6 (continued)

Chloroquine
Cisapride
Cocaine
Diphenhydramine
Erythromycin
Indapamide
Methadone
Ondansetron
Organophosphates
Pentamidine
Terfenadine
Thallium

modified in the poisoned patient (Level III recommendation). Initial resuscitation measures should include the administration of intravenous crystalloid fluid, but when appropriate, vasopressor infusion should be started early in the course of the resuscitation. Vasopressors or inotropes may be more appropriate than continued fluid administration in poisoned patients with a distributive shock (e.g., from vasodilators) or cardiogenic shock (e.g., from negative inotropes). Some patients require the placement of a central venous catheter to determine cardiac filling status and to optimize fluid and vasopressor therapy. In addition, bedside sonography is used to determine volume responsiveness and estimate cardiac contractility to further guide resuscitation [61, 62].

The debate regarding the most effective fluid to be used in the resuscitation of poisoned patients parallels the debate in critical care medicine in general [63–66]. The ideal fluid would have a chemical composition similar to that of extracellular fluid, would not accumulate in tissues, would not cause adverse metabolic effects, and is cost-effective [67]. Resuscitation fluids are broadly categorized as either colloid or crystalloid solutions. Colloids are suspensions of molecules within a carrier solution that are relatively incapable of crossing the capillary membrane, while crystalloids are ionic solutions that are freely permeable [67]. Fluids that provide oncotic pressure (e.g., albumin, fresh frozen plasma, hetastarch) and stay in the intravascular space longer than crystalloids theoretically are preferred

[68]. However, current evidence does not demonstrate improved clinical outcomes with colloids as opposed to crystalloids; as such, crystalloids should be used to resuscitate patients [69–71] (Level I recommendation). The infusion of packed red blood cells in patients with decreased hemoglobin concentrations increases plasma volume, CaO_2 , and QO_2 . As previously discussed, recent studies advocate for conservative transfusion strategies in patients not in shock [53, 54].

Colloids can be divided into albumin and semi-synthetic colloid solutions (hydroxyethyl starch [HES] and succinylated gelatin). Multiple trials have investigated albumin in the resuscitation of critically ill patients. A meta-analysis by the Cochrane Injuries Group compared albumin to crystalloid solutions or fluids without albumin in critically ill patients [66]. The analysis included 32 randomized controlled trials. In the study, albumin was associated with a significantly increased rate of death (relative risk [RR], 1.68; 95% CI 1.26–2.23; $p < 0.01$). An updated meta-analysis by the Cochrane Injuries Group in 2011 included 38 trials [72]. Albumin did not reduce mortality with a pooled RR of death of 1.05 (95% CI 0.95–1.16). The Saline versus Albumin Fluid Evaluation (SAFE) study was a blinded, randomized controlled study conducted in Australia and New Zealand [73]. Nearly 7,000 patients in ICUs in 16 different academic centers whom the treating physician judged to require fluid resuscitation were included. Mortality was compared in patients resuscitated with either 4% albumin or normal saline. Once again, albumin did not decrease mortality (RR 0.99; 95% CI 0.91–1.09; $p = 0.87$). In addition, the number of patients with new single-organ failure was similar between groups ($P = 0.85$ by Fisher's exact test). Albumin also did not decrease death at 28 days in the subgroups of patients with severe sepsis (RR 0.87; 95% CI 0.74–1.02; $p = 0.09$) or trauma without closed head injury (RR 1.00; 95% CI 0.56–1.79; $p = 1.00$). The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial was a multicenter, randomized clinical trial comparing crystalloids to colloids in patients with hypovolemic shock in the ICU [69]. The amount of fluid received and duration of treatment were at

the discretion of the treating physician. A total of 2,857 patients were enrolled. At 28 days, there were 359 deaths (25.4%) in the colloids group compared to 390 deaths (27%) in the crystalloids group (RR 0.96; 95% CI 0.88–1.04; $p = 0.26$).

Hydroxyethyl starch solutions are the most commonly used semisynthetic colloids and are produced by hydroxyethyl substitution of amylopectin obtained from sorghum, maize, or potatoes [67]. Reduced concentrations (6%) of HES are currently used due to safety concerns from concentrated (10%) HES. In a blinded, randomized, controlled trial of 798 patients with severe sepsis in Scandinavia, HES was associated with an increase in mortality as compared to Ringer's acetate (RR 1.17; 95% CI 1.01–1.36; $p = 0.03$) [74]. More patients also required renal replacement therapy (RR 1.35; 95% CI 1.01–1.80; $p = 0.04$). A secondary analysis of this data demonstrated an increased rate of severe acute kidney injury and the use of renal replacement therapy within the first 5 days of treatment [75]. Given that colloids are more expensive and are not shown to improve outcomes, they cannot be recommended for the resuscitation of most critically ill patients (Level I recommendation). HES solutions should no longer be used in critically ill patients (Level I recommendation).

Crystalloids are used more frequently in poisoned patients because they are readily available, are much cheaper, do not carry the risk of disease transmission seen with blood products, and are as effective as oncotic agents. While crystalloids should be used to resuscitate poisoned patients, practitioners should consider using a “balanced fluid” resuscitation strategy (Level II-2 recommendation). “Balanced fluids” contain organic anions such as lactate and have a lower chloride content more closely resembling the composition of normal plasma [76]. In “balanced fluids,” the difference between the strong cations and the strong anions in the fluid will be between 24 and 28, which once dilutional changes are accounted for is similar to plasma. Examples of “balanced fluids” include lactated Ringer's and PlasmaLyte; chloride-rich solutions such as normal saline are not balanced. To determine if a solution is balanced, use the strong ion difference or SID and

compare it to a patient's bicarbonate. If the SID is less than the patient's bicarbonate, the fluid will be acidotic; if the SID is greater than the patient's bicarbonate, the fluid will be alkalotic. As an example in normal saline, the difference between the Na and Cl is 0 ($154 - 154 = 0$). In a patient with a normal bicarbonate concentration (24 mEq/L), the bicarbonate is greater than the SID and so the fluid will essentially be acidotic [77]. This is the etiology of the non-anion gap metabolic acidosis in patients that receive normal saline. In comparison, lactated Ringer's has a SID of 21, which is much more similar to a patient's normal serum bicarbonate of 24 mEq/L and, therefore, much less likely to cause a metabolic acidosis. The topic of strong ion differences is reviewed in greater detail in ► [Chap. 15, “Acid–Base Balance in the Poisoned Patient”](#).

Recent literature indicates that patients that receive large volumes of “unbalanced solutions” have increased morbidity and mortality, although none of these trials have included poisoned patients. A large retrospective cohort study compared patients undergoing either elective or emergent open general surgical operations that received either NS or a balanced fluid the day of the procedure [78]. Unadjusted in-hospital mortality (5.6% CI 5.3–5.8 vs. 2.9% CI 2.0–4.2; $p < 0.001$) and the number of patients developing major complications (33.7 vs. 23%) were significantly greater in the group that received NS compared to the group that received balanced crystalloids. After using propensity scoring to correct for multiple variables, the difference in mortality was no longer significantly different; however, patients that received NS were 4.8 times more likely to require dialysis ($p < 0.001$). Additionally, patients requiring emergent general surgery showed an adjusted odds of death nearly 50% less in the cohort that received a balanced resuscitation compared to NS (OR 0.51 CI 0.28–0.95). In a prospective, open-label study of consecutive patients admitted to an ICU, those that received balanced crystalloids had a lower incidence of acute kidney injury (OR 0.52 CI 0.37–0.75; $p < 0.001$) and less need for renal replacement therapy (OR 0.52 CI 0.33–0.81; $p = 0.004$) [79]. Septic patients also had a trend

toward lower mortality when resuscitated with balanced fluids as opposed to normal saline (OR 0.78; 95% credibility intervals 0.58–1.05) [80].

Current evidence indicates that balanced crystalloid fluids should be administered for rapid volume expansion during an acute resuscitation of a critically ill patient. However, different factors need to be considered in regard to the administration of maintenance fluids in these patients. While large amounts of crystalloid solution containing high chloride concentrations are associated with deleterious effects, this may not apply to maintenance fluids, where much less volume is administered. Maintenance fluids are used to preserve the extracellular volume while maintaining a normal electrolyte balance and preventing dehydration [81]. In this context, fluids are either isotonic (sodium concentration approximately equal to plasma sodium concentration) or hypotonic (sodium concentration is less than that of plasma). Dextrose-containing solutions, while they may be hyperosmolar, are not hypertonic as the glucose is rapidly metabolized.

Traditionally, hypotonic solutions were administered to both adults and children [82, 83]. Isotonic solutions were avoided due to concerns for the development of volume overload, hyponatremia, and hypertension. However, hypotonic solutions cause hyponatremia, which many critically ill patients are already at risk of developing due to either dysregulation of sodium and water homeostasis or medication-induced syndrome of inappropriate antidiuresis. In addition to normal triggers for the release of arginine vasopressin (AVP) such as hypovolemia and hypotension, pain, stress, nausea and vomiting, hypoxemia, hypercapnia, and hypoglycemia all stimulate the release of AVP, which impairs excretion of free water and causes hyponatremia [84]. Hyponatremia affects approximately 15–30% of hospitalized patients and is generally related to the administration of hypotonic fluids in patients with elevated AVP concentrations [85, 86]. The development of hyponatremia is linked to an increase in mortality [87].

Isotonic solutions are now recommended as maintenance fluids in both adults and children

[88, 89] (Level I recommendation). While mainly investigated in pediatrics, more than 15 randomized, prospective trials involving more than 2000 patients have evaluated the safety and efficacy of isotonic fluids compared to hypotonic fluids as maintenance fluids [81]. A meta-analysis involving nearly 1000 children associated hypotonic fluids with a RR of 2.37 for the development of mild hyponatremia (<135 mmol per liter) and a RR of 6.2 for moderate hyponatremia (<130 mmol per liter) [90]. A Cochrane review compared the development of hyponatremia in patients receiving maintenance fluids composed of either isotonic or hypotonic solutions [91]. Ten studies with a total of 1106 patients were included in the review. Patients that received isotonic fluids had a lower risk of developing hyponatremia compared to those receiving hypotonic fluids (17% vs. 34%; RR 0.48; 95% CI 0.38–0.60). Importantly, many of the studies followed patients for less than 72 h, and patients with renal disease, heart disease, or cirrhosis were often excluded. In addition, the majority of patients were children. While little information exists regarding the most appropriate therapy in edematous states, isotonic fluids at a restricted rate are recommended in these patients [81].

Vasoactive Agents

The usual ICU approach to a patient with adequate fluid resuscitation and inadequate cardiac contractility is the administration of dobutamine or norepinephrine. However, the vasodilatory properties of dobutamine may worsen hypotension in a hypovolemic patient, which again stresses the need for optimal fluid resuscitation. Although norepinephrine increases mean arterial pressure, the increased afterload produced by infusion of norepinephrine may decrease cardiac output. Dopamine is considered to be a third-line agent for treating depressed cardiac contractility owing to its mixed α - and β -effects and indirect mechanism of action. However, it is still used in many pediatric intensive care units. Dopamine stimulates different adrenergic receptors at different infusion rates: dopaminergic at 1–3 $\mu\text{g/kg/min}$, β -adrenergic at 5–10 $\mu\text{g/kg/min}$, and α -adrenergic at 10–20 $\mu\text{g/kg/min}$. Further,

individual variability in response to dopamine infusions precludes the ability to predict which subset of adrenergic receptors is stimulated at a given dose of dopamine in a specific individual. Because part of dopamine's vasopressor effect is through the release of norepinephrine, dopamine has decreased efficacy in norepinephrine-depleted states, such as cyclic antidepressant toxicity [92]. Due to this mechanism, many medical toxicologists prefer the use of a direct-acting vasopressor such as norepinephrine as first-line treatment. If stimulation of β -receptors is desired, dobutamine is theoretically advisable. Norepinephrine is preferable to phenylephrine to stimulate α -receptors. Despite these considerations, the agent of choice is the one that works best for the individual patient and may not be predicted based on the abovementioned theoretical considerations. One multicenter, randomized trial compared norepinephrine to dopamine in patients with shock from multiple etiologies [93]. No difference in mortality was found between the two agents, although dopamine was associated with a greater incidence of arrhythmic events. No poisoned patients were included in the study.

There are very little data regarding the optimal adrenergic vasoactive agents in poisoned patients [94]. Case reports and retrospective case series imply that TCA-related hypotension may be more responsive to norepinephrine than dopamine [95, 96]. In a dog model, TCA-induced hypotension was equally responsive to dopamine and norepinephrine. Only high-dose dopamine infusions of 15 $\mu\text{g}/\text{kg}/\text{min}$ or higher (α -range) were as effective, however, as low doses of norepinephrine (0.25 $\mu\text{g}/\text{kg}/\text{min}$) [97]. There is some evidence that norepinephrine may be the initial vasopressor of choice for TCA-induced hypotension [96]. In a retrospective analysis of 26 adults with TCA-associated hypotension, all patients responded to norepinephrine ($n=11$), while only 60% of patients adequately responded to dopamine ($p=0.02$). A single toxicology inpatient service retrospectively reviewed their management of 48 patients following an overdose of either verapamil or diltiazem; 33 (69%) received a vasopressor [98]. No patients died after vasopressors were initiated, even though many patients

required high doses of vasopressors or multiple vasopressors (median 2; range 1–5). While direct comparisons between agents were not made, vasopressor use was associated with good outcomes with few ischemic complications.

Because of lack of data, the choice of pressor must be made on clinical and theoretical grounds. Contrary to some dogmatic beliefs, all vasopressors can initially be administered peripherally while central access is obtained [99]. Due to familiarity, traditional practice, and the belief that extravasation injuries from peripherally administered dopamine are less severe than from other vasopressors, dopamine is often the preferred agent in pediatric patients. Considerations for different xenobiotics or toxicants are reviewed in their respective chapters.

Nonadrenergic vasoactive drugs are an effective therapy for shock caused by β -adrenergic blocking agents and calcium channel antagonists (Level III recommendation). Glucagon stimulates adenylyl cyclase, which increases intracellular cyclic adenosine monophosphate (cAMP) through a nonadrenergic mechanism. The increased cAMP causes an increase in intracellular calcium, which leads to positive chronotropic and inotropic actions. Glucagon improves cardiac index, urine output, and symptoms in patients with chronic congestive heart failure [100]. Numerous case reports and laboratory investigations describe glucagon's effectiveness in reversing hypotension caused by overdoses of β -adrenergic blocking agents and calcium channel antagonists, although its mechanism of action would seem to make its effectiveness in calcium channel antagonists less likely than in overdoses from β -adrenergic blocking agents [101–104]. There are also reports of glucagon reversing TCA-induced hypotension [105, 106]. In overdose patients, glucagon can be considered in hypotension unresponsive to the usual pressors (Level III recommendation). A glucagon dose of 5–10 mg administered intravenously over 10 min should be followed by a glucagon infusion (3–15 mg/h). An antiemetic should be provided with glucagon as it decreases lower esophageal tone which causes emesis. Inamrinone, a phosphodiesterase type III inhibitor formerly known

as amrinone, prevents the breakdown of intracellular cAMP. Inamrinone administration has been reported to reverse hypotension in overdoses of calcium channel antagonists [107], chloroquine [108], and propranolol [109]. It has also reversed hypotension in calcium channel antagonist overdoses in animals [110, 111]. Milrinone, another phosphodiesterase type III inhibitor, was used in the treatment of a patient with venlafaxine-associated cardiomyopathy; this patient required milrinone for 12 days in addition to multiple other therapies [112]. Milrinone was also studied in a dog model [113]. Because phosphodiesterase inhibitors have direct peripheral vasodilatory properties, however, further worsening of hypotension may occur if the decrease in blood pressure from vasodilation is greater than the increase in blood pressure from improved cardiac output. They should be used cautiously, if at all, with continuous bedside monitoring.

More recently, high-dose insulin euglycemia therapy (HIE) was used to treat hypotension and cardiac dysfunction from β -adrenergic blocking agents and calcium channel antagonists. In overdose, calcium channel antagonists decrease insulin release from pancreatic β -cells, cause insulin resistance in the myocardium, and change myocyte metabolism from fatty acids to carbohydrates [114]. Under stressful conditions such as in shock from both β -adrenergic blocking agents and calcium channel antagonists, the myocardium changes its preferred energy substrate from fatty acids to carbohydrates [114, 115]. High-dose insulin euglycemia therapy improves myocyte use of carbohydrates as an energy source and, therefore, increases cardiac contractility and improves perfusion. In the laboratory, insulin infusions increase myocardial contractility, possibly through increases in intracellular calcium [116]. Compared with calcium chloride, epinephrine, and glucagon, HIE decreased mortality in dogs poisoned with verapamil [114, 116, 117]. In a swine model, HIE was more effective than epinephrine and vasopressin, combined [118]. An increasing amount of data supports the efficacy of insulin in poisoning from β -adrenergic blockers and calcium channel antagonists. Insulin-glucose therapy improved hemodynamic

parameters in five patients with calcium channel antagonist overdoses who were persistently hypotensive despite multiple therapies (calcium, atropine, glucagon, adrenergic agonists) [119]. All five patients survived. A 60-year-old male presented after ingesting 5.4 g of extended-release diltiazem [120]. His shock resolved after receiving HIE. One patient received 6 U/kg/h for 5 h with clinical improvement without experiencing an adverse event [121]. In a review of 78 patients with toxicity from either calcium channel antagonists or β -adrenergic blocking agents treated with HIE, 88% survived [115]. High-dose insulin euglycemia therapy was successfully used in another case series in 11 of 12 patients; the single fatality occurred in a patient 1 h after HIE was discontinued in favor of vasopressor therapy [122].

Based on current knowledge, insulin and glucose infusion should be used in shock caused by calcium channel antagonists and β -adrenergic blocking agents that is unresponsive to fluid resuscitation [123] (Level III recommendation). While glucagon can be considered in shock from β -adrenergic blocking agents in the author's opinion, many practicing medical toxicologists prefer HIE or vasopressors, instead. The dosing of HIE generally used is a bolus of 1 U/kg of regular insulin with 0.5 g/kg of dextrose, followed by an infusion of 1 U/kg/h of insulin titrated to effect. There are reports of patients receiving infusions as high as 22 U/kg/h [115]. To prevent hypoglycemia, glucose infusions should accompany insulin infusions. Plasma potassium concentrations should be closely monitored while the patient is receiving HIE. Consideration can be given to even initiating HIE prior to other therapies such as vasopressors. The clinical pharmacology of HIE is discussed in ► [Chap. 147, "Euglycemic Insulin Therapy."](#) Its clinical use is discussed in greater detail in chapters on specific agents.

Limited evidence also supports the use of methylene blue in the treatment of shock from calcium channel antagonists [124, 125]. In a single case report, methylene blue was successfully used in a mixed atenolol and amlodipine ingestion [126]. Amlodipine stimulates the release of nitric oxide, thereby causing vasodilation and

worsening hypotension. Methylene blue acts as a nitric oxide scavenger. In addition, it inhibits nitric oxide synthesis and decreases the production of cyclic guanosine monophosphate production, which is generated by nitric oxide and increases vasodilation. Given the limited experience with methylene blue, it should not be viewed as a therapy to be used routinely in calcium channel antagonist toxicity. Based on current evidence, the author recommends that it be used in cases of refractory circulatory shock due to amlodipine toxicity.

Calcium sensitizers (e.g., levosimendan) have been proposed to treat shock from calcium channel antagonists. They act as inotropic agents and increase the association of myosin and actin cross-bridges while slowing down their dissociation rate [127]. In patients with congestive heart failure, they decrease afterload while increasing cardiac contractility and output. Case reports describe levosimendan reversing shock from calcium channel antagonists [128–130]. However, the overall evidence is still limited and these agents are not currently available in the United States or in many other countries.

Lipid Emulsion Therapy

The administration of lipid emulsion therapy (LET) is one of the most recent advances in the care of the critically ill poisoned patient. Originally investigated as a treatment for patients with local anesthetic toxicity, it has since been used in the management of toxicity from other xenobiotics [131]. Its mechanism of action is still not fully understood. The most accepted theory is that LET acts as a lipid sink and binds “lipid-soluble” xenobiotics removing them from their site of toxicity [132]. While there are multiple successful reports of LET reversing toxicity from lipophilic xenobiotics (e.g., calcium channel antagonists [133], tricyclic antidepressants [134]), there are also reports of its effectiveness in reversing toxicity from xenobiotics that are not lipophilic [135]. Other potential mechanisms of action include improving intracellular metabolism and ion channel activation.

Lipid emulsion therapy was first used in nonlocal anesthetic toxicity to resuscitate a

17-year-old with cardiovascular collapse following an ingestion of bupropion and lamotrigine [136]. Since then, there are many reports of LET successfully reversing toxicity from multiple agents (e.g., atenolol [135], diphenhydramine [137], quetiapine [138], cocaine [139], venlafaxine [140]). However, it is important to recognize that these anecdotal reports cannot be used to validate the efficacy of LET and are undoubtedly vulnerable to publication bias as unsuccessful use of LET in critically ill patients is unlikely to be reported.

A case series from the Toxicology Investigators’ Consortium (ToxIC) identified nine patients with presumed non-survivable cardiac toxicity (either cardiac arrest or hypotension refractory to vasopressors) that received LET [141]. Five of the patients survived including two patients in cardiac arrest; eighty percent of survivors were neurologically intact. Adverse effects associated with LET include DVT, pancreatitis, and laboratory interferences [141, 142]. As such, there is still disagreement as to if and when to administer LET. The position of the American College of Medical Toxicology (ACMT) is that there is no standard of care in regard to the use of LET, but if and when it is administered, it should be as a 20% lipid emulsion as a 1.5 ml/kg bolus followed by an infusion of 0.25 ml/kg/min [143] (Level III recommendation). LET is further discussed in ► [Chap. 152, “Lipid Resuscitation Therapy”](#) and in chapters dealing with specific relevant agents.

Extracorporeal Membrane Oxygenation

In venoarterial extracorporeal membrane oxygenation (ECMO), either the right atrium or ventricle is cannulated. Hypoxic blood is pumped through an oxygenator and returned to the systemic circulation via a central arterial catheter. Extracorporeal membrane oxygenation is indicated in poisoned patients in refractory shock that are failing conventional treatment [144] (Level III recommendation). There are multiple reports of poisoned patients successfully resuscitated with ECMO [145, 146]. In a retrospective review of poisoned patients in arrest or shock, mortality was improved in those that received ECMO (12/14) compared to those that did not (23/48) (86%

vs. 48%, $p < 0.02$) [147]. In many cases, poisoned patients are ideal candidates for ECMO as they tend to be otherwise healthy and are suffering from a reversible illness. In these patients, ECMO serves as a bridge until the toxic xenobiotic is metabolized or eliminated, at which time the patient should regain normal cardiovascular function. While adverse events are associated with ECMO, recent advances in technology have made this a more practical alternative during emergency resuscitation of critically ill patients [148]. The use of ECMO in poisoned patients is further discussed in ► Chap. 4, “Extracorporeal Membrane Oxygenation and Cardiopulmonary Bypass in the Poisoned Patient.”

Overdose and Cardiac Arrest

Few studies specifically address the issue of cardiac arrest as a direct consequence of poisoning. The AAPCC reported 1,835 exposure-related fatalities in 2014 [2]. The fatalities involved single substances in 42% of cases, two substances in 25% of cases, and three or more substances in the remainder of cases. There were 88 deaths in children (<20 years old), which was an 11.1% decrease from the previous year in that population; 16 deaths occurred in children less than 5 years old (1.4% of exposure-related fatalities). Nearly 66% of fatalities occurred in patients between 20 and 59 years of age. Only 2 deaths occurred in a pregnant patient. A recent analysis of data from the European Monitoring Centre for Drugs and Drug Addiction estimated that there were between 10,000 and 20,000 deaths a year in Europe from opioids [149]. In 2011, the average mortality rate due to overdoses in Europe was estimated at 18 deaths per million people aged 15–64 years old. Most countries reported an increase in overdose deaths from 2003 until 2009, when the number of deaths began to decline. Overall, there were approximately 6,500 overdose deaths reported in 2011. Over 19 years, there were 118 cases of cardiac arrest from intoxication at the Vienna General Hospital [150]. After resuscitation, 39 patients had a favorable outcome, defined as good neurologic

function or moderate disability on the Pittsburgh Cerebral Performance Category. However nearly a quarter of patients were arrested from opioid intoxication and nearly a third of patients were deteriorated and arrested in the hospital, so the results may have limited external validity. Autopsy findings revealed that only 76% of older adults and 25% of young adults had atherosclerotic coronary artery disease as a cause of cardiac arrest. This finding should influence the medical management of drug-induced cardiac arrest. Advanced Cardiac Life Support (ACLS) algorithms [151] should be altered when cardiac arrest, ventricular tachycardia, or ventricular fibrillation is caused by drug overdose because the mechanisms for these arrests are significantly different from the cardiovascular events for which ACLS protocols were created. Specific therapies, such as sodium bicarbonate, glucagon, HIE, LET, and ECMO should be considered. Tox-ACLS was specifically developed to incorporate differences in the resuscitation of the critically ill, poisoned patient [152]. The management of acute coronary syndrome with cocaine toxicity, cocaine-associated dysrhythmias, and opioid-induced respiratory failure with naloxone are examples of important topics covered in Tox-ACLS. The post-arrest management of these patients is discussed in greater detail in ► Chap. 5, “Post-Resuscitation Management of the Poisoned Patient.”

Invasive and Noninvasive Measurements of Hemodynamic Function

When patients are in shock, further information should be obtained to guide the resuscitation. Historically a pulmonary artery catheter (PAC), or Swan-Ganz catheter, was placed. Data obtained from a PAC includes central venous pressure, right ventricular pressure, pulmonary artery pressure, and left atrial pressure via the pulmonary capillary wedge pressure. Other data that can be obtained include oxygen saturation of mixed venous blood (SvO_2), thermodilution Q_T , systemic and pulmonary vascular resistance, QO_2 , shunt fraction (Q_S/Q_T), and VO_2 . However,

Table 7 Clinical uses of the pulmonary artery catheter

Determine etiology of shock state and assess efficacy of therapy
Assess intravascular volume
Renal failure, hypovolemia
Assess cardiac contractility
Cardiac output, mixed venous saturation (i.e., efficacy of therapy in CCA overdose)
Diagnosis of constrictive pericarditis or pericardial effusion
Waveform analysis
Measurement of pulmonary artery pressure
Pulmonary hypertension
Determine PCWP in the setting of pulmonary edema
High pressure (CHF) versus low pressure (ARDS) (i.e., hydrocarbon aspiration, toxic gas inhalation)
<i>ARDS</i> adult respiratory distress syndrome, <i>CCA</i> calcium channel antagonist, <i>CHF</i> congestive heart failure, <i>PCWP</i> pulmonary capillary wedge pressure

noninvasive monitoring techniques and a lack of an effect of PACs on outcome have sharply curtailed their use in poisoned patients. Some situations in which PACs may be useful are listed in Table 7. Because most overdose patients leave the ICU in 1–2 days, they rarely require a PAC and their use has not been studied in poisoned patients. The PAC may add useful data in some overdose situations such as [1] assessment of left heart filling pressures when persistent pulmonary edema is present (e.g., hydrocarbon aspiration or adult respiratory distress syndrome) and [2] assessment of myocardial contractility (cardiac output and stroke volume) to determine the severity of myocardial depression and efficacy of therapy (e.g., calcium channel antagonist overdose). Although several case reports describe the use of a PAC in a calcium channel antagonist overdose [101, 108, 153–155], no studies address either the indications for placement or whether the information obtained from the pulmonary catheter changes the outcome in these patients.

There are risks associated with the insertion of a PAC. Common complications include pulmonary artery injury, valvular injury, endocarditis, heparin-induced thrombocytopenia, catheter or balloon embolization, pulmonary infarction, ventricular arrhythmia, and cardiac perforation [156]. In addition, PACs are technically

challenging to use [157–159]. Due to these limitations, there is a shift toward using less invasive and less challenging methods to monitor hemodynamic function [160] (Level III recommendation). As with PACs, these methods are not investigated in poisoned patients. Arterial pulse contour and pulse power analyses are less invasive alternatives to measure cardiac output [161]. Lithium dilution cardiac output (LiDCO PlusTM) uses these principles to estimate cardiac output [162]. Isotonic lithium chloride is injected via a central or peripheral venous route to calculate cardiac output. The lithium doses used are too small to cause any pharmacologic effect. LiDCO was found to be an effective alternative to PAC [163]. Other non-invasive devices that provide similar information include the PiCCO PlusTM and FloTracTM [164]. These devices use different calibration schemes to model the transfer of arterial pulse pressure to stroke volume. Doppler cardiac monitoring devices are alternatives that require neither arterial or venous cannulation [165]. Esophageal or transthoracic Doppler probes measure flow in the descending aorta and estimate cardiac output. These products suffer from technical limitations, as probe position is crucial to obtaining accurate measurements. In addition, basic central venous catheters can measure central venous pressure and SvO₂ with fewer complications than PACs.

Bedside sonography is an even less invasive alternative used to guide resuscitation. The rapid ultrasound in shock (RUSH) protocol can determine the etiology of cardiovascular collapse [62]. The RUSH protocol is an easily learned technique that involves assessing the heart (“the pump”), inferior vena cava (IVC) and internal jugular (IJ) (“the tank”), and arterial vessels such as the aorta (“the pipes”). RUSH can exclude cardiac tamponade, decreased cardiac contractility, hypovolemia, hemothorax, pneumothorax, and aortic aneurysm as the cause of shock. In addition, a standard focused assessment in trauma (FAST) exam is included to exclude hemoperitoneum as the etiology of the hypotension.

Sonography also provides information about left and right ventricular function, central venous pressure, and fluid responsiveness. In addition to excluding tamponade, cardiac sonography is

useful to evaluate both left and right ventricular function. Ventricles with good contractility will have a large change in volume between systole and diastole [166]. Motion of the anterior leaflet of the mitral valve also assess contractility. In the parasternal long axis, the anterior leaflet should nearly touch the septum in diastole if the ventricle is contracting normally. The normal ratio of the left to right ventricle is 1:0.6. Right ventricular dilation indicates increased pressure within the pulmonary vascular circuit, such as with a large pulmonary embolism or pulmonary hypertension, as the cause of hypotension [167, 168]. Inferior vena cava measurement is used to determine volume status and fluid responsiveness; it also acts as a surrogate for central venous pressure (CVP) [169]. The size and change in size of the IVC during inspiration accurately estimates CVP [170]. An IVC with a diameter less than 2.1 cm that collapses more than 50% correlates with normal CVP and volume responsiveness [171]. Serial measurements as opposed to a single measurement during the resuscitation are recommended to more accurately guide volume management [62]. The IJ can be used instead of the IVC [172]. Common carotid velocity time integral (VTi) with passive leg raise (PLR) also measures volume responsiveness. In PLR, a patient's legs are raised 45° while their upper body is kept horizontal, and the patient is assessed for changes in stroke volume or cardiac output [173]. Carotid artery flow velocity is measured with Doppler sonography to determine VTi. The common carotid artery's diameter is measured using Doppler to evaluate the flow [174]. Increases in VTi following PLR accurately predict volume responsiveness [175]. A 20% increase in VTi following PLR predicted volume responsiveness with a sensitivity of 94% and specificity of 86% [175]. This topic is further discussed in ► Chap. 14, "The Assessment and Management of Hypotension and Shock in the Poisoned Patient."

Sedation and Paralysis

When a patient is intubated and is in the ICU, sedation and analgesia are important to minimize discomfort. Some patients have vivid recall of

events that occurred in the ICU [176]. These events (discomfort, being in unfamiliar surroundings, invasive procedures performed by total strangers) are terrifying because the patient's consciousness is clouded from illness and partial sedation; in fact, inadequate sedation and analgesia can lead to post-traumatic stress disorder (PTSD) [177]. At the same time, excess sedation causes delirium, with some literature associating it with distress and PTSD [178, 179]. Worse yet is being paralyzed without adequate sedation or analgesia and being unable to communicate [180]. For overdose patients, the patient's underlying emotional instability may complicate management further (see ► Chap. 6, "Psychiatric Issues in the Critically Poisoned Patient").

Patients intubated due to their toxicologic exposure may be agitated and require sedation. Until recently, this was typically achieved via benzodiazepine administration (continuous infusion or intermittent, around-the-clock dosing) or by continuous propofol infusion, with greater than 80% of critically ill patients sedated with one of these agents [181]. The α -2 agonist dexmedetomidine is now being used either in addition to these agents or replacement of them (Level I recommendation). A multicenter, randomized, double-blind trial compared midazolam or propofol to dexmedetomidine in intubated patients and was found to be non-inferior in maintaining light to moderate sedation [182]. It did reduce the duration of intubation compared to midazolam ($p = 0.03$) but not propofol ($P = .24$). As dexmedetomidine is unlikely to cause respiratory depression, it can be used with noninvasive positive pressure ventilation [183]. However, this is controversial and one randomized, double-blind, placebo-controlled pilot study did not find that it improved tolerance to noninvasive ventilation [184]. Recent trials in patients with sedative-hypnotic withdrawal indicate that dexmedetomidine may be a useful adjunct; however, more studies are required to determine its safety and efficacy in this population [185, 186]. Dexmedetomidine was administered to 22 poisoned patients who were intubated in an ICU [187]. Most patients (77%) required additional sedatives or analgesics and five patients

suffered adverse events. Further studies are needed to determine the role of dexmedetomidine in poisoned patients.

Continuous infusion provides a constant serum drug concentration and decreases the chance of the patient awakening or becoming agitated [188, 189]. Continuous sedative infusions of benzodiazepines and propofol, compared with intermittent dosing, prolong ventilator time and ICU time, however, as a result of overmedication [190]. For poisoned patients, as for all ICU patients, analgesia is as important as sedation. Neither benzodiazepines nor propofol provide analgesia, which is problematic as the endotracheal tube is a significant source of pain and discomfort [191]. Dexmedetomidine may provide analgesia in addition to sedation via receptors in the spinal cord [187]. Narcotic analgesics, such as fentanyl and morphine, may decrease the pain and discomfort patients experience from intubation, having invasive devices in place, and an inability to move. Combining narcotics with sedative-hypnotics decreases the amount of sedative-hypnotics required for comfort [192]. Simultaneous administration of opioids and propofol may cause hypotension, especially if large doses are used. Caution is warranted in patients who are poisoned by cardiovascular agents and therefore prone to hypotension.

Lorazepam and propofol are commonly used sedatives in the ICU. Continuous infusion of midazolam, compared with continuous infusion of propofol or lorazepam, lengthens time until the patient is awake and extubated after sedation has been stopped [193–195]. In critically ill patients, the midazolam half-life and volume of distribution are increased [196]. The half-life is prolonged further in renal failure [197]. In addition, sedation with midazolam may lead to higher rates of PTSD compared to other sedatives [179]. Benzodiazepines can also cause delirium [198], which is an independent predictor of death and prolonged ICU length of stay [199]. Infusions of propofol for greater than 48 h are associated with propofol infusion syndrome (PRIS) [200]. PRIS is a syndrome of refractory bradycardia, metabolic acidosis, rhabdomyolysis, hyperlipidemia, and fatty liver; patients can even

develop myocardial failure or cardiovascular collapse. Patients sedated with dexmedetomidine and other α -2 agonists develop bradycardia and hypotension. Haloperidol is also used as an adjunctive therapy for sedation. Independent of which sedative agents are used, daily interruption of sedation to assess the patient's neurologic status shortens the duration of mechanical ventilation and ICU length of stay [201].

Analgesia-based sedation or analgosedation is another option in the intubated patient [198, 202] (Level II-2 recommendation). Here, the primary objective is to control pain with an analgesic and only administer a sedative-hypnotic if necessary [203]. Analgosedation was demonstrated to be as effective as a sedative-hypnotic approach while reducing the dose of administered sedatives. Patients treated with analgosedation were able to be weaned from the ventilator sooner and had shorter ICU lengths of stay compared to standard management [204]. Just as with sedative-hypnotics, dosing of analgesics may need to be adjusted due to altered pharmacokinetics in critically ill patients [205].

In postoperative patients, the use of topical anesthetics to the pharyngeal, laryngeal, and tracheal mucosa statistically decreased the amount of sedation required [206]. As patients begin to regain consciousness and experience discomfort from the endotracheal tube, the use of topical anesthetics may relieve discomfort without requiring consciousness-altering medications. This may also be true of nonsurgical, intubated patients. Topical anesthetics must be administered judiciously because overzealous administration may cause significant methemoglobinemia and local anesthetic systemic toxicity.

In the overdose patient, sedation is often less problematic as patients are often intubated due to taking central nervous system depressants and can usually be extubated within 24 h. Overdose patients with depressed mental status may not require sedation if they were intubated due to their depressed mental status and inability to protect their airway. When the clinical effects of the overdose begin to resolve, either further sedation or ventilator liberation must be performed. In these situations if additional sedation is required,

intermittent administration of fentanyl (or another short acting opioid) or an infusion of dexmedetomidine, combined with the use of topical anesthetics, may be the best choice (Level III recommendation). This combination avoids oversedation and allows for continuous assessment of the patient's mental status and other clinical signs and symptoms indicating that the patient is ready to be liberated from the ventilator. Benzodiazepines, propofol, or dexmedetomidine can always be added to opioids if further sedation is required. Many patients, especially those presenting following polypharmacy overdoses, are delirious or have a fluctuating level of alertness. They may benefit from small amounts of sedation, until enough of the substances have worn off for them to be extubated. In general if the patient is sufficiently awake and can protect their airway, rapid ventilator liberation and extubation is appropriate. For otherwise healthy overdose patients, extubation usually can be accomplished safely without a "wean from the ventilator."

Neuromuscular blocking agents (NMBAs) should be used in only two circumstances in the poisoned patient: [1] in patients who, despite adequate sedation, still have a high oxygen demand owing to the work of respiratory muscles and [2] in patients poisoned with xenobiotics such as strychnine (Level III recommendation). Normally, about 5% of oxygen consumed by the body (VO_2) is used by the respiratory muscles. In critically ill patients, this can be 25% or greater [207]. Although therapeutic paralysis decreases VO_2 , it has been shown that administering an NMBA to patients who are adequately sedated does not decrease VO_2 further [208]. Critically ill patients who have received NMBAs may develop persistent muscular weakness after discontinuation of the NMBA [209–211], even after short-term or intermittent NMBA administration [212]. The effect may last for weeks or months. The presence of renal dysfunction allows for the accumulation of active metabolites from some NMBAs (e.g., vecuronium). Addition of steroids (e.g., in patients with either upper airway obstruction or lower airway bronchospasm) increases the risk and severity of prolonged muscular weakness

[209]. NMBAs should be administered only if the patient can benefit from decreasing VO_2 requirements. NMBAs should never be used to control an agitated patient. The cause should be investigated and treated (e.g., increase sedation or analgesia, change the vent settings), which will likely improve the agitation without the need for NMBAs. Paralysis should not be used as a punitive intervention or to absolve the physician from the need to sedate an agitated patient. A poisoned patient seldom requires the use of an NMBA, unless adult respiratory distress syndrome, sepsis, hyperthermia from severe neuromuscular agitation (e.g., severe serotonin syndrome), or a toxicant such as strychnine is part of the clinical picture.

Ventilator Liberation

When the patient begins to show improvement, the issue of ventilator liberation arises. *Liberation* is a more desirable term, and a better mind set, than *weaning* for discontinuing ventilatory support. Weaning implies a gradual withdrawal of ventilator support, and most poisoned patients do not need to be "weaned" from the ventilator. Of 456 patients evaluated for participation in a trial designed to compare ventilator modes during liberation, 347 (76%) were liberated after an initial 2-h, spontaneous-breathing T-piece trial [213]. These findings have been confirmed in other studies [214]. As many overdose patients are intubated due to agitation or decreased mental status, most can be extubated as soon as their mental status improves and do not require a formal wean (Level III recommendation).

The conditions that led to the patient's being intubated and ventilated need to be resolved. In the case of overdoses, most respiratory failure is type II (hypercapnic) from decreased mental status and respiratory drive. When the patient regains his or her respiratory drive and the ability to protect their airway, ventilator liberation should proceed rapidly. If type I (hypoxemic) respiratory failure was involved, adequate oxygenation on 40% FiO_2 and PEEP of less than 5 cm H_2O should be present before liberation is attempted [215]. In

type IV (shock) respiratory failure, the patient should be hemodynamically stable and metabolic abnormalities corrected. If type II (hypercapnic) respiratory failure from respiratory muscle weakness has complicated the clinical course, liberation may require a more thoughtful approach, which is outlined subsequently.

Indices previously used to determine whether respiratory muscle strength was adequate for liberation have included a negative inspiratory force less than -20 cm H₂O, respiratory rate less than 35 breaths/min, V_T greater than 5 mL/kg, V_E less than 10 L, and forced vital capacity greater than 10 mL/kg [216, 217]. All of these parameters are moderately sensitive but poorly specific [218]. Their utility in the overdose or poisoned patient population has not been evaluated.

The rapid shallow breathing index (RSBI) was developed to assist in the bedside assessment of patients who are potentially ready for ventilator liberation [219]. The RSBI quantifies what we intuitively know about patients' breathing patterns: patients who take deep breaths at a slow rate are ready for ventilator liberation, whereas patients breathing rapidly are unlikely to be successfully liberated. The RSBI is performed while the patient is spontaneously breathing for 1 min without any ventilator assistance. The respiratory rate is divided by the spontaneous V_T in liters. Patients with an RSBI greater than 105 are at risk of failing ventilator liberation. The RSBI is highly sensitive (0.97) and moderately specific (0.64) in medical ICU patients [219]. Further studies have shown a sensitivity and specificity equal to the original study when the RSBI is performed after 30 min of spontaneous breathing [220]. The RSBI is valid in surgical patients, as well [221]. Analysis of patients failing liberation with RSBI less than 100 found that most fail due to new problems unrelated to the original process that caused them to be intubated, such as new-onset congestive heart failure, upper airway obstruction, and aspiration [222]. The utility of the RSBI in overdose or poisoned patients has not been studied.

Questions may arise about which ventilator mode to use during ventilator liberation. As mentioned previously, the SIMV mode can increase the work of breathing. For the general ICU

population, once-daily trials of spontaneous breathing lead to extubation three times faster than SIMV and two times faster than pressure support ventilation [214]. It is not known whether this applies to toxicology patients.

If there is concern that the patient may not be ready for ventilator liberation, a simple five-step procedure can be followed:[218].

1. Ensure all underlying abnormalities that led to intubation are corrected.
2. Assess the RSBI. If the RSBI is greater than 105, therapy to decrease respiratory workload and increase respiratory muscle strength should be employed.
3. For patients with an RSBI less than 105, perform a 2-h spontaneous breathing trial (SBT). This is accomplished by placing the patient on a T-piece or on continuous positive airway pressure with minimal or no pressure support.
4. Evaluate the patient during the SBT. Failure of a SBT manifests as diaphoresis, tachypnea, desaturation, tachycardia, hypotension, or arrhythmias.
5. If the patient tolerates a 2-h SBT, he or she is ready to be liberated from the ventilator.

Ventilator liberation does not imply that extubation should be performed, just as an inability to protect the airway does not imply respiratory failure. Other factors need to be considered, especially in cases of upper airway injury such as following a caustic injury. Bedside assessment of airway adequacy may be determined by endotracheal tube "cuff leak." The cuff-leak test can be performed in one of two ways. The first is to disconnect the patient from the ventilator, deflate the endotracheal tube's cuff while it is still in place, occlude the end of the tube, and listen for air passing around the tube. The second is to leave the endotracheal tube connected to the ventilator, deflate the cuff, and measure the difference between the V_T delivered by the ventilator and the V_T returned to the ventilator. If there is a leak, the delivered V_T will be greater than the returned V_T . Prospective evaluation of 72 patients with upper airway obstructions using the first method led to successful extubation in 89% of patients

with a cuff leak [223]. Using the second method, patients who did not develop stridor on extubation averaged 360 mL cuff leak with average V_T of 650 mL [224]. Patients who did develop stridor, given the same average V_T , had cuff leaks of only 180 mL. These data, along with direct visualization of the upper airway, can assist the clinician in deciding whether patients with upper airway obstruction are ready for extubation.

Ancillary Issues in the Intensive Care Unit Management of Poisoned Patients

Certain management issues need to be addressed in all patients who enter the ICU. Any patient who is critically ill, is intubated, or has a PAC requires a daily chest x-ray. New findings are discovered in 15–45% of daily chest x-rays [225–228], 8% had findings of “major” clinical significance (e.g., pneumothorax, improperly positioned endotracheal tube), and 42% of these findings (3.3% of total) were not suspected previously from bedside assessment [229].

Critically ill, poisoned patients are at increased risk of GI bleeding. Of ICU patients, 75% have endoscopic evidence of gastric mucosal injury by 18 h after admission, with 5% of patients developing overt bleeding [230]. GI bleeding prophylaxis should be started on admission to the ICU and can be achieved best through the use of histamine₂-receptor antagonists or proton-pump inhibitors [231] (Level I recommendation).

Poisoned ICU patients are at risk for venous thromboembolic disease if they have a prolonged course requiring them to remain in bed. Approximately 33% of all ICU patients develop ultrasonographically detectable DVTs despite receiving prophylaxis. Meta-analyses show that the use of heparin or pneumatic compression stockings decreases the incidence of DVT by at least 50% [232]. DVT prophylaxis should be initiated with unfractionated heparin, low-molecular-weight heparin, or compression devices as soon as the patient is admitted to the ICU if a prolonged stay is anticipated (Level I recommendation).

The goal of nutritional support is to meet the patient’s nutritional needs without overfeeding. This may be difficult because critically ill patients can be catabolic with a negative nitrogen balance. Exact caloric requirements can be determined through indirect calorimetry (“metabolic cart”). Overfeeding should be avoided because excess carbohydrates can lead to increased carbon dioxide production, which leads to higher minute ventilation needs. The increased ventilation needed to blow off the excess carbon dioxide may prevent liberation from the ventilator. Enteral feedings, which help maintain integrity of the gut’s mucosal barrier, are preferred over the parenteral route. If a prolonged stay is anticipated, feedings optimally should be initiated within the first 24 h after admission. If ventilator liberation is anticipated within the first 24–48 h, as is typical of many poisoned patients, enteral feedings are not necessary.

Gastrointestinal Decontamination

Gastrointestinal decontamination, once a mainstay in the management of the intoxicated patient, has greatly fallen out of favor. It is generally relegated to patients that present very early (less than an hour after their ingestion) or for those patients who took a very large or dangerous overdose, where an antidote does not exist (e.g., verapamil) (Level III recommendation). While once common, the administration of syrup of ipecac or the performance of gastric lavage should not be done, and administration of even single-dose activated charcoal (AC) is now rare. Intuitively GI decontamination should decrease absorption of many xenobiotics. However, its use is not associated with improved patient-centered outcomes (e.g., mortality, length of stay) [233–235].

If GI decontamination is attempted, it should be done as early as possible in the patient’s treatment to have any chance of being beneficial. If it is preformed, this should occur in the emergency department, shortly after the patient arrives; the patient is very unlikely to benefit from decontamination started in a delayed fashion, such as in the ICU. However, patients who ingest sustained

release preparations, have heavy metals in their GI tract, or are body packers may benefit from whole bowel irrigation (WBI) (Level II-3 recommendation). In addition if the patient has a bezoar, GI decontamination may be beneficial.

Activated charcoal is produced in a two-step process, starting with pyrolysis of various carbonaceous materials. It is then treated at high temperatures with oxidizing agents such as steam or carbon dioxide that “activate” it and increase its adsorptive capacity. Activated charcoal adsorbs many xenobiotics but does not adsorb metals or strongly ionized substances. In addition, it should not be administered to patients with caustic injuries, as it will obscure landmarks during the endoscopy. Serious adverse events include chemical pneumonitis following aspiration, peritonitis if it is administered to a patient with perforation of their GI tract, and pseudo-obstruction in patients with an ileus or obstruction. In their most recent position statement, the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) compared 122 studies in human volunteers [235]. There was a large amount of variability in the types of xenobiotics ingested, the amount of xenobiotic ingested, and the amount of charcoal administered. While absorption was decreased when AC was administered within 30 min, the mean reduction was only 16% when administered two hours after the ingestion. Studies of AC in patients with ingestions are difficult to interpret as they include patients receiving multiple types of decontamination in addition to AC or have serious methodological or statistical flaws. Merigian et al. investigated the outcome of 451 asymptomatic patients who received either 50 g of AC or no treatment and did not find a statistically significant change in clinical outcomes between the groups [236]. Buckley et al. conducted a retrospective, non-randomized study on 981 consecutive patients admitted following acetaminophen overdoses [237]. Activated charcoal was administered in 36% of patients and 39% of patients were not decontaminated. Patients that received AC were significantly less likely (odds ratio 0.36) to have acetaminophen concentrations in the probable or high-risk portion

of the nomogram. However, the mean time to presentation in the no treatment group was 385 min versus 135 min in the treatment group. If AC is administered, it should be dosed at 1 g/kg if the dose is unknown or in a 10:1 ratio of AC to xenobiotic if known; most adults receive approximately 100 g of AC. Administration of a cathartic with AC is controversial. The current position of the AACT does not support the routine use of activated charcoal, even though benefit cannot be excluded if AC is administered more than one hour after the ingestion [235] (Level I recommendation). AC may be considered in patients that present within one hour of a toxic ingestion, which would still exclude its use in patients after they are admitted to the ICU. Multidose activated charcoal (MDAC) is used to enhance the elimination of various xenobiotics. Multidose activated charcoal may benefit patients at risk from delayed absorption due to ingesting delayed release products or if they ingested xenobiotics that cause pylorospasm or bezoar formation, such as salicylates [238]. In these scenarios, MDAC prevents absorption of the xenobiotic. Patients that ingest xenobiotics that undergo enteroenteric or enterohepatic circulation may also benefit from MDAC. In enterohepatic circulation, absorbed substances are secreted into the bile and then into the small intestine before being reabsorbed. In enteroenteric circulation, absorbed substances are secreted into the intestine before being reabsorbed. By administering MDAC, charcoal can adsorb xenobiotics that are secreted into the intestine before being reabsorbed, thereby enhancing elimination. In these scenarios, the xenobiotic has already been absorbed so MDAC is not being used for the purpose of decontamination but as an adjunct to increase elimination by preventing reabsorption. Both animal and human data demonstrate that MDAC increases xenobiotic elimination [239–241]. However, MDAC has not been shown to decrease morbidity or mortality [242]. MDAC is generally administered at a dose of ½ gram/kg following the initial standard dose of charcoal. In pediatric patients, the dose may need to be decreased. Cathartics should not be administered with MDAC as repeated dosing causes electrolyte disturbances and dehydration.

Multidose activated charcoal may be administered every four hours. However, the timing of MDAC administration is patient and provider specific. Multidose activated charcoal should be withheld in patients with altered mental status and an unprotected airway, GI tract obstruction or disruption, and an ileus. Currently, the AACT/EAPCCT only recommends the administration of MDAC in patients who have ingested life-threatening amounts of either carbamazepine, dapsone, phenobarbital, quinine, or theophylline [243] (Level II-3 recommendation). Xenobiotics whose elimination may be increased by MDAC are discussed in their respective chapters.

Over the last 10–20 years, the use of gastric lavage has drastically decreased due to concerns that complications from the procedure outweigh any benefit. Given the real risks associated with it, the AACT and EAPCCT do not recommend the use of gastric lavage [234]; in situations where a clinician believes lavage may be appropriate, either AC or supportive care should be considered instead (Level II-2 recommendation).

Whole bowel irrigation prevents absorption by attempting to enhance the flow of xenobiotics through the gut. In order to achieve this, a nasogastric or orogastric tube must be placed. Large amounts, approximately 1–2 l/h, of osmotically balanced polyethylene glycol solution (PEG) are administered until the patient has at least two clear, liquid stools. Unlike other forms of GI decontamination, WBI may be started or continued in the ICU. Patients that have ingested sustained release preparations may be candidates for WBI in order to prevent delayed absorption; this is also why WBI may be considered in patients with bezoars. If patients are suspected of ingesting metals and have radiopaque foreign bodies on imaging, WBI may prevent absorption, as AC will not adsorb metal. Lastly, body packers are traditionally treated with WBI. Body packers internally smuggle large amounts of packets in order to smuggle narcotics. Should a packet leak, each one has a potentially lethal amount of drug in it. There are multiple retrospective case studies and cohorts in body packers that received WBI [244–246]. Interpretation of some of the literature is limited due to patients either refusing to drink

the PEG solution or WBI not recorded as being completed. While efficacy of WBI is difficult to interpret, no adverse events were reported in these studies; however, aspiration has been reported with WBI [247, 248]. In body packers, WBI should be initiated in order to remove the packets as soon as possible, given the life-threatening risk associated with even a single packet leaking. Contraindications include patients with an ileus or obstruction or an injury to their GI tract. While there are multiple reports suggesting that WBI can assist with the passage of tablets or packets, there is no evidence to support that WBI improves clinical outcomes [249]. The AACT and EAPCCT do not routinely recommend the use of WBI, but it can be considered in select situations (Level II-2 recommendation).

Antidotes

Most poisoned patients can be treated with standard supportive care, as detailed earlier. In certain instances specific therapy or antidotes are required. Specific therapies are described in subsequent chapters dealing with specific substances. Properties of specific antidotes are described in chapters at the end of the book. Some antidotes that may be administered in the ICU are listed in Table 8.

Table 8 Examples of antidotes that may be used in the ICU

Toxin/poison	Antidotes
α-2 agonist (clonidine, guanfacine, guanabenz, tizanidine, methyl dopa)	Naloxone
Acetaminophen	N-acetylcysteine
Anticholinergic agents	Physostigmine
Benzodiazepines	Flumazenil (with caution)
β-Adrenergic blocking agents	Glucagon Lipid emulsion therapy
Black widow envenomation	Latrodectus antivenin
Botulism	Botulin antitoxin
Calcium channel antagonists	Calcium Glucagon

(continued)

Table 8 (continued)

Toxin/poison	Antidotes
	Insulin and glucose
	Methylene blue (amlodipine)
	Lipid emulsion therapy
Carbamate insecticides	Atropine
Carbon monoxide	Oxygen or hyperbaric oxygen
Cyanide	Amyl and sodium nitrites
	Hydroxocobalamin
	Sodium thiosulfate
Digoxin/digitoxin	Antidigoxin antibodies
Dystonic reactions	Diphenhydramine
	Benzotropine
Ethylene glycol	Ethanol
	Fomepizole
	Thiamine and pyridoxine
Fluoride	Calcium salts
Heparin	Protamine
Heavy metals	Dimercaprol (BAL)
	Penicillamine
	Dimercaptosuccinic acid (DMSA)
	Calcium ethylenediaminetetraacetic acid (EDTA)
	Dimercaptopropanesulfonic acid (DMPS)
Isoniazid/hydrazines (<i>Gyromitra</i>)	Pyridoxine
Iron	Deferoxamine
Methanol	Ethanol
	Fomepizole
	Folate or folinic acid
Methemoglobinemia	Methylene blue
Methotrexate, trimethoprim, pyrimethamine	Folinic acid
	Glucarpidase
New oral anticoagulants	Prothrombin complex concentrates (Xa inhibitors)
Opiates	Hemodialysis (dabigatran)
	Idarucizumab (dabigatran)
	Naloxone (methylnaltrexone only reverses opioid induced constipation)
Oral hypoglycemics	Glucose infusion
	Octreotide
Organophosphate insecticides	Atropine
	Pralidoxime/obidoxime
Rattlesnake envenomation	<i>Crotalidae antivenin</i>

(continued)

Table 8 (continued)

Toxin/poison	Antidotes
Scorpion envenomation	Anascorp [®] antivenin
Sodium channel blockade (TCAs, type I antiarrhythmics)	Sodium bicarbonate
	Hypertonic saline
Warfarin	Vitamin K
	Fresh frozen plasma

Subspecialty Care

In the United States, medical toxicology is a recognized subspecialty by the American Board of Medical Specialties. There are currently 500–600 board-certified practicing medical toxicologists in the United States. These individuals have the greatest experience in the care of critically poisoned patients. When available, on-site or telemedical consultation is recommended. In some areas highly specialized regional poison treatment centers have been established to which critically poisoned patients might be transferred.

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Extracorporeal Membrane Oxygenation and Cardiopulmonary Bypass in the Poisoned Patient

4

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Cardiopulmonary deterioration is a final common pathway of many life-threatening conditions, including those induced by toxins. Despite advances in resuscitation and critical care, severe pulmonary and cardiac failures are associated with a high risk of organ failure and death. Extracorporeal membrane oxygenation (ECMO) is a growing rescue modality for patients with acute reversible life-threatening cardiopulmonary conditions.

ECMO Principles

Extracorporeal membrane oxygenation (ECMO), also referred to as extracorporeal life support (ECLS), leverages the technological advances of intraoperative cardiopulmonary bypass to provide temporary, miniaturized, closed-circuit support in the intensive care unit. In most instances, ECMO is a rescue technique for severe but reversible heart or lung failure that is predicted to be imminently lethal despite conventional support. Prime ECMO candidates have acute, severe, but reversible cardiac or respiratory failure. In this context, ECMO provides physiologic support for anticipated native organ recovery. Underlying advanced, chronic organ dysfunction and age greater than 65 years are common relative contraindications based on decreased capacity to survive life-threatening illness in this group. Extracorporeal membrane oxygenation may also be used to bridge patients with irreversible cardiac or respiratory disease to a more durable form of support such as ventricular assist device (VAD) or heart or lung transplant.

The ECMO system consists of intravascular cannulae, an extracorporeal circuit with oxygenator that provides gas exchange, and a pump to drive blood flow (Table 1, Fig. 1). Cannulation configuration dictates the mode of support. Venovenous (VV) ECMO cannulation provides gas exchange for lung failure, while veno-arterial (VA) ECMO configuration supports both cardiac and pulmonary functions. Interposition of a hemodialysis limb in the ECMO circuit enables concurrent renal replacement therapy. Altered volume of distribution, drug adsorption to

Table 1 ECMO components

Drainage cannula
Large-bore circuit tubing
Blood pump
Control unit
Membrane oxygenator
Heater/cooler unit
Return cannula

ECMO components, and underlying organ dysfunction impact the pharmacokinetics of many therapeutic (and toxic) agents and highlight the need for clinical and laboratory monitoring [1].

Systemic anticoagulation with vigilant monitoring is generally required to prevent patient and circuit thrombosis and embolization. Heparinized circuits and high flow rates can abrogate the need for anticoagulation in some circumstances where systemic bleeding risk is high. Large vessel instrumentation and systemic anticoagulation underlie the significant risk of clinically important hemorrhage with this modality. Life-threatening hemorrhage occurs in up to 10 % of cases with intracranial hemorrhage impacting 4–6 % [2–4]. Other recognized complications are listed in Table 2. Peripheral percutaneous cannulation (i.e., jugular vein and femoral vein and artery) is preferred to limit infectious and bleeding complications compared to central thorax instrumentation. However, technical issues may prioritize central cannulation, especially in patients with an open chest or with severe lung dysfunction. Carotid artery cannulation also remains a viable option for neonates and children.

Extracorporeal membrane oxygenation is a unique high-intensity resource (Fig. 1) that is not available in all facilities. Early transfer to a capable center should be considered for patients whose clinical trajectory predicts possible need for this modality [5, 6]. Patient retrieval by ECMO teams, including cannulation prior to transport, is an option supported by some centers [7]. Dedicated ECMO clinicians manage patients on this modality. Extracorporeal membrane oxygenation-trained specialists or perfusionists provide continuous bedside management in concert with the intensive care unit staff. Specialty

Fig. 1 Adult male undergoing ECMO for viral cardiopulmonary failure (Courtesy of Sara Lookabill, PharmD)



Table 2 Potential complications of ECMO

Mechanical
Pump failure
Circuit interruption (bleeding, air embolization)
Circuit thrombosis and emboli
Heater failure (hypothermia)
Oxygenator failure
Surgical
Local and regional bleeding from large-bore vascular catheters
Vascular injury (transection and dissection)
Nidus for deep venous thrombosis formation
Vascular occlusion (central nervous system and distal limb ischemia)
Systemic
Bleeding at distant site due to anticoagulation (intracranial, gastrointestinal, pulmonary, mediastinal)
Thrombocytopenia
Hemolysis
Infection

ECMO physicians typically manage patient selection and ECMO support.

Anticipated meaningful recovery needs to be considered for ECMO candidacy. Advanced multi-organ failure, severe chronic organ dysfunction, and age greater than 65 years are common relative contraindications based on decreased capacity to survive severe life-threatening illness in patients with these characteristics. We advise multi-professional conference to clarify ECMO goals and patient eligibility prior to cannulation,

when time allows. A time limit of ECMO support should similarly be discussed with the care team and patient family based on expectation for recovery [8].

Veno-Venous ECMO (VV ECMO)

Veno-venous ECMO cannulation drains blood from the central circulation and reintroduces the blood to the proximal venous circulation following extracorporeal gas exchange via the artificial membrane oxygenator. In addition to providing critical blood oxygenation and carbon dioxide removal, reliance on extracorporeal gas exchange enables attenuation of ventilator support to avoid both ventilator-induced lung injury and adverse hemodynamic effects of aggressive ventilator support [9]. Because oxygenated blood is returned to the venous circulation in this configuration, systemic oxygen delivery is determined by native cardiac performance. Other than removing the untoward effects of mechanical ventilation, VV ECMO does not provide material cardiovascular support.

Clinical conditions requiring rescue VV ECMO are typically associated with severe bilateral lung disease. Severe hypoxemia due to acute respiratory distress syndrome (ARDS) stemming from a variety of insults and refractory

Table 3 Example clinical criteria for VV ECMO consideration

Criteria of lung failure
Refractory hypoxemia
PaO ₂ /FiO ₂ < 60 with FiO ₂ ≥ 80 % for > 3 h despite optimized mechanical ventilation
PaO ₂ /FiO ₂ < 80 with FiO ₂ ≥ 80 % for > 6 h despite optimized mechanical ventilation
PaO ₂ /FiO ₂ < 100 and PaCO ₂ ≥ 100 for > 1 h
Oxygen index [(FiO ₂ × mean airway pressure × 100)/PaO ₂] > 30–35
Refractory hypercapnia
pH < 7.2 with PaCO ₂ ≥ 80 for > 6 h despite optimized mechanical ventilation
Ventilator induced barotrauma or severe air leak syndrome
Relative contraindications to VV ECMO support
Acute respiratory failure with high mechanical ventilation setting > 7 days
Moderate to severe underlying cardiopulmonary disease
Additional severe organ dysfunction
Life expectancy due to premorbid disease < 6 months
Age > 65 years

hypercarbia in status asthmaticus are conditions where ECMO is a cost-effective treatment that improves survival [10]. Severe unilateral lung disease such as pneumonia, pulmonary contusion, and bronchopleural fistula can also result in life-threatening failure of pulmonary gas exchange. Individual center patient selection criteria for ECMO vary but are generally based on criteria predicting greater than 50–70 % mortality. Examples of candidate criteria for rescue VV ECMO are provided in Table 3.

Veno-Arterial ECMO (VA ECMO)

The return limb of veno-arterial ECMO distributes to a central systemic artery such that VA ECMO provides both gas exchange and artificial hemodynamic support similar to traditional cardiopulmonary bypass. Refractory cardiogenic shock is the clinical situation that prompts consideration for rescue VA ECMO. Typical acute conditions are myocardial infarction, refractory

Table 4 Example clinical criteria for VA ECMO consideration

Criteria of refractory cardiogenic shock
Sustained CI ≤ 2.2 with evidence of malperfusion despite optimization by volume resuscitation, inotropes, and vasopressors
Consideration of any alternative form of extracorporeal support (intra-aortic balloon pump, temporary ventricular assist device)
Minimal and reversible secondary organ dysfunction
Absolute contraindications
Known intracranial bleeding
Irrecoverable myocardial insult and not a candidate for transplant or ventricular assist device
Relative contraindications
Bleeding risk from anticoagulation
Age > 65 years
Life expectancy due to premorbid disease < 6 months
Chronic organ dysfunction that limits meaningful recovery (end-stage liver disease)
Peripheral vascular disease that limits vascular access

dysrhythmias, myocarditis, massive pulmonary embolus, cardiotoxic overdose, postcardiotomy shock, decompensated chronic heart failure, sepsis-induced cardiomyopathy, and deep hypothermia. Cardiac arrest represents the extreme case of shock and is an emerging focus of ECMO in the form of extracorporeal cardiopulmonary resuscitation. Extracorporeal cardiopulmonary resuscitation (ECPR) appears feasible in settings experienced with this modality but outcome evidence is purely observational to date [11, 12]. Examples of candidate criteria for rescue VA ECMO are provided in Table 4.

Unique and important clinical considerations for VA ECMO support include adequate peripheral arterial access to allow appropriate-sized arterial cannulation, heightened need for systemic anticoagulation to avoid intracardiac and arterial thromboembolism, and risk of differential regional hypoxemia with peripheral cannulation in patients with severe lung failure. Prioritized patient selection issues focus on early identification and ECMO implementation prior to irrecoverable organ failure and a distilled plan for durable cardiovascular support. Native heart recovery is a reasonable

expectation in some conditions (ECMO as a bridge to recovery). However, ECMO frequently bridges patients to a point where native function is incompletely restored. As such, longitudinal mechanical cardiac support options such as ventricular assist device (VAD), total artificial heart, or cardiac transplant candidacy should be discussed prior to ECMO cannulation, when time allows.

ECMO in Xenobiotic-Induced Cardiopulmonary Failure

Although not a novel therapeutic modality, the use of veno-venous or veno-arterial ECMO has recently gained more interest and momentum for treating toxin-induced pulmonary or combined cardiopulmonary failure. At one time, extracorporeal life support was rarely used to treat toxins due to the availability, timeliness, and invasive nature of instituting cardiopulmonary bypass. However, the advent of percutaneous vascular access rather than open chest techniques in the 1980s rendered ECLS more amenable for use outside of the operating room to aid in the treatment of severe xenobiotic intoxication. ECMO has since been used to treat a wide variety of pharmaceutical, chemical, environmental, and natural toxins. Over 170 ECMO cases involving greater than 50 xenobiotics appear in the English language medical literature (Tables 5 and 6).

The evidence to weigh the true value of ECMO for toxins is challenging. There are few experimental animal models (level III evidence), and the published clinical experience is comprised of case reports and a limited number of case series (level III evidence). Thus the level of evidence is low and there is significant publication bias especially due to the large proportion of single case reports. In reality however, the relatively low prevalence of toxin-induced cardiopulmonary failure precludes any large-scale definitive, prospective human study such as a randomized clinical trial. With these evidentiary limitations in mind, the majority of cases where ECMO was employed for refractory shock or outright cardiac arrest are associated with good outcomes.

Experimental Evidence

Three preclinical studies evaluated the efficacy of ECMO for toxin-induced shock (level III evidence). Each study utilized the veno-arterial ECMO technique that proved superior to other experimental treatments. One study involved lidocaine toxicity and two investigated cyclic antidepressants. In the lidocaine study, canines were poisoned with a large intravenous bolus (30 mg/kg) until animals developed cardiovascular collapse and then received either standard pharmacological resuscitation or ECMO for 90 min. All animals receiving ECMO treatment survived compared with only 25 % for those receiving standard treatment [89]. Extracorporeal life support increased survival (6/6 vs. 1/6 animals) and decreased vasopressor requirements in canines with desipramine-induced cardiac arrest versus standard advance cardiac life support drugs plus mechanical cardiopulmonary resuscitation (CPR) [90]. Swine infused with amitriptyline to induce severe shock were treated for 90–120 min with ECMO or standard pharmacological therapy. As in the first two studies, there was impressive survival in the ECMO group (100 vs. 10 %) at 6 h [91].

Although all three preclinical studies provide positive evidence for ECMO use in drug-induced cardiogenic shock and cardiac arrest, there are critical limitations to translating the impressive results in these models to the human experience. Foremost, there was no delay to ECMO in the models. Animals were instrumented prior to poisoning and treatment was immediately instituted upon reaching toxicity. This model does not replicate the human scenario where treatment delays to ECLS are expected. Secondly, these studies were conducted over relatively short durations (hours) and did not assess for long-term clinical outcomes such as neurological outcome or complications due to therapy itself. Lastly, the trials evaluated one local anesthetic and two cyclic antidepressants. No other common cardiovascular xenobiotics have been studied in this manner.

Table 5 Case report summaries

Xenobiotic ^a	Age	VV vs. VA ECMO	Duration	Other treatments C,G,HD,HDI,L,TH	Complications	Survival	Neurological outcome
Acebutolol [13]	27 years	VA	12 h	G,HD,V	DVT	Yes	No comment
Ajmaline [14]	27 years	VA	43 h	TH	No comment	Yes	Cognitive dysfunction, paraplegia at 1 year FU
Amiodarone [15]	37 weeks	VA	36 h	Not specified	No complications	Yes	Normal at 1 year FU
Amiodarone [16]	65 years	VV	16 days	Not specified	No comment	Yes	No comment
Amlodipine [17]	50 years	VA	8 days	C,G,HD,HDI,L,MB, V	No complications	Yes	Normal at discharge hospital day 56
Amlodipine, amitriptyline, carvedilol [18]	21 years	VA	5 days	C,G,HDI,TH,V Plasmapheresis	No comment	Yes	Normal at discharge
Arsenic [19]	4 months	VA	36 h	HD,V Chelation	No comment	No	
Atenolol [20]	44 years	VA	48 h	C,G,HD,V	Mild hemolysis	Yes	Normal at discharge hospital day 12
Betaxolol [21]	38 years	VA	4 days	G,HD,V	Bleeding, limb ischemia	Yes	Femoral nerve paralysis
Bupivacaine [22]	27 years	VA	1.5 h	C,V	Low flow rates, extremity dysesthesia	Yes	Normal at 1 year FU
Bupropion [23]	11 months	VA	71 h	L,V	No comment	Yes	Normal at 1 year FU
Bupropion [24]	15 years 16 years	VA, VV VA	10 days 3 days	CPR,V,HD CPR,V,L	Pulmonary hemorrhage Compartment syndrome, rhabdomyolysis	Yes yes	No CNS injury at DC hospital day 24 Normal mental at discharge hospital day 16
Carbamazepine [25]	26 years	VA	6 days	T(12u),V	Bleeding, thrombosis, DIC	Yes	Normal at 2 years FU
Carbon monoxide/ smoke inhalation [26]	34 years	VV	7 days	V	No comment	Yes	Normal at discharge
Chloroquine [27]	24 years	VA	Unknown	L,V	No complications	No	
Cocaine [28]	22 years	VA	7 days	V	No comment	Yes	No comment
Colchicine [29]	68 years	VA	10 days	V	Bleeding	Yes	Normal at transfer out of ICU hospital day 26
Colchicine [30]	51 years	VA	10 days	HD,V	No comment	Yes	CPC 1 at discharge hospital day 52
Colchicine [31]	50 years	VA(?)	1 day	T("massive"),V	Bleeding	No	
Cyclophosphamide [32]	4 years	VA	5 days		Intracerebral and myocardial bleeding	No	
Desipramine [33]	18 months	VA	36 h	C,V Pacemaker	No complications	Yes	Normal at 6 months FU
Digoxin [34]	65 years	VA	4 h	V Digoxin Fab	No comment	No	
Diltiazem [35]	16 years	VA	48 h	C,G,V	Bleeding	Yes	Normal at 2 months FU
Diltiazem [36]	36 years	VA	8 days	C,G,HDI,V Pacemaker	Thrombocytopenia, bleeding, compartment syndrome	No	
Fentanyl [37]	23 years	VV	5 days		Upper-extremity DVT	Yes	Normal at discharge
Flecainide [38]	30 years	VA	24 h	V Pacemaker	Bleeding, coagulopathy	Yes	Normal at discharge

(continued)

Table 5 (continued)

Xenobiotic ^a	Age	VV vs. VA ECMO	Duration	Other treatments C,G,HD,HDI,L,TH	Complications	Survival	Neurological outcome
Flecainide [39]	20 years	VA	30 h	V Pacemaker	Coagulopathy, thrombosis, neuropathy	Yes	
Flecainide [40]	7 months	VA	24 h	L,V,TH	No comment	Yes	No comment
Flecainide [41]	52 years	VA	24 h	L Pacemaker prior to ECMO	No complications	Yes	CPC 1 at discharge
Flecainide [42]	20 years	VA	10 h	Pacemaker	Bleeding	No	
Flecainide/ acebutolol [43]	55 years	VA	Unknown	G,HD,L,V	Bleeding	Yes	Normal at discharge
Flecainide/ betaxolol [44]	40 years	VA	48 h	G,V	No comment	No	Cardiac, renal, liver harvested for transplant day 4. 45 months after transplants, all organs functioning normally
5-Fluorouracil [45]	32 years	VA	6 days	V	No comment	Yes	No comment
Hydrocarbon pneumonitis [46]	16 months 17 months 13 months	VA VA VA	13 days 19 days 25 days		Bleeding Bleeding Bleeding	No No no	
Hydrocarbon pneumonitis [47]	19 pt 10–18 months	VA	6–26 days		Bleeding (32 %) Hemolysis (26 %) Mechanical comps (26 %)	13/19	No comment
Hydrocarbon pneumonitis [48]	15 months 16 months	VA VA	12 days 7 days	L(TPN),V V	Bleeding, coagulopathy No complications	Yes Yes	Hemiparesis, seizures Normal at 6 weeks FU
Ibuprofen [49]	14 years	VA	4 days	G,V,T(10u)	Bleeding	Yes	Normal at discharge hospital day 9
Imipramine [50]	37 years	VA	7 h	V	No complications (due to ECMO), but pt developed bowel ischemia leading to demise at 4 weeks	No	
Lidocaine [51]	20 months	?	14 days		Bleeding	Yes	Normal at 1 year FU
Marijuana [52]	27 years 20 years	VA VV	35 days 10 days		Pneumothorax, hemothorax No comment	Yes Yes	Mild pulmonary dysfunction 6 months after DC Mild pulmonary dysfunction 3 months after DC
Mepivacaine [53]	9 months	VA	4 days	C,V	No complications	Yes	Normal at discharge hospital day 14
Methadone [54]	16 years 19 years	VA VA	3 days 3 days	None V	Foot drop due to cannula No complications	Yes Yes	Foot drop Normal at discharge
Metoprolol [55]	47 years	VA	3 days	C,G,HDI,L,V	No comment	Yes	Normal at discharge hospital day 10
Nitric acid [56]	56 years	VA	4 days		Limb ischemia	No	
Organophosphate [57]	50 years	VA	39 h	V Oxime, hemoperfusion	No comment	Yes	No comment

(continued)

Table 5 (continued)

Xenobiotic ^a	Age	VV vs. VA ECMO	Duration	Other treatments C,G,HD,HDI,L,TH	Complications	Survival	Neurological outcome
Paraquat [58]	23 years	VV, VA	8, 12 days	HD, immunosuppression	No comment	No	Died with multisystem organ failure awaiting transplant
Paraquat [59]	24 years	VV	12 days	HP, immunosuppression, transplant	No comment	Yes	Alive and well 1 year after transplant
Paraquat [60]	31 years	VV	5, 19 days	HD, HP, immunosuppression, transplant	No comment	No	CVA 3 months after second lung transplant
Phosphine gas [61]	15 months	VA	2 days		No comment	No	Care withdrawn due to poor neurological exam
Prajaline [62]	25 years	VA	17 h	“Conventional treatment” Hemoperfusion	No comment	Yes	Ataxia and cognitive dysfunction at discharge hospital day 35
Propranolol [63]	1 month	VA	5 days	V Peritoneal dialysis	No complications	Yes	Normal at discharge
Propranolol [64]	20 years	VA	10 h	G,V Pacemaker	No comment	Yes	Normal at discharge
Quetiapine [65]	40 years	VA	48 h	HD,V	No comment	Yes	Normal at discharge hospital day 10
Quinidine [66]	16 months	VA	12 days	HD,V Pacemaker	No comment	Yes	Normal at hospital discharge day 30
Radiocontrast [67]	62 years	VV	52 h	V	No comment	Yes	No comment
Taxine[68]	44 years	VA	3 days	V Pacemaker	No comment	Yes	Normal at discharge hospital day 17
Taxine [69]	46 years	VA	50 h	V	No comment	Yes	Normal at discharge hospital day 7
Taxine [70]	19 years	VA	36 h	TH,V Digoxin Fab	No comment	Yes	Normal at discharge hospital day 12
Tramadol [71]	33 years	VA	8 days	HD,V	No comment	Yes	No comment
Tramadol [72]	22 years	VA	7 days	No comment	No comment	Yes	Normal at discharge hospital day 35
Verapamil [73]	15 years	VA	Unknown	C,HD,HDI,L,V	No comment	Yes	Normal at discharge
Verapamil [74]	25 months	VA	4 h	C,V Pacemaker	No comment	No	
Verapamil [75]	41 years	VA	5 h	C,G,V Pacemaker pre-ECMO	No comment	Yes	Normal at 6 months FU
Verapamil [76]	51 years	VA	4 days	C,L,V Pacemaker plasmapheresis	ECMO filter changes attributed to lipid infusion	Yes	Alert at discharge hospital day 18
Verapamil [77]	45 years	VA	6 days	C,G,HD,V Plasmapheresis	No comment	Yes	Normal at discharge hospital day 14
Verapamil/sotalol [78]	29 years	VA	2 days	C,G,HD,HDI,V Pacemaker	Bleeding, rhabdomyolysis, forearm compartment syndrome	Yes	Minimal left arm dysfunction at 6 months FU
Zinc chloride [79]	23 years	VV	17 days	Steroids	No comment	Yes	No comment

^aPlease refer to the manuscripts for other coingestants

Abbreviations: C calcium, G glucagon, HD hemodialysis, HDI high-dose insulin, HP hemoperfusion, L intravenous fat emulsion, MB methylene blue, T transfusion (no. units), V vasopressors

Table 6 Case series summaries

Citation	N subjects (tox vs. nontox)	Xenobiotics	Shock	CA	Age range (mean; range)	CPR duration (mean; range)	Duration (mean; range)	Survival to DC (tox vs. nontox)
Chyka 1994 [47]	24:0	Hydrocarbon pneumonitis	na	na	10–18 months	na	12 days; 6–26	15/24 (63 %)
Massetti 2000 [80]	7:0	Antidysrhythmics	0	7	Unknown	79 min; na	57 h; na	5/7 (71 %)
Massetti 2005 [81]	6:34	“Medical intoxication”	0	6	Survivors 35 years; na	Survivors 129 min; 45–170	Survivors 91 h; 20–240	4/6 vs. 4/34 (66 vs. 12 %)
Megarbane 2007 [82]	12:5	Acebutolol (3) Chloroquine (2) Colchicine (1) Flecainide (2) Propoxyphene (1) Propranolol (1) Verapamil (2)	0	12	49 years; 33–59	120 min; 45–180	56 h; 5–108	3/12 vs. 0/5 (25 vs. 0 %)
Daubin 2009 [83]	17:0	Acebutolol (2) Cibenzoline (1) Disopyramide (2) Flecainide (1) Metoprolol (1) Propafenone (1) Propranolol (3) Sotalol (1) TCA (1) Tramadol (1) Verapamil (4)	10	7	39 years; na	101 min; 50–170	5 days; 2–11	13/17 (77 %) shock: 8/10 (80 %) CA: 5/7 (71 %)
Vanzetto 2009 [84]	6:65	Chloroquine (1) Diuretic (1) Hydroxychloroquine (1) Propafenone (1) Plauromecresol (1) TCA (1)			Medical cases 49 years; na	medical cases 49 min; na	35 h; 5–96	? (66 %)
Masson 2012 [85]	14:0		12	2	na	na	6 +/– 2.9 days	12/14 (86 %)
Mohan 2015 [86]	7:0	Aluminum phosphide			36 years; 17–50		74 h; 43–144	5/7 (71 %)
Wang 2015 [87]	10:0	Bitter almond (1) CO/smoke (2) Diphenhydramine (2) Flecainide (1) Metformin (2) Methanol (1) Verapamil (1)	1	3	17 years; 0.5–48	na	7 days; 0.5–12	8/10 (80 %)
Brunet 2015 [88]	19:45	Severe drug intoxication	?	?	?	?	?	15/19 vs. 9/45 (79 vs. 20 %)

Clinical Reports

Early ECMO for humans began primarily with toxin-induced lung injury and ARDS in children, owing to the prior experience with ECMO for neonatal lung dysfunction. Survival from hydrocarbon pneumonitis varied in initial papers: 0 % and 63 % [46, 47]. The application of ECMO has since broadened to a variety of other xenobiotics and ages following the early experience. The majority of published cases now involve direct cardiovascular toxins historically associated with high morbidity and mortality such as β -adrenergic blocking drugs, calcium channel antagonists, and sodium channel antagonist drugs. Extracorporeal membrane oxygenation was employed in cases of acute respiratory distress syndrome and cardiopulmonary failure due to other drug classes including analgesics, antimalarials, newer antidepressants, chemotherapeutics, and other miscellaneous agents. Environmental and chemical exposures have been managed with ECMO as well (Tables 5 and 6).

While both veno-venous and veno-arterial ECMO are utilized, the vast majority of toxic cases were managed with the veno-arterial modality. The duration of ECMO therapy in cases of direct myocardial toxins varies in the modern series, averaging between 35 h and 7 days [80, 82–87]. The shortest ECMO use (1.5 h) was described during intraoperative resuscitation of bupivacaine toxicity [22]. Extracorporeal membrane oxygenation requirement is generally longer in the treatment of primary and secondary pulmonary injury [47]. The longest duration (35 days) involved a complicated case of marijuana/phencyclidine lung injury [52].

Clinical outcome has improved since the initial publications: likely a reflection of wider availability and better technology. Observational series published after 2000 demonstrate survival rates averaging 68 % and ranging from 25 % to 86 % [80–88]. Interestingly, the majority of these cases experienced cardiac arrest before or at the time ECMO was initiated. Extracorporeal membrane oxygenation was often delayed during resuscitation with CPR averaging 79–120 min in three series [80, 82, 83]. Cardiopulmonary resuscitation duration ranged from 45 to 180 min [82, 83].

Although details regarding quality of life associated with successful ECMO are not always provided or described in a systematic fashion, long-term outcome and function are generally good. Of 20 survivors in three combined series, 16 had cerebral performance category (CPC) score 1 and four survivors had CPC score 2, indicating normal and near-normal function, respectively [81–83]. In another series, all survivors, including xenobiotic-related cases, were described as alive and well without neurological sequelae at follow-up (mean 17 months) [84].

Direct-Acting Cardioactive Agents

The majority of individual cases and published series involve direct-acting cardiac toxins including antidysrhythmics [14, 15, 62, 66], β -adrenergic blockers [13, 18, 20, 21, 43, 44, 55, 63, 64, 78], calcium channel antagonists [17, 18, 35, 36, 73–78], digoxin [34], local anesthetics [22, 51, 53], and both sodium channel agonists and antagonists [18, 22, 24, 25, 28, 33, 38–44, 50, 68–70]. In ECMO series containing both toxic and nontoxic causes of cardiopulmonary failure, outcomes are significantly higher for patients with a toxic etiology. In three series totaling 120 patients, 22/37 (59 %) with toxin-induced cardiopulmonary failure survived versus 13/83 (16 %) that were due to medical causes of failure (coronary ischemia, dysrhythmia, cardiomyopathy) [81, 82, 88]. The greater survival was attributed to the temporary nature of xenobiotic intoxication. Coronary artery disease produces myocardial injury that may or may not be reversible. Toxins on the other hand typically interfere with receptor or ion channel activity and this dysfunction can be reversed with specific or supportive therapy. Thus, drug-induced cardiovascular collapse may be an optimal targeted use for ECMO.

Direct Pulmonary Toxins

Extracorporeal membrane oxygenation may be used to treat primary and secondary toxin-related lung injury. The toxic lung insults may occur due

to a variety of mechanisms. Ideally, veno-venous ECMO may be used to restore adequate oxygen delivery to tissues until pulmonary tissue recovers. However, veno-arterial ECMO was utilized in the majority of the cases and series where there was a toxic lung injury. Extracorporeal membrane oxygenation requirement for pulmonary toxicity is generally longer than that of direct myocardial toxins: up to 35 days in one recent report of ARDS after smoking marijuana and phencyclidine that was dipped in embalming fluid [52]. This is likely due to the presence of tissue injury following pulmonary toxin exposure rather than reversible receptor dysfunction in the case of myocardial toxins.

Childhood hydrocarbon exposure is common as a result of accidental ingestion. The earliest experiences with ECMO were derived from treating hydrocarbon-induced lung injury and associated complications in children. Hydrocarbons interfere with surfactant that leads to altered compliance and also initiate tissue inflammation. Both processes decrease gas exchange and result in inadequate ventilation and hypoxia. Although most patients experience mild to moderate pneumonitis, some patients may progress to fulminant respiratory failure. Veno-venous or veno-arterial ECMO was applied to 24 children with hydrocarbon pneumonitis refractory to supportive measures [46, 47, 48]. Extracorporeal membrane oxygenation duration in these patients averaged 13 days (range 6–26 days). Outcome was generally good: 19 of 24 patients survived.

Extracorporeal membrane oxygenation has been used in three cases of severe pulmonary toxicity following the ingestion of the bipyridyl herbicide, paraquat [58–60]. Paraquat may injure mucous membranes, kidneys, muscle, and lungs. Of these targeted organs, lung injury is primarily responsible for mortality. Paraquat has a unique mechanism that involves accumulation of the herbicide in lung tissue and generation of free radicals that selectively injure type I pneumocytes. The clinical expression of the injury is progressive pulmonary fibrosis that may be rapid and irreversible. Reported mortality is high: 30–80 % depending on the dose [92, 93]. Survivors may suffer long-term restrictive pulmonary

dysfunction [93, 94]. Although a variety of pharmacological therapies have been used and studied, there are no proven antidotes. With few alternatives, patients with fulminant pulmonary failure have undergone lung transplant [58–60, 95–97]. Initial transplant attempts failed [60, 95, 96]. These early failures may have been due to challenging surgery and immunosuppression for the time period. One other contributing factor may have been persistent paraquat in the tissues that injured the transplanted lung. Paraquat has been detected in the lung and muscle 6–59 days after exposure [59, 96, 97]. In some cases, it was present in the tissue, but absent in serum [97].

In one report, veno-venous ECMO was used on two separate occasions until transplant [60]. Extracorporeal membrane oxygenation supported the patient for 8 days prior to transplant. However, the transplant failed with evidence of paraquat toxicity. Extracorporeal membrane oxygenation was reinstituted for 19 days until a second transplant took place. The patient died of myopathy and surgical complications 3 months after the second transplant. Because of the potential to injure the transplanted tissue, another group advocates delayed transplant as long as possible until paraquat is cleared using ECMO as bridge [58]. In their case, veno-venous followed by veno-arterial ECMO sustained the patient for 20 days. Unfortunately, the patient died awaiting a donor. In the third case, a patient was started on ECMO on hospital day 44 and then maintained on veno-venous ECMO for 12 days until successfully transplanted 56 days post-ingestion [59]. Interestingly, the explanted lung still contained measurable paraquat. Although the persistence of paraquat is variable and optimal timing of transplant after exposure is undefined, these cases demonstrate that ECMO can successfully serve as a bridge to transplant for a sustained period of time. Paraquat-induced pulmonary injury is discussed in greater detail in the paraquat and diquat chapter.

Extracorporeal membrane oxygenation was used in severe pulmonary injury due to other xenobiotics including amiodarone [16], carbon monoxide/smoke inhalation [26, 87], nitric acid [56], radiocontrast [67], tainted marijuana/phencyclidine

[52], and zinc chloride [79]. It was successful for the cases involving amiodarone, carbon monoxide/smoke inhalation, marijuana/phencyclidine, radio-contrast, and zinc chloride.

Anti-inflammatory Drugs

Colchicine is an antimitotic drug used to treat gout, pericarditis, and Familial Mediterranean fever. It has a low therapeutic index and, following therapeutic misadventure or large ingestion, may cause multisystem organ failure that includes cardiogenic shock and dysrhythmias. Mortality is high in cases when there is multi-organ involvement. Extracorporeal membrane oxygenation was used to treat three intentional colchicine overdoses and an accidental ingestion of *Colchicum autumnale* [29–31, 82]. Cardiogenic shock developed in all cases. Two received 10 days of ECMO support and survived with normal cardiac and neurological function [29, 30]. The third patient experienced extraordinarily rapid collapse in the first few hours after overdose and received less than 24 h of ECMO support, and care was withdrawn on hospital day 2 after massive bleeding [31]. Extracorporeal membrane oxygenation duration was not specified in the fourth case [82].

A massive, intentional ibuprofen ingestion with severe hypotension and acidosis received 4 days of ECMO and survived [49].

Antimalarials

Acute ingestion of the antimalarial/immunosuppressive drugs, chloroquine and hydroxychloroquine has resulted in refractory cardiac dysrhythmias and shock due to myocardial sodium channel inhibition and potassium channel dysfunction. One might surmise that ECMO is a viable treatment option for severe chloroquine and hydroxychloroquine toxicity based on their underlying cardiac mechanism and good outcomes following ECMO use in other direct-acting cardiac agents. However, ECMO use was unsuccessful in three cases [27, 82].

Chemotherapeutic Agents

Cardiogenic shock and dysrhythmias are well-recognized complications during chemotherapy with cyclophosphamide, a nitrogen mustard, and 5-fluorouracil, a pyrimidine analogue. Extracorporeal membrane oxygenation support for 6 days allowed myocardial function to recover from 5-fluorouracil toxicity and the patient survived [45]. In a case of cyclophosphamide-induced cardiogenic shock with pericardial effusion and cardiac arrest, 5 days of veno-arterial ECMO permitted myocardial recovery [32]. However, the clinical course was complicated by intracranial bleeding and care was eventually withdrawn.

Newer Antidepressants

Bupropion is a cathinone derivative with antidepressant activity due to dopamine, serotonin, and norepinephrine reuptake inhibition. Toxicity affects the central nervous system (agitation, seizures) and cardiovascular system (ventricular dysrhythmias, initial hypertension, hypotension). In rare cases, cardiogenic shock may occur. In three cases of severe bupropion toxicity, healthcare providers incorporated ECMO into resuscitation. One case resulted from an accidental ingestion that developed persistent hypoxia and hypotension [23]. Two other cases resulted in cardiogenic shock after intentional ingestion [24]. All three patients survived without evidence of neurological injury. One patient had residual leg weakness related to cannula placement and required rehabilitation [24].

Opioid Analgesics

Opioid overdose may infrequently result in severe ARDS and, even more rarely, combined cardiopulmonary failure. Veno-venous and veno-arterial ECMO was used in five such cases that included dextropropoxyphene [82], fentanyl [37], methadone (two cases) [54], and tramadol [71, 72]. All of the patients survived with good outcome except for the dextropropoxyphene ingestion.

Pesticides

In addition to paraquat, previously highlighted in the direct pulmonary toxin section, ECMO has been used to treat aluminum phosphide and organophosphorus compound exposures. Aluminum phosphide is a common fumigant that may cause multisystem injury due to inhibition of enzymes, inhibition of oxidative phosphorylation, and depletion of antioxidant compounds. The acute respiratory distress syndrome and cardiovascular shock may occur. When cardiogenic shock is present, mortality approaches 70 % [86]. In one pediatric exposure that resulted from lawn fumigation with aluminum phosphide, ECMO was started but care was withdrawn due to severe neurological injury [61]. In a case series involving intentional ingestion, ECMO appeared beneficial [86]. Seven patients received ECMO for an average of 74 h (range 43–144 h) to treat acidemia and cardiogenic shock. Five of seven survived and were reported to do well at 2–8 months of follow-up.

Following intentional ingestion of a commercial mixture of fenitrothion/malathion insecticide complicated by environmental hypothermia, a patient underwent 39 h of ECMO (with aortic balloon pump) for refractory hypotension and rewarming. The patient survived [57].

Plants

Numerous plants contain cardioactive compounds that may result in toxicity after intentional ingestion of extracts, teas, or the plants themselves. The yew (*Taxus* species) is a coniferous shrub that contains taxine, a cardiotoxic alkaloid. Ingestion of the leaves may result in ventricular dysrhythmias due to interference with sodium and calcium channel activity. Three patients that intentionally ingested yew survived ventricular dysrhythmias, ventricular failure, and cardiac arrest following management that included veno-arterial ECMO [68–70]. One case of accidental *Colchicum autumnale* ingestion was treated with ECMO as discussed in the anti-inflammatory section [29]. Although there are no current published cases of ECMO use for plant-related digitalis

toxicity, it could potentially be used to treat severe cardiac glycoside exposure based on anecdotal experience with pharmaceutical digoxin overdose [34]. Several species such as foxglove, oleander, and squill contain cardioactive glycosides that can result in typical digitalis cardiotoxicity following ingestion and, in severe toxicity that is refractory to immunotherapy, might benefit from ECLS.

Miscellaneous Xenobiotics

ECMO has been undertaken following exposures to arsenic [19], carbamazepine [25], diphenhydramine [87], metformin [87], methanol [87], and quetiapine [65].

Bridge to Organ Donation

Extracorporeal membrane oxygenation served as a bridge to organ harvesting after intentional ingestion of flecainide and betaxolol [44]. In this case, veno-arterial ECMO facilitated critical organ recovery in a neurologically devastated patient. The heart, kidneys, and liver were successfully transplanted and demonstrated normal function in each recipient at 45 months of follow-up.

Complications

Complications due to the ECMO procedure are common and can be life threatening. Of 67 case reports (73 total cases) that were reviewed for this chapter, 27 report one or more complications (see Tables 5 and 7). In ten cases, authors specifically state that there were none [15, 17, 27, 33, 41, 48, 50, 53, 54, 63]. The remainder do not discuss the presence or absence of complications. The complications observed following ECMO in these cases and several case series are similar to those associated with nontoxic-related ECMO experience with bleeding being the most common [21, 25, 29, 31, 32, 35, 36, 38, 42, 43, 45–49, 51, 78, 82–85]. The bleeding complication rate in the nine published case series (103 total patients)

Table 7 Case series of complications and neurological outcomes associated with ECMO

Citation	All complications	Neurological outcomes for toxic survivors
Chyka 1994 [47]	Bleeding (32 %), hemolysis (26 %), mechanical (26 %)	No comment
Masseti 2000 [80]	Limb ischemia, compartment syndrome	No comment
Masetti 2005 [81]	Bleeding (17 %), limb ischemia, compartment syndrome	4/4 CPC 1
Megarbane 2007 [82]	Bleeding (47 %)	3/3 CPC 1
Daubin 2009 [83]	Bleeding, limb ischemia, thromboses	9 CPC 1, 4 CPC 2
Vanzetto 2009 [84]	Bleeding, limb ischemia	No serious sequelae at mean 17 months FU
Masson 2012 [85]	Bleeding (14 %), limb ischemia (29 %), thromboses (7 %)	
Mohan 2015 [86]	Bleeding (100 %), thrombocytopenia (29 %)	“Doing well” at 2–8 months FU
Wang 2015 [87]	na	na
Brunet 2015 [88]	Unable to discern in toxicology cases	88 % alive 1 year for entire pt cohort

ranged from 12 % to 71 % [47, 81–86]. Bleeding may be local or systemic. Although percutaneous vascular access has widened the availability of ECMO, the large-bore vascular catheters are the most common source of bleeding complications. Bleeding may occur at the percutaneous site and, less frequently, into adjacent tissues such as the mediastinum or retroperitoneum. Anticoagulation is necessary during ECMO and may lead to additional bleeding sites including the brain, peritoneum, lung, myocardium, and gastrointestinal tract. Large-volume transfusion and/or surgery is often required to correct the bleeding [25, 31, 35, 49, 81, 82, 84–86]. One additional downside to

percutaneous access is vascular occlusive events due to placement of large-bore catheters needed to maintain adequate blood flow. Limb ischemia is common, sometimes leading to compartment syndrome and necessitating fasciotomy and surgical revascularization [21, 36, 56, 78, 81, 83]. The frequency of limb ischemia and related complications may be decreased when ECMO access is modified to include placement of a second vascular catheter that maintains distal limb flow [80]. The placement of large-bore vascular catheters has caused extremity nerve palsies [22, 24, 54]. Large vessel thrombotic events may occur as well even in the face of anticoagulation [13, 25, 37, 39, 83]. Hemolysis is reported [20, 47]. Coagulopathy occurs [25, 38, 39, 48]. Lastly, mechanical events related to the pumps, oxygenator, heater, and lines are reported [22, 47, 76].

Compatibility

Extracorporeal membrane oxygenation is never used in isolation for resuscitating xenobiotic pulmonary or cardiopulmonary failure; all of the toxic-related cases also received pharmacological agents (antidotes, antidysrhythmics, vasopressors, and supportive drugs) or other technology-based treatments (cardiac pacing, dialysis, therapeutic hypothermia).

Pharmacokinetic Considerations

Currently, there is very limited experience and understanding (primarily in the neonatal ECMO literature) with how pharmacological and technological treatments impact each other. Concomitant use of specific toxicological pharmacotherapy during ECMO includes calcium [17, 18, 20, 22, 35, 36, 53, 73, 75, 78], chelation [19], digoxin Fab [34, 70], glucagon [13, 17, 18, 20, 21, 35, 36, 44, 49, 55, 64, 75, 78], high-dose insulin [17, 18, 36, 55, 73, 78], methylene blue [17], and oxime [57]. None of these reports address kinetics, complications, effectiveness, or toxicity of these antidotes related to ECMO.

Several factors that are often encountered with critically ill patients or related to the ECMO procedure itself may impact antidote pharmacokinetics. For example, patients with cardiopulmonary failure frequently have multi-organ dysfunction, especially liver and renal dysfunction, with subsequent impaired drug metabolism and elimination. ECMO itself affects drug behavior. The pump, circuitry tubing, oxygenator, gas exchange unit, and filters create additional volume that is not accounted for in weight-based dosing, resulting in xenobiotic dilution and apparent increased drug volume of distribution [98–100]. This is likely more pronounced in children than in adults. Extracorporeal membrane oxygenation circuitry sequesters many xenobiotics, resulting in xenobiotic loss as demonstrated in *ex vivo* studies of pediatric [101–105] and adult patients [106]. In these reports, ECMO circuits used polyvinylchloride and silicone tubing with crystalloid and/or blood as circuit priming agents. Each study demonstrated some degree of drug loss to the circuit including anticonvulsants (fosphenytoin, phenytoin), analgesics (fentanyl, morphine), anticoagulants (heparin), sedatives (diazepam, lorazepam, midazolam, propofol), and vasopressors (dopamine, epinephrine). Clinically, this translates to challenges in anticoagulation and sedation drug dosing during ECMO. Heparin requirements are greater for neonates while on ECMO [107]. Sedative drug dose requirements are also increased in order to achieve adequate patient comfort and safety during ECMO [108]. Although not directly studied in ECMO, insulin is also known to bind to intravenous tubing and glass, possibly affecting high-dose insulin [109, 110]. No preclinical or clinical studies address sequestration of antidotes used to resuscitate drug-induced cardiopulmonary failure. Thus, the compatibility or impact of ECMO on antidote pharmacokinetics and dynamics remains largely unknown in this evolving technology.

Intravenous fat emulsion infusion (“lipid rescue”) is sometimes used in an attempt to reverse severe drug-induced cardiotoxicity, possibly by serving as a lipid sink that removes lipophilic compounds from target tissues [111, 112]. Additionally,

critically ill patients often require prolonged hospitalization, so lipid emulsions may be given for nutritional support while undergoing ECMO. These concentrated fat emulsions have potential to complicate or interfere with ECMO. Rescue lipids are known to interfere with routine laboratory analysis and may result in fat deposition in the lungs [113]. In two *in vitro* studies and a clinical series, investigators inspected ECMO circuits during and after 24 h of lipid infusion and found fat deposition in areas of low flow, broken stop cocks, and blood clotting within the oxygenator despite anticoagulation [114–116]. To decrease the interference with ECMO, neonatologists recommend infusing nutritional lipid therapy separately into patients and not directly into the ECMO circuit [114, 115]. Lipids and ECLS were used in twelve cases involving seven adults and five children [17, 23, 24, 27, 36, 40, 41, 43, 48, 55, 73, 76]. Twelve involved acute lipid rescue therapy prior to or during ECMO and one child received fat emulsion for nutritional support while undergoing ECMO [48]. In four cases, authors specifically commented (in the manuscript or via personal communication with this chapter authors) that lipid infusion was uncomplicated [17, 24, 27, 55]. Minor complications occurred in two instances: lab interference [27] and need for multiple ECMO filter changes [76]. Although there are potential complications with intravenous lipid infusion during ECMO, the current literature suggests that lipid rescue may be lifesaving for lipophilic cardiovascular toxins, and the limited downside of infused lipid should not prevent its use in appropriate circumstances when ECMO is also under consideration.

Concomitant Use of Other Technological Treatments

Extracorporeal drug elimination measures such as high-flux hemodialysis, continuous veno-venous hemofiltration, continuous renal replacement therapy, charcoal hemoperfusion, and plasmapheresis can be added to the ECMO circuit [13, 18–21, 24, 30, 43, 57, 62, 65, 66, 71, 73, 76–78, 86]. The primary indication for dialysis in most of these

cases was acute renal injury and metabolic acidosis. There were no unexpected complications due to simultaneous use of ECMO and the various dialysis techniques. In several cases, ECMO stabilized hemodynamics allowing for effective extracorporeal drug clearance [13, 20, 73].

Transvenous pacemaker was used in thirteen cases [18, 33, 36, 38, 39, 41, 42, 64, 66, 68, 74, 76, 78] and successfully increased heart rate in four [18, 33, 36, 76] and transiently in two patients [66, 74]. Failure of pacemaker capture in the remaining cases was most likely related to the drug insult rather than the ECMO procedure.

Therapeutic hypothermia involves cooling post-cardiac arrest patients to target temperature of 32–34 °C to protect the brain from ischemic reperfusion phenomenon. Two recent series discuss the experience with therapeutic hypothermia for xenobiotic-induced cardiac arrest [117, 118]. As many toxin-related ECMO cases experienced cardiac arrest prior to starting ECMO, it is not surprising that therapeutic hypothermia and ECMO have begun to intersect. Both treatments were used in four adults [14, 18, 55, 70] and in one child [40]. None of these reports describe complications due to simultaneous use of these two therapies. However, cooling to target temperature impacts drug behavior and may further complicate pharmacokinetics of resuscitation when used alongside with ECLS. The limited pharmacokinetic understanding with therapeutic hypothermia suggests both similar and opposing effects on drug kinetics compared to ECMO. Unlike ECMO, cooling generally decreases the volume of distribution due to hemoconcentration [119]. Cooling also prolongs drug clearance due to decreased enzymatic activity and decreased cardiac output [119]. This may result in drug accumulation and exaggerated effect and toxicity or, if the xenobiotic requires activation through metabolism, loss of effect. However, there are no pharmacokinetic studies for patients undergoing both ECMO and therapeutic hypothermia. From a practical standpoint, ECMO may facilitate more controlled cooling, maintenance of target temperature, and rewarming due to in-line cooling/heating rather than relying on cold intravenous fluid administration and external cooling devices.

Complication and Compatibility Summary

Resuscitation of xenobiotic-induced cardiopulmonary failure continues to evolve. Both standard and emerging pharmacological and technological treatments rendered for drug-induced cardiopulmonary failure appear to be safe and compatible with ECMO. However, evidenced-based understanding of the effects with combined resuscitation modalities on efficacy, pharmacokinetics, and complications is on the upslope of the experiential learning curve. As the frequency of ECMO and other emerging treatments increases in cardiopulmonary resuscitation, vigilance for optimal use of combined modalities as well as for unexpected complications and untoward effects is necessary.

Suggested Use of ECMO for Xenobiotic Toxicity

Extracorporeal membrane oxygenation is ideally considered for severe xenobiotic-induced pulmonary or combined cardiopulmonary failure that is refractory to maximal antidotal, conventional supportive pharmacological or technological modalities and meets suggested parameters outlined in Tables 3 and 4. In this regard, the insult should be recoverable following the addition of ECMO support. The potential exception to this general principle of recoverability is toxin-induced injury where ECMO may serve as a bridge to transplant, such as in the case of paraquat. Contraindications are limited and the only absolute contraindication known is intracranial bleeding. Relative contraindications include severe hypoxic brain injury, irrecoverable insult, poor clinical severity score, and comorbidities such as severe bleeding disorder (that prevents anticoagulation) or peripheral vascular disease (that might impede vascular access). Other relative contraindications include comorbidities with shortened life expectancy such as advanced age, cirrhosis, and advanced malignancy.

The challenge of when to initiate ECMO is twofold. First, healthcare providers must perform a benefit–risk assessment and determine if

there is a potential benefit from this relatively high-risk procedure. Most severe cardiopulmonary insults can be successfully managed with lower-risk therapies. The second challenge lies in deciding when standard therapies have reached their maximal effect and are now failing in a manner that affords sufficient time to institute ECMO before the pulmonary or myocardial insult becomes irreversible. Intuitively, the faster the restoration of critical organ perfusion, the better the chances of good long-term outcome; hence ECMO should be started as soon as possible. That being said, many of the cases involving toxins experienced cardiac arrest prior to ECMO and survived with good neurological performance scores despite delays to ECMO and prolonged CPR.

Conclusions

ECMO provides temporary support for lung and combined lung and heart failure. It has a history grounded in treating neonates with lung dysfunction, growing use in adults with cardiopulmonary failure, and more recent interest for severe toxic insult due to a variety of xenobiotics including drugs, natural toxins, and chemicals. In experienced centers, ECMO may be a lifesaving rescue option for severe xenobiotic toxicity when standard of care measures fail. As its use increases for toxins, scientific scrutiny is needed regarding efficacy, safety, optimal duration, and impact on concomitant treatments.

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Post-Resuscitation Management of the Poisoned Patient

5

Michael Lynch and Jon C. Rittenberger

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The care of patients by protocol following cardiac arrest has been associated with significant improvement in survival to hospital discharge in recent years, with studies citing >50% survival in patients suffering pulseless ventricular tachycardia or ventricular fibrillation cardiac arrests [1–3]. Survival improvements have been suggested but are less clear following cardiac arrest with an initial rhythm of asystole or pulseless electrical activity [4]. Management of cardiac arrest as a result of poisoning as well as subsequent postarrest care present unique challenges to providers. Concepts applied to postarrest care in all patients, including aggressive temperature management, maintenance of end-organ perfusion, oxygenation and ventilation, and correction of metabolic derangements, are likely to be transferrable to a poisoned patient population. However, the etiology and necessary interventions required to manage the arrest and postarrest sequelae vary greatly among poisoned patients and are distinct from patients suffering cardiac arrest as a result of underlying cardiopulmonary disease. At the same time, underlying disease must continue to be considered as a contributor and complicating factor of acute poisoning. Depending upon the inciting agent, management may include specific antidotal therapy, serum and/or urinary alkalinization, and/or rescue therapy such as extracorporeal membrane oxygenation (ECMO) in addition to standard advanced cardiac life support. Treatment

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modalities geared toward specific agents will be addressed in corresponding chapters.

Few data exist regarding standardized care after toxin-induced cardiac arrest. Review of 85 out of hospital cardiac arrests felt to be related to drug overdose, primarily from recreational drugs, indicated several key differences in this group compared to patients suffering “natural” cardiac arrest. Patients in the overdose group were found to be younger, have fewer comorbidities, presented more frequently with non-shockable rhythms (e.g., asystole or pulseless electrical activity), and had worse baseline neurologic function. Nevertheless, despite the seemingly poorer presenting characteristics, survival was similar to the non-overdose group and neurologic recovery was superior [5]. The conclusions in this study were reproduced on subsequent examinations of larger populations in two separate databases of cardiac arrest victims [6, 7]. These studies did not evaluate in-hospital cardiac arrest and was geared primarily to evaluating cardiac arrest secondary to drugs of abuse. Cardiac arrests related to cardiovascular agents and other antidysrhythmics such as sodium channel blockers likely carry a very different prognosis.

In this chapter, general principles of post-cardiac arrest care will be discussed with special consideration given to unique aspects of the poisoned patient including challenges in the neurologic evaluation of postarrest patients, the influence of temperature regulation on drug disposition, and ECMO. Potential complications of lipid emulsion therapy, sometimes used during attempts to resuscitate poisoned patients, will also be discussed.

Initial Post-cardiac Arrest Clinical Assessment

After resuscitation and return of spontaneous circulation (ROSC), initial evaluation using a standardized examination and scoring system may be used to assist in management decisions as well as prognosis. While several scoring systems have been suggested, we recommend the Pittsburgh Post-Cardiac Arrest Category (PCAC) score

Table 1 Clinical components used to determine the Pittsburgh Cardiac Arrest Category. Vasopressor doses are in $\mu\text{g/kg/min}$. *FOUR* Full Outline of UnResponsiveness, *SOFA* Sequential Organ Failure Assessment, *Dop* dopamine, *Dob* dobutamine, *Epi* epinephrine, *Nor* norepinephrine

<i>FOUR score: motor component</i>
4 points: follows commands
3 points: localizes to pain
2 points: flexion response to pain
1 points: extensor response to pain
0 points: no response to pain OR generalized myoclonic status
<i>FOUR score: brainstem component</i>
4 points: pupil AND corneal reflexes present
3 points: unilateral fixed/dilated pupil
2 points: pupil OR corneal reflexes absent
1 points: pupil AND corneal reflexes absent
0 points: pupil AND corneal AND cough reflexes absent
<i>SOFA score: cardiovascular component</i>
4 points: $\text{Dop} > 15$ OR $\text{Epi} > 0.1$ OR $\text{Nor} > 0.1$
3 points: $\text{Dop} > 5$ OR $\text{Epi} \leq 0.1$ OR $\text{Nor} \leq 0.1$
2 points: $\text{Dop} \leq 5$ or Dob (any dose)
1 points: $\text{MAP} < 70$ mmHg
<i>SOFA score: respiratory component</i>
4 points: $\text{PaO}_2/\text{FiO}_2 < 100$ AND on ventilator
3 points: $\text{PaO}_2/\text{FiO}_2 < 200$ AND on ventilator
2 points: $\text{PaO}_2/\text{FiO}_2 < 300$
1 points: $\text{PaO}_2/\text{FiO}_2 < 400$

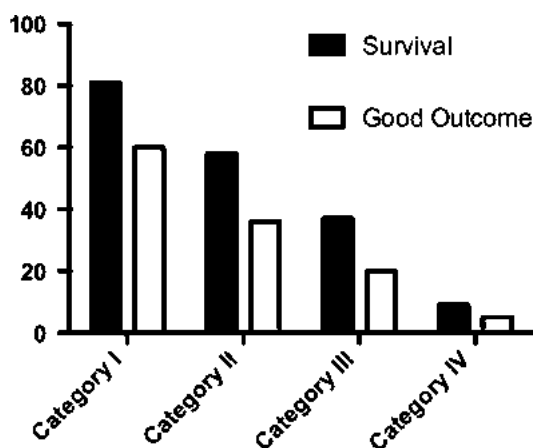
because it is based on objective factors obtainable through bedside examination of the patient rather than reliance on historical factors. The PCAC is a validated postarrest assessment tool using brainstem and motor components of the Full Outline of UnResponsiveness (FOUR) score of initial neurologic function as well as cardiovascular and respiratory components of the Sequential Organ Failure Assessment score of cardiopulmonary dysfunction [8, 9] (Tables 1 and 2).

In the typical postarrest population, this scoring system places a patient on a four-tiered prognostic stratification system, which predicts both survival to hospital discharge as well as the likelihood of good neurological outcome (Fig. 1).

Tools such as the PCAC have significantly advanced our ability to predict clinical outcome and course following out of hospital cardiac arrest with ROSC. However, their use is predicated on the absence of sedative agents for neurologic evaluation. In the case of the poisoned patient, the

Table 2 PCAC category based upon FOUR and SOFA scores including a description of the corresponding clinical examination

Category	Clinical description	FOUR score Motor + brainstem	SOFA score Cardiovascular + respiratory
I	Awake, follows commands	8	Any
II	Moderate coma with preservation of some brainstem reflexes	4–7	≤3
III	Moderate coma with preservation of some brainstem reflexes and severe cardiopulmonary failure	4–7	≥4
IV	Deep coma with loss of most or all brainstem reflexes	≤3	Any

**Fig. 1** Survival and good neurologic outcome based upon PCAC category at the time of initial evaluation. Good neurologic outcome is defined as discharge to home or acute rehabilitation facility (Data from Ref. [8])

presence of a central nervous system sedative agent such as an opioid or GABA-A agonist is common. Significant neurologic toxicity can mimic brain death thereby placing a poisoned patient in PCAC IV and a less than 10% survival rate [10]. Additionally, the initial cardiovascular evaluation assumes that dysfunction represents cardiac injury and hypoperfusion. However, in the case of cardiovascular toxicants such as sodium channel blockers, beta-blockers, calcium channel blockers, and cardiac glycosides, persistent cardiovascular insufficiency following ROSC is often the result of ongoing toxicity, which, though potentially severe and difficult to reverse, would be expected to be transient and self-limited. These observations likely account for the

disparity identified in the review of drug-induced out of hospital cardiac arrest victims in whom survival and neurologic outcome were better than would have otherwise been anticipated [5]. While prognostic scoring systems have significantly improved our ability to predict outcomes and make informed treatment decisions in postarrest patients, the limitations of neurologic and cardiovascular evaluation make accurate prediction of outcome following toxin-induced cardiac arrest difficult requiring further investigation to identify accurate prognostic indicators in this population.

Post-cardiac Arrest Management

Resuscitation approaches in the poisoned patient are largely driven by the specific agent and toxic mechanism. However, in cases that are not related to poisoning, initial evaluation must begin with consideration of myocardial ischemia and early cardiac catheterization [11, 12]. Evaluation of potential underlying contributing coronary artery disease in appropriate patients must also remain part of the evaluation of the presumed poisoned patient. Electrocardiographic abnormalities assumed to be related to acute toxicity including sodium channel blockade and heart block may also represent primary myocardial ischemia necessitating intervention. Bedside echocardiography may help determine volume and pump status. In addition to specific toxin-based interventions, optimization of post-cardiac arrest care with the goal of minimizing ongoing

neurologic and cellular injury while maximizing recovery potential involves employing a standardized protocol requiring significant resources and institutional support [13].

Ventilator Management

In addition to treating the underlying toxicity, standard postarrest care consists of a multifaceted approach to maintain end-organ perfusion, particularly cerebral perfusion. In order to meet cellular demands, adequate oxygenation must first be addressed. The vast majority of patients who have suffered cardiac arrest will require mechanical ventilation. Obvious exceptions would be patients discovered shortly after easily treated causes of arrest, most notably opioid intoxication with naloxone reversal.

As in all critically ill patients, assurance of appropriate airway security is the first priority. Once a secure airway has been verified, mechanical ventilation goals are of normoxia and normal to slightly elevated PaCO_2 levels. Persistent hypoxemia with subsequent diminished cellular oxygen delivery following cardiac arrest should be avoided. Persistently elevated partial pressure of oxygen may also be harmful. A meta-analysis of 14 observational studies of patients with ROSC after cardiac arrest indicated that, while there was no difference in neurologic outcome, there was increased mortality in patients with hyperoxia, $\text{PaO}_2 > 300$ mmHg [14]. In the poisoned patient, there may be exceptions to this recommendation. For example, treatment of patients suffering cardiac arrest as a result of a cellular asphyxiant (e.g., azide, carbon monoxide, cyanide, hydrogen sulfide) theoretically calls for delivery of 100% oxygen, regardless of oxygen saturation, with the goal of maximizing mitochondrial oxygen supply and, in some cases, displacing the offending agent. In the case of carbon monoxide specifically, high flow oxygen is recommended and hyperbaric oxygen is debated [15]. This controversy is discussed in detail in ► Chap. 96, “Carbon Monoxide”. The potential risks versus benefits of hyperoxygenation in this patient population are not clear. However, if there is no indication for hyperoxia,

titrating FiO_2 to maintain a PaO_2 of approximately 100 mmHg is reasonable to ensure adequate cellular oxygen delivery without potentially worsening overall outcome. An alternative end point that may be used to assess adequacy of oxygen delivery is central venous oxygen saturation of greater than 70%, based upon extrapolation from sepsis data [16]. However, this marker may not accurately reflect cellular oxygen delivery and extraction in patients suffering mitochondrial toxicity or hemoglobinopathies.

Despite diminished baroreceptor function, chemoreceptor response to hypocarbica remains intact in the postarrest brain [17]. As a result, hyperventilation can lead to cerebral arterial vasoconstriction and impaired cerebral perfusion [18]. Hyperventilation may also lead to diminished venous return. Decreased cardiac output secondary to falling preload may further exacerbate hypoperfusion injury [19]. For these reasons, the American Heart Association guidelines recommended that PaCO_2 be maintained at approximately 40–45 mmHg [20]. In cases of severe metabolic acidosis that is refractory to treatment, hyperventilation may be necessary to raise pH. Salicylate poisoning is especially sensitive to changes in pH, with even a relatively small decrease contributing to an increase in the nonionized fraction and worsened toxicity. Unless mandated by the toxicant or severity of metabolic acidosis, hyperventilation for therapeutic purposes should be avoided in postarrest patients in order to prevent cerebral hypoperfusion (Grade III recommendation).

Hemodynamic Management

The primary goal of hemodynamic management at any time, including following cardiac arrest, is to maintain adequate perfusion of tissue to avoid further injury. Following cardiac arrest, the brain is at particular risk of secondary injury and is extremely sensitive to even brief periods of hypoperfusion [21]. A number of physiologic phenomena account for hypotension, hypoperfusion, and enhanced brain injury. Reperfusion injury following a period of reduced

oxygen delivery, as is seen in the postarrest patient, causes a distributive shock similar in pathophysiology to septic or systemic inflammatory response states. Moreover, myocardial dysfunction as a result of a period of diminished or absent coronary flow results in reduced cardiac output [22]. Finally, loss of cerebral autoregulatory mechanisms impairs the brain's ability to adapt to fluctuating cerebral perfusion pressure leading to ongoing secondary neurologic injury in addition to the initial anoxic insult [23, 24].

Secondary injury is prevented or minimized by closely monitoring and maintaining organ perfusion. Evaluation of cellular perfusion entails evaluation and interpretation of a number of physiologic end points. No single data point is sufficient to predict satisfaction of cellular oxygen demands. Blood pressure is often used as the primary surrogate for perfusion. While not a perfect reflection of cellular oxygen delivery, it correlates closely with perfusion and alterations in blood pressure, especially decreases in mean arterial pressure (MAP), is associated with worsened outcomes following cardiac arrest [25]. Therefore, we recommend arterial catheter placement in patients requiring vasopressor therapy to ensure accurate and continuous monitoring of blood pressure. Due to observed loss of cerebrovascular autoregulation, studies have suggested the need for maintaining a higher MAP in postarrest patients as compared to patients suffering shock without cardiac arrest [24]. Specialists in post-cardiac arrest care at our institution recommend a goal MAP of 80 mmHg in non-poisoned patients when reasonably attainable. The American Heart Association Guidelines published in 2010 concede that human studies have not determined an ideal MAP and recommend that MAP remains greater than 65 mmHg [20]. Maintenance of MAP will frequently require the use of vasoconstricting and/or inotropic agents. The potential benefits of neuroprotective strategies must be weighed against the practical cardiovascular risks of accentuating cardiac oxygen demand and strain, particularly while managing cardiovascular intoxication. Care can also be negatively impacted if excessive vasoconstriction causes poor perfusion of other organs such as the

kidneys and gut leading to progressive kidney injury or mesenteric ischemia [26]. Other indicators of cellular perfusion include urine output, central venous oxygen saturation, serum bicarbonate, pH, and lactic acid measures. All of these measures can be directly affected by individual toxins such that abnormalities may not indicate cardiovascular dysfunction in the poisoned patient. Therefore, all of these measures should be taken in aggregate and in consideration of the underlying toxic etiology.

In contrast to many victims of cardiac arrest for whom the event is relatively sudden, the poisoned patient has often had a protracted course of poor cellular oxygen delivery, either as a result of reduced respiratory effort or lung injury leading to impaired gas exchange, cardiovascular toxicity causing progressive prolonged hypoperfusion, alteration in hemoglobin-carrying capacity and oxyhemoglobin dissociation, poisoning of oxidative phosphorylation, or a combination of these. In the case of hypoxic cardiac arrest resulting from an isolated respiratory depressant agent, no ongoing toxic effect would be expected, and postarrest management would mirror that of patients whose arrest was nontoxic in etiology. However, in patients suffering cardiovascular toxicity, ongoing impairment of normal physiologic function will continue to complicate the postarrest course. As a result, patients are at very high risk of suffering ongoing perfusion deficits, brain and other organ injury, and subsequent cardiac arrest despite aggressive management.

Hemodynamic management following cardiac arrest from any cause involves first ensuring adequate volume resuscitation. Poisoned patients are frequently relatively volume depleted because of vomiting, insensible losses, and prolonged periods of unresponsiveness with diminished intake. Therefore, initial resuscitation with 1-2 L of isotonic solution, either normal saline or lactated Ringer's, is reasonable. Further volume resuscitation will vary among patients using end points such as measured urine output of at least 0.5 cc/kg/h, bedside echocardiographic evaluation of venous return, or central venous pressure, if available, of 8-12 mmHg. Patients with underlying heart disease or who are suffering inotropic

cardiac toxicity should be monitored closely for development of pulmonary edema.

Vasopressors

Following correction of hypovolemia and venous return, ongoing hypotension or hypoperfusion requires management with vasopressors and/or inotropes. Choice of vasoactive agents is frequently debated; however the data do not support superiority of any specific drug [27]. The choice of vasopressor typically reflects the primary presumed cause of hypoperfusion. Epinephrine may be chosen in a case of primarily cardiogenic shock or norepinephrine in a patient with combined cardiogenic and vasoplegic hypoperfusion. On the other hand, in patients with vasodilatory shock and significant tachycardia secondary to alpha-adrenergic blockade, phenylephrine may be preferred given its pure alpha-agonist effects without associated exacerbation of tachycardia. Norepinephrine, epinephrine, and, less frequently, phenylephrine may be employed individually or in combination depending upon the clinical scenario and pathophysiology of shock for each patient. More important than the specific agent chosen is attentive titration of the agent and response to such physiologic cues of peripheral perfusion as capillary refill and urine output as well as data indicating cardiac output and systemic vascular resistance when available. Bedside echocardiography may be useful in gauging cardiac contractile response to inotropic agents. An inotrope such as dobutamine may be employed as an adjunctive agent in the treatment of cardiogenic shock [28]. Finally, dopamine is associated with a greater incidence of arrhythmias in hypotensive patients [27]. Dopamine is also not an ideal agent in a poisoned patient population. As a mixed-acting sympathomimetic, vasoconstrictive activity is dependent upon indirect alpha-adrenergic effects at lower doses. While not specifically proven, toxicity from a reuptake inhibitor, such as a tricyclic antidepressant, could theoretically limit indirect vasopressor effect. As a result, likely because of dopamine's vasodilatory effect on splanchnic vascular beds, we have observed its use to be associated with exaggeration of

hypotension that improves with discontinuation. A distinction between patients suffering toxicity and other postarrest populations is the doses of vasoactive agents that may be required to achieve a desired effect. In many cases, vasoactive agents are being used to competitively displace a toxicant or overcome downstream inhibition of a desired metabolic pathway's effect. For this reason, vasopressors are best rapidly titrated to effect with continuous evaluation of markers of perfusion. This may require administration of doses not typically used in alternative diagnoses such as septic or nontoxic cardiogenic shock [29].

Poison-Based Interventions

Additional interventions that may be considered for the treatment of cardiovascular toxicity including glucagon, calcium salts, hyperinsulinemia-euglycemia (HIE), intravenous fat emulsion (IFE) or intralipid therapy, methylene blue, and specific antidotes will be discussed in the corresponding chapters. The potential benefits of these therapies in the treatment of a variety of cardiotoxic agents in addition to and, in some cases, in lieu of traditional vasopressor therapy has been debated [29, 30]. Unfortunately, the incidence and variable nature of severe toxicity leading to cardiovascular collapse and cardiac arrest render the disease process and therapeutic interventions difficult to study in a prospective, randomized way in human patients. Evidence for these interventions, therefore, is limited to animal models, case reports, and observational series. Review of these publications does not yield strong evidence to support any one treatment strategy in favor of another [31]. Nevertheless, given the refractory nature of severe toxicity, it is likely that patients suffering cardiac arrest will receive several or all of these therapies in addition to titrated vasopressor support in an effort to maximize all potential beneficial effects until toxicity has resolved. Potential complications of these measures must be anticipated and ameliorated.

Hyperinsulinemia-Euglycemia

High-dose insulin therapy has shown promising results in animal studies and human observational reports of beta-blocker and calcium channel blocker toxicity [30, 32]. Typical high-dose insulin dosing calls for initial bolus dosing of 0.5–1 U/kg followed by 1 U/kg/h infusion that can be rapidly increased, based upon clinical response, to doses of 10 U/kg/h or higher [30]. Administration of these doses of insulin carries the risk of clinically significant hypoglycemia and hypokalemia [31]. In the case of calcium channel blocker poisoning, hypoglycemia is rarely reported. But, blood glucose should be monitored frequently, especially at the outset of therapy in order to identify and treat hypoglycemia. Not only is early hypoglycemia a risk, patients on high-dose insulin would be expected to have residual hypoglycemic effects following resolution of acute toxicity. Once hyperinsulinemia therapy has been discontinued, frequent blood sugar monitoring should continue for at least 24 h [30]. In patients with acute kidney injury and impaired renal clearance of insulin, hypoglycemic effects may be even more protracted. In the postarrest population, periods of hypoglycemia have been associated with worsened neurologic outcomes further emphasizing the importance of vigilant glycemic monitoring with an ideal goal glucose range of 140–180 mg/dL [33].

Potassium supplementation is required for patients receiving high-dose insulin therapy. Significant hypokalemia, though primarily due to intracellular sequestration rather than decreased total body potassium load, can contribute to cardiac conduction abnormalities and lower the threshold for ventricular dysrhythmias. Another potential complication of high-dose insulin therapy is hypervolemia. The recommended dosing of insulin may result in the administration of hundreds of units of insulin per hour to a patient. Typically, insulin is mixed in crystalloid solution at a 1 unit/mL concentration. This can lead to the necessary infusion of multiple liters of fluid each day with the associated risks of pulmonary and peripheral edema in patients with impaired cardiac function [34]. Sequelae of volume overload

including prolonged ventilator dependence can complicate the ICU course and recovery following high-dose insulin therapy. Higher concentrations, including 16 units/mL, have been found to be stable and may mitigate the risk of hypervolemia [35]. High-dose insulin therapy is discussed in greater detail in the chapter devoted to its use and in the chapters related to specific relevant agents.

Intravenous Lipid Emulsion

Intravenous lipid emulsion (ILE) therapy with isotonic 20% long chain fatty acid solution for the management of lipophilic cardiotoxin poisoning has become widespread with an increasing volume of case reports and animal studies. ILE was initially identified as a resuscitation method for local anesthetic systemic toxicity in animal studies in the late 1990s and in human case reports beginning in 2006 [36]. Since then, successful ILE resuscitation of patients intoxicated with a variety of lipophilic agents (including bupropion, tricyclic antidepressants, β -blockers, and calcium channel blockers) has been reported [37]. While there are a multitude of positive reports, there are no human randomized trials to offer firm evidence of benefit, and the anecdotal reports may result in a publication bias inflating the perceived efficacy of ILE. Dosing of ILE is typically 1.5 mL/kg bolus followed by 0.25–0.5 mL/kg infusion [38]. Lipid rescue therapy, as it is sometimes referred to, might have antidotal activity through several proposed mechanisms: (1) introduction of an intravascular fatty compartment to absorb lipophilic drugs, the so-called “lipid sink,” (2) contribution of free fatty acids as a myocardial energy source, and (3) increased myocardial calcium concentrations mediated by triglyceride effects on cardiac calcium channels [39]. Several adverse effects attributed to ILE therapy have also been reported that could interfere with resuscitative efforts and contribute to therapeutic complications. ILE administration has been associated with acute lung injury, pancreatitis, critical laboratory interference lasting for hours despite ultracentrifugation of samples, and thrombotic phenomenon such as extremity deep venous

thrombosis [40, 41]. Additionally, lipid therapy has been associated with clotted lipemic blood obstruction of circuits in both hemodialysis and ECMO rendering these interventions ineffective [42, 43]. Based upon available literature comprised primarily of animal studies and human case reports, pending further study, it is reasonable to consider ILE therapy for patients suffering severe cardiovascular toxicity from a lipophilic drug that is unresponsive to standard interventions [40]. At the same time, indiscriminate use is not advised given the potential complication of ongoing critical care and resuscitation. In vitro and animal model investigation of liposome-based targeted antidotal therapy is also ongoing and may represent a future clinical therapeutic option [44]. ILE is discussed in greater detail in the chapter devoted to its use and in the chapters related to specific relevant agents.

Extracorporeal Membrane Oxygenation

Cardiopulmonary bypass (CPB) and ECMO, also referred to as extracorporeal life support (ECLS), offer management options for patients with cardiopulmonary failure unresponsive to medical and antidotal therapy. Deployment of ECMO is rapid and portable at centers experienced in the use of this invasive procedure offering benefits compared to formal CPB. It can be initiated through peripheral vascular entry at the bedside in the intensive care unit but is time and resource intensive. ECMO should only be performed at experienced centers with necessary institutional support and ancillary services [45]. Venovenous ECMO (VV-ECMO) is available for the management of respiratory failure without impaired cardiac function as has been seen in the management of critically ill patients with influenza. Venoarterial ECMO (VA-ECMO) can be used to support arterial perfusion in patients with cardiac failure as a temporizing measure until the underlying pathology improves or a permanent treatment, such as a ventricular assist device implantation or transplant, is performed and is considered a “bridge to recovery” [46]. Following placement of large bore percutaneous venous and arterial catheters, venous blood is removed, pumped through a circuit allowing oxygenation,

removal of carbon dioxide, and instillation of medications before being returned to the arterial circulation. Catheters may be placed in the groin or neck vessels. As acute cardiac failure secondary to intoxication would be anticipated to be a transient phenomenon, VA-ECMO is a reasonable consideration [47]. A number of case reports and observational studies have indicated successful management of drug-induced cardiovascular failure despite typical critical care management and improved survival rates regardless of the causative agent [48].

One observational non-randomized series of 62 patients with drug-induced persistent cardiac arrest or severe shock despite standard critical care management were treated with conventional therapy in one center vs. conventional therapy plus ECLS in a second center. In the ECLS group, 12/14 (86%) survived while 23/48 (48%) of the patients who did not receive ECLS therapy survived. One third of the ECLS group had ischemic or hemorrhagic complications requiring urgent vascular surgical intervention [49].

While results such as these are encouraging and merit further evaluation and investigation of the use of VA-ECMO in the management of toxin-induced cardiovascular failure, optimism must be tempered by the limitations of the available evidence including sample sizes and variability of treatment prior to the initiation of VA-ECMO. Additionally, VA-ECMO is associated with significant adverse events including life-threatening hemorrhagic and thrombotic events, limb ischemia, differential hypoxia, and pulmonary hemorrhage [46, 48]. Nevertheless, for cases of refractory toxicity and cardiovascular collapse in which all other available therapies have been employed without success, VA-ECMO is an appropriate consideration despite the lack of definitive evidence and associated risk as there are few, if any, alternatives. The optimal timing of initiation of therapy is another as yet unanswered question. VA-ECMO and other therapies stand a greater chance of success if instituted earlier in the course of treatment; however, this increases the risk of selecting patients that may not have required such heroic therapy and exposing them to the significant associated risk without

proof of benefit. Use of VA-ECMO in the treatment of cardiovascular toxicity and shock that fails to respond to conventional therapy requires further analysis but is a reasonable, ethical, and cost-effective therapeutic option in patients with a realistic expectation of meaningful recovery [48, 50]. ECMO and CPB use in the poisoned patient is discussed in greater detail in the chapter devoted to its use and in the chapters related to specific relevant agents.

Hypothermia

Therapeutic hypothermia (TH) has emerged as a critical part of postarrest care and has been associated with a significant improvement in survival and neurologic outcomes following out of hospital cardiac arrest [51, 52]. No prospective or randomized study of therapeutic hypothermia has been performed in patients following toxin-induced arrest to produce specific data suggesting benefit or harm of TH in this population. But, based on the large body of literature supporting its use after resuscitation of cardiac arrest from all causes, strong consideration should be given to its use.

There is debate regarding the optimal temperature goal in postarrest care. Most published studies have evaluated TH with a temperature goal of 32–34 °C, but more recent studies have shown similar results with targeted temperature management (TTM) at 36 °C [1, 53–55]. More importantly, hyperthermia is definitively associated with worsened outcomes after cardiac arrest and should be prevented in all populations [56]. Temperature management should be considered in any patient who is not following commands or showing purposeful movements following resuscitation from cardiac arrest. Generally, the only absolute contraindication is a known do not resuscitate order; however, this may be debated in the poisoned patient, particularly when self-inflicted harm as a result of a depressive episode is suspected. While future studies will determine optimal temperature for subgroups, it is reasonable to target the temperature for either 32–34 °C or 36 °C in the postarrest patient.

Prior to induction of either TH or TTM, patients should be intubated, sedated if necessary, and have a core temperature monitor in place. Core temperature monitoring is accomplished with, in order of preference, endovascular, esophageal, bladder, or rectal thermometer placement [57]. Brain injury and cerebral edema, frequently identified on CT scan of the brain, are common and deadly complications of prolonged hypoxemia and cardiac arrest [58]. TH is the preferred treatment strategy in patients with demonstrated or increased risk of intracerebral hypertension, cerebral edema, and postarrest seizure activity as there is evidence of reduction of intracranial pressure and seizure risk [59–63]. Once the goal temperature has been chosen, cooling typically begins by rapidly infusing 20–30 ml/kg of isotonic crystalloid solution stored at 4 °C. Each liter of 4 °C solution infused over 15 min decreases the core temperature by 1 °C, comparable to intravascular cooling devices [63–65]. Patients with compromised cardiac function, renal failure, or signs of volume overload and pulmonary edema may not be able to tolerate the necessary rapid infusions of this volume of fluid. Additional methods of cooling include surface cooling and placement of intravascular cooling devices. Surface cooling is achieved with cooling blankets (ideally placed above and below the patient), cooling vests, and placement of ice packs in the neck, groin, and axillae. Surface cooling has been associated with temperature decreases of 0.5–1 °C/h and is similarly effective as intravascular cooling [66]. Importantly, survival did not differ between surface and intravascular cooling groups; the decision on method to achieve goal temperature should be determined by the treating clinician.

A critical component in achieving and maintaining temperature, regardless of the goal temperature, is prevention and treatment of shivering. A natural response to TH and TTM, even subclinical shivering can complicate appropriate maintenance of temperature [67]. The shivering threshold in healthy individuals is approximately 36.6 °C [68]. Thus, temperature management at either 33 °C or 36 °C will require suppression of shivering [1]. Prevention of shivering primarily involves sedation. A number of agents have been

used with varying effectiveness. For the most part, sedative agents that have classically been evaluated are appropriate for and often used in the poisoned patient, including propofol, benzodiazepines, and dexmedetomidine. However, fentanyl and meperidine can be used as adjuncts to prevent shivering [69]. Given the serotonergic properties of both meperidine and fentanyl, treating toxicologists may want to avoid these medications in patients with known or suspected ingestion of a serotonergic agent. The combination may result in exacerbation of toxicity including increased hyperreflexia and tremor, which would further complicate shivering [70, 71]. Nondepolarizing neuromuscular blockers may also be used in the treatment of uncontrolled muscle activity or shivering, particularly when blood pressure will not accommodate further sedation. However, electroencephalogram monitoring is necessary in paralyzed patients given the risks associated with unrecognized seizure activity or nonconvulsive status epilepticus [72, 73].

Seizures

Seizure activity is a well-recognized complication of anoxic brain injury. A number of anticonvulsants including valproic acid, phenytoin, phenobarbital, midazolam, and propofol have been evaluated for the treatment of status epilepticus without clear superiority of any particular agent [74, 75]. A number of cardiotoxic agents are also associated with CNS toxicity and seizures. It may be difficult to differentiate seizures caused by toxicity versus those caused by brain injury. In the poisoned patient, treatment of seizure activity with agents exhibiting GABA-A properties such as propofol, midazolam, and phenobarbital is likely most appropriate as valproic acid and phenytoin are typically not effective, and potentially deleterious, in the management of most toxicant-induced seizures [76]. Poisoning-related seizures are discussed in greater detail in ► Chap. 20, “Toxicant-Induced Seizures.”

Drug Metabolism During Induced Hypothermia

Another factor to consider when managing patients following return of spontaneous

circulation after toxin-induced cardiac arrest with TH and TTM is the potential metabolic effect on drug disposition. At temperatures below 36.5 °C, midazolam clearance via CYP3A4/5 begins to slow and continues to decrease at lower temperatures [77]. Similar results have been found for phenobarbital, phenytoin, vecuronium, propofol, fentanyl, and morphine [78]. Based on these findings, it is logical to infer that temperature reduction may not only slow the metabolism of various therapeutic drugs but may have a similar effect on the toxic agent. Depending upon perceived ongoing toxic effects, rapid elimination of the offending agent may offset the potential benefit of hypothermia for neurologic recovery. No data exist to guide the toxicologist in selection of patients appropriate for induced hypothermia despite the potential delay in resolution of drug toxicity. However, at the very least, hyperthermia should clearly be avoided as discussed in the previous section.

Other Considerations in Hypothermic Patients

Additional complications of TH include impairment of normal coagulation, increased risk of infection after 24 h of cooling, bradycardia, QT interval prolongation, diuresis, hypokalemia, hypomagnesemia, and hypophosphatemia [79]. Hyperglycemia as a result of insulin resistance is another recognized complication of TH, which could have implications in the use of high-dose insulin therapy [80]. With the exception of hypokalemia, the rates of adverse events do not differ between TH and TTM [1]. Hypothermia-induced changes in arterial blood gas reporting must also be recognized when interpreting results [81] Table 3.

Table 3 Recommended adjustments to interpretation of blood gas findings during temperature management

Blood gas value	For every degree below 37 °C
PaO ₂	Subtract 5 mmHg
PaCO ₂	Subtract 2 mmHg
pH	Add 0.012 units

Rewarming

After the desired period of temperature management has been completed, slow and gradual rewarming should occur at a rate of 0.2–0.25 °C [82]. More rapid rewarming can result in nullification of the benefits of temperature management as well as adverse outcomes such as cerebral edema, seizures, hypoglycemia, and hyperkalemia [83]. As the patient is rewarmed, TH-induced changes can resolve very quickly necessitating frequent clinical evaluation and close laboratory monitoring of electrolytes and glucose.

Therapeutic Hypothermia in the Poisoned Patient

While TH has not been specifically prospectively evaluated in victims of toxicant-induced cardiac arrest, the demonstrated benefits observed in patients suffering cardiac arrest from any cause provide reasonable evidence to extrapolate results to the poisoned population. Postarrest physiology and associated neurologic injury are most likely applicable to patients regardless of the primary etiology of arrest. Several key distinctions must be considered in the toxic arrest patient. For instance, the inciting cause of toxicant-induced cardiac arrest has exerted its effect for a period of time prior to arrest and will continue to do so after the arrest. Typically, there is no definitive way to hasten the resolution of toxicity from agents not amenable to hemodialysis or other enhanced removal methods. Therefore, the benefits of TH in postarrest care should be weighed against the ongoing need to manage toxicity. In particular, it is unclear if induction of TH delays clearance of the offending agent to an extent that overall cardiovascular toxicity is prolonged. If so, the potential risk of TH may outweigh the clearly demonstrated benefits in nontoxic patients. In the case of CNS depressant toxicity, delayed resolution of toxic effects may prolong time on the ventilator but otherwise would be unlikely to significantly worsen overall outcome. In this case, TH following cardiac arrest is likely advisable. Patients suffering direct cardiovascular toxicity may benefit from TTM rather than TH as hypothermia may contribute to prolonged toxicity and

ischemic injury. In the end, decisions will need to be made by individual providers based on the specific illness of each patient as there is no universally applicable evidence to support TH after toxin-induced arrest. Regardless of temperature management strategy chosen, fever should be avoided.

Neuroprognostication

Predicting neurological outcome in the postarrest patient involves incorporation of data from a variety of different sources, including physical examination, somatosensory-evoked potentials, electroencephalography, and neuroimaging. Computed tomography of the brain should be performed on comatose postarrest patients. Intracranial hemorrhage complicates up to 7% of cases and cerebral edema is a grim prognostic indicator [58]. Electroencephalogram (EEG) monitoring of postarrest patients is also recommended. Nonconvulsive status epilepticus is a common finding on continuous EEG and is associated with poor survival and neurologic outcomes [73, 84]. Despite available adjunctive tests, early prognostication at 72 h remains difficult and likely insufficient to make a final determination of perceived outcome potentials [85]. Withdrawal of care based upon perceived neurologic injury and prognosis has been identified as the leading cause of hospital death in patients suffering out of hospital cardiac arrest [85].

The lack of reliable evidence to support early neuroprognostication would suggest that family discussions regarding final treatment decisions are done with the understanding that prediction of outcome is difficult and should be delayed, though optimal timing has yet to be elucidated. In the poisoned patient, this is particularly true as the potential presence of CNS depressant medications can further confound the issue. In addition to serial neurologic examinations, analysis of the presence of sedating agents in serum may be of use in determining the ongoing exogenous sedative effect [86]. In an effort to provide a more reliable neurologic examination in the comatose postarrest patient, reversal agents such as

naloxone and/or flumazenil may be considered. However, their potential utility as a diagnostic aid may be outweighed by the risk of inducing physiologically significant withdrawal symptoms including tachycardia, hypertension, seizures, and vomiting. Moreover, reversal of these agents may have a negative effect on neurologic recovery as studies have shown neuroprotective benefits of opioids and benzodiazepines [87, 88]. Prognosis of neurologic recovery should be delayed in the postarrest patient and include ongoing communication with the patient's family prior to making a final determination of viability or futility. In the toxicant-induced patient population, favorable neurologic outcomes have been observed despite typically poor early predictors [5]. This topic is discussed in greater detail in ► **Chap. 13, "Poisoning Fatalities."**

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Clinical care of the seriously poisoned patient is usually multidisciplinary, commonly involving various medical specialists, including emergency physicians, anesthesiologists, intensivists, and toxicologists. The role of a psychiatrist is sometimes overlooked, especially in texts that focus on the ABCs (airway, breathing, circulation) of toxicologic management. Reviews of the topic often make little or no mention of the psychiatric management of these patients [1]. Yet patients who deliberately overdose have a high prevalence of suicidal ideation and pre-existing psychiatric disorders that may impact medical management [2], and it is also common for patients admitted to intensive care units (ICUs) to develop a psychiatric disturbance (e.g., delirium) during their admission, regardless of their premorbid psychiatric state [3]. Delirium is now being recognized as a condition to be prevented when possible and managed aggressively to minimize short- and long-term sequelae; therefore, psychobehavioral expertise is becoming vital in the critical care setting. Furthermore, drug misadventures in patients with addictive disorders comprise a growing percentage of acutely poisoned patients. Many toxicology patients have intentionally exposed themselves to their poisons, and a portion of those carry an elevated risk of subsequent suicide with a rate of 1.6% (CI 1.2–2.4) after 12 months and 3.9% (CI 3.2–4.8) after 5 years; and repetition of nonfatal self-harm or self-poisoning of 16.3% (CI 15.1–17.7) after 12 months [4], so attention to the psychosocial determinants of self-poisoning

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and to underlying mental health needs is essential. This chapter outlines the psychiatric aspects of critical care toxicology and describes the potentially useful role of a psychiatric service in the multidisciplinary management of seriously poisoned patients. It is organized to mirror the temporal course of patient care and mental health issues that arise, from the precipitants of toxicologic exposure through the course of critical illness to post-recovery intervention.

Epidemiology

Serious poisoning has a spectrum of etiologies and manifestations. Various informal classifications exist (Table 1). Despite a lack of consensus in classification, it is well recognized that deliberate self-poisoning (DSP), recreational drug use, chronic substance misuse, iatrogenic poisoning, and accidental poisoning in children account for most cases requiring hospitalization and treatment.

One of the most widely accepted definitions of DSP is as follows:

The deliberate ingestion of more than the prescribed amount of medicinal substances, or ingestion of substances never intended for human consumption, irrespective of whether harm was intended. This definition takes an epidemiological stance, defining attempted suicide on the basis of behavior alone, rather than by an inference about intent [5].

There is still incomplete agreement, however, concerning the definitions used. Some large-scale

studies have preferred the term *parasuicide* [6, 7]. Attempts have been made to operationalize the definitions for all types of self-harming behavior [8] and for suicide [9]. Personal motivations in DSP are difficult to classify for many patients. Intensity of suicidal ideation can both surge and abate quickly over short periods of time, often substantially reduced by the time a patient reaches hospital. This observation may reflect ambivalence – the simultaneous experience of intense but opposing feelings – that has patients both wishing for death in the face of overwhelming upset and wishing for relief and care that would obviate the perceived need to be dead. Studies of personal motivation tend to suggest that communicating distress, expressing hostility, influencing others, relieving an unpleasant state of mind, and frank suicidality are all common. Patients with significant suicidal intent often disclose this early in assessment interviews [10].

In the United States, the National Co-morbidity Study reported a lifetime suicide attempt rate of 4.6% [11], and a Canadian study of school-age adolescents reported an attempt rate of 3.5% [12]. It is unknown what proportion of these attempts result in a presentation to hospital, but most hospital-treated events are due to DSP. Although institutional data is generally considered to be an underestimate of the true picture, a summary of the number of presentations and population-based rates of nonfatal hospital-treated DSP in the United States in 2013 is presented in Fig. 1. A study conducted in the mid-1980s reported that 5% of all ICU admissions in a US center resulted from a drug overdose [13], but this is likely to vary as a consequence of service mix and admission practices.

Deliberate self-harm (DSH) is a common reason for presentation to acute care, and DSP or overdose is overwhelmingly the most common form of DSH requiring general hospital admission and treatment [14]. In a year-long survey of 15 - European centers of all adult hospital-treated parasuicides, mean admission rates of 167/100,000/year for men and 222/100,000/year for women were reported, although there was wide variation among centers [15]. An epidemiologic center in Oxford, United Kingdom,

Table 1 Classification of poisoning types

Classification of overdose ^a	Classification of poisonings and envenomations ^b
Accidental	Deliberate self-harm
Suicidal behavior	Recreational
Recreational/experimentation	Accidental
Compulsive	Iatrogenic
Indeterminate	Envenomations
	Other

^aFrom Reilly et al. [305]

^bFrom Whyte et al. [26]

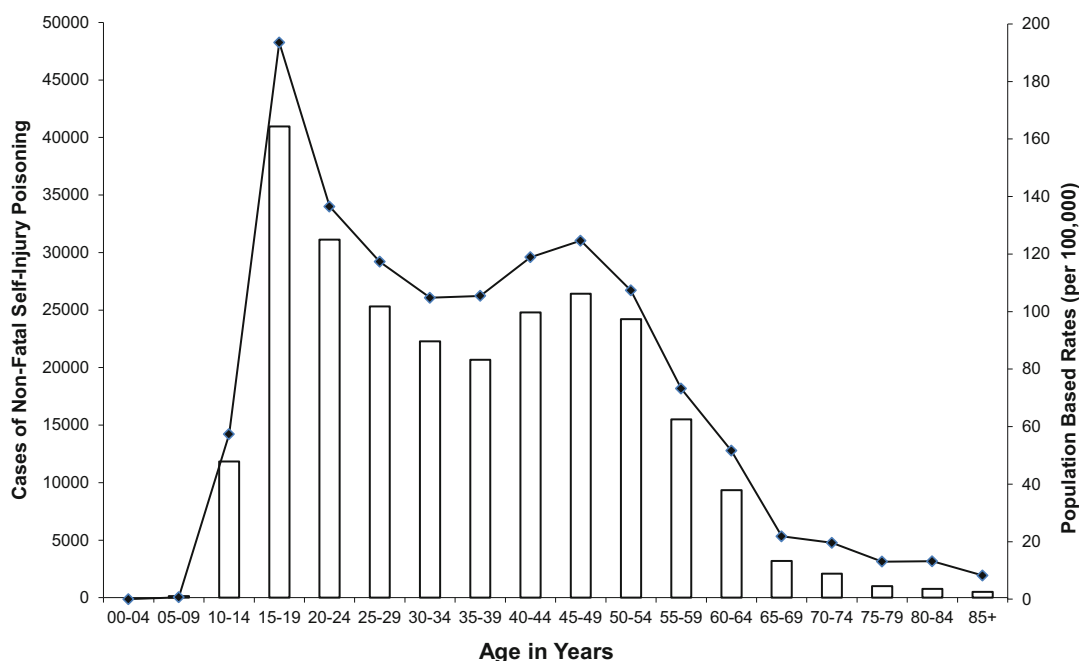


Fig. 1 Nonfatal deliberate self-poisoning in the United States, 2013

estimated the national DSH admission rate at approximately 400/100,000/year [16, 17]. Deliberate self-harm is one of the five leading causes of hospital admission for men and women in the United Kingdom, with DSP resulting in 150,000 hospital referrals a year [16, 18]. In the United States, DSP has been reported to account for 1% of all emergency department (ED) presentations, with a subsequent admission rate twice that for all other ED patients [19]. In Australia, one regional catchment center estimated a rate of approximately 200/100,000/year for hospital-treated DSP [20]. DSP may account for more than 5% of Australian general hospital admissions and almost 20% of all ICU admissions [21], although more recent changes in psychotropic prescribing, DSP trends, and acute hospital care routines are likely decreasing admission rates there and in other countries [22–24].

Not all cases of poisoning result in serious toxicity. Some units admit all presentations of DSP as a matter of policy, but this is by no means universal, particularly in the United States. In a New Zealand survey, 69% of all patients presenting with DSP were admitted to hospital,

with 10% admitted to the ICU [25]. There may be threefold to fourfold differences in the rate of direct discharge (nonadmission) from EDs in different settings, with 50% of patients with such presentations not admitted in the United Kingdom [16]. Emergency department staff are more likely to discharge patients without admission or psychiatric assessment when the presentation occurs before or after daytime business hours or on weekends [14], and more than 50% of all cases may present during these times [14, 26]. Definitions of toxicologically or medically serious cases also vary, although there is, at best, only a modest association between toxicologic severity and suicidal intent [27]. In New Zealand, a study of adolescents and young adults defined a “medically serious attempt” (at suicide) as one requiring hospitalization for at least 24 h and at least one of the following: treatment in an ICU, hyperbaric unit, or burns unit; surgery under general anesthetic; or medical treatment beyond gastric lavage, activated charcoal, or routine neurologic observation [28]. Older studies defined *medically serious* differently, reflecting the poisonings common at the time and a simpler approach to

classification (e.g., a coma level of particular severity, serum salicylate >50 mg/dL (360 μ mol/L), or carboxyhemoglobin $>30\%$) [27], or simply considered admission to the ICU or critical care unit (CCU) as appropriate to define a *serious poisoning* [29].

Poisonings from misuse of medications and addictive substances in adults are second in frequency to DSP, with alcohol and opioids being the most common agents used. Benzodiazepines, anticholinergics, cocaine, amphetamines, phencyclidine, and hallucinogens also are used recreationally and may cause serious toxicity. Psychotropics available over-the-counter like dextromethorphan are popular with adolescents, and a number of synthetic compounds that function as cannabinoids, serotonergics, and psychostimulants have taken hold in the toxicologic landscape via Internet commerce [30]. Other therapeutic compounds such as neuroleptics, antidepressants, and dopamine agonists also are used, albeit less frequently, as drugs of abuse and occasionally may produce toxicity. Even after patients survive acute poisoning, persistent psychosis caused by addictive substances like methamphetamine is a recognized phenomenon [31, 32]. Novel synthetic cannabinoids and phenethylamines may also carry risk for symptoms that require ongoing psychiatric treatment once acute intoxication has abated [33, 34], not unlike persisting perception disorders from lysergic acid diethylamide, psilocybin, or 3,4-methylenedioxymethamphetamine (MDMA) [35, 36]. In some instances, there may be serious long-term neuropsychiatric effects from drugs used recreationally (e.g., former users of MDMA may have memory impairment, which is related to the degree of exposure [37]), although these cases rarely require acute toxicologic intervention.

Iatrogenic poisonings may be a less frequent occurrence, but their potential seriousness should not be underestimated. Psychopharmacologic agents are frequently implicated in iatrogenic poisoning and may give rise to potentially fatal toxidromes, such as lithium toxicity [38], neuroleptic malignant syndrome (NMS) [39], serotonin syndrome [40, 41], and anticholinergic toxicity [42], and other serious systemic effects (e.g.,

cardiac arrhythmias, seizures, catatonia, pseudotumor cerebri, ataxia, nephrotic syndrome, priapism, or agranulocytosis) [43]. These complications occur more frequently in patients with a psychiatric history, even though the poisoning event is not driven by suicidal urges, addiction, or chronic misuse. Psychopharmacologic drugs of almost any class can produce serious toxicity in therapeutic use [44] and occasionally may give rise to a serious withdrawal syndrome [45], which may further complicate an admission for self-poisoning.

There is a degree of interplay between psychiatric illness and toxicity. Obviously, mental health difficulty is associated with DSP, with affective illnesses (major depressive disorder and bipolar disorder) and Cluster B personality disorders (borderline, narcissistic, histrionic, and antisocial) conferring the greatest risk [46, 47]. Borderline personality disorder (BPD) patients not only have the highest rates of repeat DSP and a 10% lifetime suicide rate [48], but their intensely shifting affects and behavior patterns along with high rates of polypharmacy and comorbid substance use can make critical toxicologic care even more challenging.

In any psychiatric patient, a new drug or increased dose of an existing drug can create a mixture of psychiatric symptoms and toxic effects that adds a layer of complexity to diagnosis and management. One example would be the case of a depressed patient whose therapy is changed from a tricyclic antidepressant to a selective serotonin reuptake inhibitor with an inadequate washout period, leading to a mixed affective state with features of both depression and mania that may evolve to frank serotonin syndrome with delirium [49]. Another example is a schizophrenic patient treated with antipsychotic medication who develops NMS and presents with symptoms of parkinsonism, rigidity, evolving malignant catatonia, and psychosis [50]; bromocriptine could alleviate NMS but worsen the psychosis. Still another issue is the role of addiction. Patients who misuse substances have high rates of mood disorders, anxiety, and behavior problems that can complicate assessment and management of toxicities and withdrawals. In cases of critical toxicologic

illness, standard protocols for management of agitation and use of sedatives to maintain mechanical ventilation may fail due to high levels of cross-tolerance and the emergence of withdrawal during the course of ICU care. A history of witnessing and experiencing trauma, which is common in patients with addictions and suicidal actions, also increases the likelihood of behavior disturbance in the clinical setting [51].

The elderly represent a demographic for whom there are unique psychiatric issues in critical care toxicology, as well. Although more DSP attempts are made by young people, death by suicide is more common with increasing age in certain segments of the population in the United States and some other industrialized countries [52]. Suicide rates in elderly white males are particularly high and have also spiked recently in those of late middle age who have occupational problems. One reason is the greater burden of medical illness that comes with age (especially chronic pain and cancer) and corresponding increased vulnerability to the impact of toxins. Additionally, older people have prescription medications available to them to manage those underlying conditions, medications which have narrow safety margins in overdose (e.g., antihypertensives, antiarrhythmics, heart failure agents, insulin, oral hypoglycemics, and anticoagulants). A baseline level of cognitive impairment is also more common with age, so older patients are more likely to experience delirium and more complicated hospital stays than younger adults when they suffer from acute toxicity [53]. Regardless of whether the cause is DSP, accidental poisoning, or iatrogenesis, the elderly are more vulnerable to protracted recovery and failure to return to a previous level of neuropsychiatric functioning [54, 55].

Childhood poisoning is usually accidental and tends to be associated with less morbidity and mortality than poisoning in adults, which is usually deliberate (suicide attempt or parasuicide) [56]. Nevertheless, a study of child psychiatric patients (<13 years old) found a substantial rate of self-reported suicide attempts [57], so an appropriate level of clinical suspicion is warranted. In addition, a larger proportion of young people with mental illness are being treated pharmacologically

for their conditions and gaining exposure to a wider variety of potentially toxic and sometimes addictive agents. Thus the use of prescription drugs in overdose by children appears to be increasing and the gender gap closing, with more boys taking purposeful ingestions in recent years [58]. More ingestions and other attempts with greater lethal potential are occurring in preadolescents as well [59]. Increasing rates of substance use problems in young people involving a variety of more acutely toxic agents also has led to more pediatric critical illness. Very young children and toddlers only rarely require admission to an ICU as a result of toxicity, and common household products are typically involved [60]. However, more prescription medications are now found in the environments where children live and play, and the ingestion of drugs such as clonidine, methadone, and buprenorphine does increase the likelihood of ICU treatment [61–64].

Although childhood poisoning is usually accidental, it remains a public health issue with psychiatric implications. Concern is growing for the toxic misuse of medicines by parents to address unwanted behavior in children. The administration of over-the-counter products for this purpose is not uncommon and results in a significant number of cases of morbidity and mortality in the United States each year [65]. Rarer types of poisoning include poisoning driven by factitious disorders like Munchausen syndrome or Munchausen syndrome by proxy. Although uncommon phenomena, these disorders can lead to serious toxicity, especially if the agents used are insulin [66], anticonvulsants, opiates [67], or laxatives [68]. The epidemiology of these conditions is hard to establish. A 2-year prospective study in the United Kingdom and Ireland reported 128 cases of Munchausen syndrome by proxy, nonaccidental poisoning, and nonaccidental suffocation in children younger than 16 years old, with an estimated rate of 0.5/100,000/year and a rate greater than 2.8/100,000/year in children younger than 12 months old [67]. Even the clinical classification of “accidental” childhood poisoning needs to be approached with some caution. A study of 50 childhood poisonings from a US poison control center documented recording of

“accidental” cases as “suicidal,” “intoxication,” and one attempted homicide with only a few remaining as “accidental” [69]. Whether or not a case clearly involves psychopathology in a child or unhealthy parent–child relationships, the majority of critical poisonings in this age group represent an opportunity to screen for psychosocial issues underlying the event, so the threshold for mental health consultation should be low (Level II-3 recommendation).

Roles for Consultation-Liaison Psychiatry

Psychiatry offers expertise in the interplay of central nervous system (CNS) function and behavior. Since the brain is the organ most commonly affected by acute poisoning [70], and patients with mental illness are overrepresented in critical care toxicology, there is clinical logic to support having a psychiatrist involved in the multidisciplinary endeavor of care. Consultation-Liaison (C-L) psychiatry is the subspecialty that manages the psychiatric needs of patients in the general hospital setting [71, 72]. This discipline, with formal training under the title of psychosomatic medicine, aims to maintain bridges between psychiatry and other specialties to provide biopsychosocial care to patients in nonpsychiatric settings [71]. *Consultation* generally refers to direct assessment and clinical management of individual patients, and *liaison* denotes coordination between and among treatment teams, families, and service organizations, sometimes without direct clinical contact with the patient [73–75]. In most clinical situations, a blend of these two modes is employed, with the latter time-consuming process often providing invaluable aid in supporting caregivers to help patients with complex patterns of illness. Toxicologists and other clinicians managing poisoned patients may choose to involve available C-L psychiatry services in patient care, or they may manage these patients entirely without psychiatric input (particularly in hospitals where consultation cannot be rapidly obtained). In the past, utility of psychiatric assessment has been questioned largely because

there had been no demonstrated effect on subsequent suicide deaths or repetition of DSP/DSH [76, 77]. Furthermore, acute and chronic problems related to addiction are frequently given differential (i.e., comparatively decreased) attention and resources in hospitals compared to those arising from DSP. As a result, practices vary widely across different countries and within different systems of care, from emergency departments to general medical floors and ICUs, regarding the involvement of mental health professionals of various kinds [26, 78–82]. But before the question arises of “what to do now that this toxic episode is resolved,” a host of issues surrounds the care of critically poisoned patients with which a C-L psychiatrist may be helpful.

From the very start of an episode of care in acute toxicologic practice, unique circumstances threaten to complicate the process. Stigma against mental health patients, pervasive in most societies and harbored by healthcare professionals at all levels, conspires against optimal treatment. Although not directly articulated, most caregivers have expectations for how patients should behave. Suicidal poisoned patients challenge expectations by participating directly in the cause of their own critical illness and sometimes obstruct workup and treatment by virtue of symptoms of mental illness that led to the toxic exposure. The ICU is a repository of finely honed lifesaving skills and high-technological equipment; yet these often limited resources are expended at times, in apparent paradox, in the care of patients who have expressed a wish to die. There may be a tendency for staff to consider aggressive lifesaving treatment in these patients as antithetical to the purpose of an ICU [83]. This attitudinal set represents not only a lack of compassion but also a failure to understand patients’ illnesses and motives. Even repeat attempters are not necessarily intent on ending their lives. Rather, they may be seeking relief or escape from intolerable feelings of hopelessness and despair, often complicated by problems of (negative) cognitive distortion and impaired problem-solving abilities [84], which may have their origins in childhood neglect [85], physical or sexual abuse [86–88], parental loss [89], family violence [89], or family histories of

depression, substance abuse, and parent–child discord [90] – all recognized risk factors for suicidal behavior in later life. Psychotropic medications are frequently prescribed to control symptoms in these troubled patients, and the very same medications are becoming more common in overdose attempts [24]. Many patients who ingest psychiatric medications may not be seeking death *per se*, but rather an obliteration of consciousness that has been fraught with overwhelming negative thoughts and emotions [24]. Patients who achieve relief in this manner and survive by virtue of advanced critical care may produce negative feelings in those caregivers who see them awaken from coma looking “fine” and “not suicidal.”

Although health care professionals may be less likely than laypersons to be judgmental in their attitudes toward attempted suicide, it also has been reported that medical staff may view attempted suicide merely as attention-seeking behavior [91]. In a study of almost 300 critical care nurses and more than 80 physicians working in Australian EDs and ICUs, it was found that both groups were frequently negative in their attitudes toward patients who had attempted suicide, with more than half considering parasuicide patients as manipulative [83]. Almost two thirds indicated that they did not enjoy caring for these patients. The results seemed to be independent of the gender or professional status of the respondent and of the number of years of experience in the critical care environment. A sense of frustration was a theme frequently conveyed through individual comments. This study suggested that it is common for physicians and nurses to have attitudes that would work against the establishment of sound therapeutic relationships with these patients. Similar negative attitudes toward DSP patients have been found in studies of junior physicians and nurses in the United Kingdom [92]. A Scandinavian study of 40 consecutive suicide attempters admitted to the ICU found that ICU personnel did not discern patients’ underlying feelings but responded to observable behavior, with reactions ranging from empathy to distancing and even to aggression [93]. Other factors that have been reported as contributing to negative

attitudes in ICU staff are perceptions of poor institutional support, a lack of positive reinforcement from the patients themselves, and inadequate educational preparation to provide optimal care for these patients [94], the lack of which conceivably could reinforce misconceptions and stereotypes that prevail in both professional and lay communities.

Appropriate nursing goals in the care of suicidal patients in CCUs have been identified and disseminated: developing an understanding of the patient’s response after a suicide attempt, accepting the patient in the unit, developing trust, conveying a sense of hope, providing psychosocial support, preparing the patient for discharge or transfer from the CCU, and managing problematic patient behavior [95]. Achieving these goals requires education, training, support, and reinforcement. Consultation-Liaison psychiatry staff, sometimes accompanied by nurse educators, may be invaluable in helping ICU staff to develop the skills necessary to meet these goals while adequately managing their own experience of the patients and the work. Teaching and modeling can help staff to understand how “manipulative” or “difficult” behavior may reflect patterns of human adaptation to trauma and stress that improve with attuned caregiving [96]. (Level I recommendation) Based on models developed at the Massachusetts General Hospital, a number of acute care practices have found value in having early intervention and routine guidance from C-L Psychiatry in the treatment of mental health patients who are critically ill, with special attention to the psychological impact of such cases on caregiver staff [97]. Knowledge of this type can foster the empathy necessary to manage mental illness comorbidity in DSP patients.

Additional skills and support can often be necessary to work with families of toxicology patients. DSP patients frequently experience relationship problems and psychosocial disadvantage [98, 99], so it is not merely the care of the critically poisoned individual that can be complicated by interpersonal unrest. For patients who have attempted suicide, relationships with family or significant others may be strained by events leading up to the suicide attempt and/or may be

chronically dysfunctional. Family or significant others may express ambivalence or hostility and aggression toward the patient and be unable or unwilling to provide even limited support [100] or direct these negative feelings toward staff, or the medical care process, itself. Family members may withdraw support from the patient or even file “do not resuscitate” orders – sometimes as a form of “passive euthanasia” [101]. This may reflect ambivalence in pre-existing relationships or the inability to deal with a deteriorating depression with suicidality that preceded the self-poisoning episode. Even when family and others intend to offer support, a patient who *perceives* his or her social or familial support as inadequate or falling short of what he or she needs may reject or frustrate further efforts of support. A patient acting on this perception then may engender feelings of rejection or indifference in others – family, friends, and caregivers alike – thus exacerbating the patient’s sense of isolation [102–104].

Psychobehavioral Problems

Seriously poisoned patients may exhibit a range of behavioral disturbances resulting from delirium, agitation, anxiety, suicidal ideation, relationship problems with staff or family, personality traits, persecutory delusions, hallucinatory phenomena, misunderstandings, pain, withdrawal, or a combination of these and other factors. For patient safety and comfort, treatment requirements, and staff safety, there may be occasions when it is necessary to reduce the degree of behavioral unrest. Toxicologic practice may largely focus on pharmacologic management strategies. Psychiatric perspectives can be helpful in this arena as well. But before simply intervening with sedatives, an understanding of the principles of “abnormal illness behavior” and “abnormal treatment behavior” may be useful in harnessing the power of interpersonal therapeutics [75, 102, 105, 106]. An important point to consider is that patients’ unrest usually involves some interactive influence of service providers; conflicts do not emerge from a psychosocial vacuum. This understanding may suggest strategies

for change within the treatment system and opportunities for direct, nonpharmacologic management of the patient.

Cognitive and behavioral interventions are common modes of effective nonpharmacologic intervention currently used. The more sophisticated forms of these psychological interventions are not generally applicable while the patient is in the ICU and are deployed more usefully during the recovery phase. (Level III recommendation) Nuanced understanding can enhance caregiver satisfaction and support empathy, but most useful interventions do not involve the patient’s direct participation in such insights. As has been noted for patients with the condition that produces the highest rates of repeat DSP episodes, BPD, “[i]n the medical setting, psychoanalytic interpretations of the unconscious are destined to fail; noninterpretive behavioral approaches are the ones that work” [103]. Practical, concrete interventions are usually of greater use during the period of treatment for severe toxicity.

Impact of the Hospital Environment

The nonmedical aspects of management of a self-poisoned patient in the intensive care setting – aspects of care that relate to the patient’s cognitive, emotional, behavioral, and psychological state, as opposed to the requirement to address ABCs of emergency management and detoxification – are important. Psychological disturbance associated with ICU admission is well described even in patients without prior psychiatric morbidity. Disorientation, restlessness, agitation, confusion, and frank delirium are seen frequently in ICU patients regardless of the reason for admission. Many aspects of the intensive care environment are in themselves sufficient to produce psychological disturbance. The ICU is an intrinsically frightening place – it is difficult to imagine a more disturbing experience than the gradual or sudden regaining of consciousness coupled with the realization of the presence of an endotracheal tube and mechanical ventilation. ICUs often do not respect the distinction between day and night; they may be uncomfortable, confusing, and

disorienting places, which can contribute easily to a patient's sense of depersonalization.

Despite these challenging experiences that frequently contribute to behavioral disturbances during an episode of critical care, it has been suggested that most patients have little or no memory of their stays in an ICU [3]. More recently, though, it has been recognized that medical trauma including the influence of an intensive care unit admission and memories of it can play a major role in the development of mood and anxiety disorders. Post-traumatic stress related to intensive care can be particularly problematic. Rates of both of these classes of mental disorders range from 8% to over 50%, with the likelihood being greater for those with premorbid mental illness [107, 108]. Since the majority of toxicologic patients have one or more pre-existing psychiatric diagnoses that contributed to their need for such medical intervention (e.g., mood disorder driving suicidal behavior), they comprise a particularly vulnerable population with respect to trauma-based iatrogenic mental illness. Most patients who do develop symptoms from medical trauma will require long-term follow-up, as depressive symptoms often fail to remit until at least the second year after an ICU stay [108], and post-traumatic stress disorder (PTSD) symptoms tend to persist even longer [107].

Delirium has been recognized as an independent risk factor for development of psychiatric illness in the wake of medical trauma. In addition to delirium, amnesia for the early portion of hospitalization, lack of education and social support, trait anxiety, and female gender all make PTSD a more likely sequela [109]. Risk factors for depression are similar, with delirium being a major covariate, along with an independent, dose-dependent risk from exposure to benzodiazepines in the ICU [110, 111]. Some types of poisoning (e.g., organophosphate poisoning, lithium toxicity, anoxic injury from opioids) may lead to prolonged stays in the ICU and require a range of invasive procedures. This prolonged exposure to traumatic events and mind-altering medications may increase the risk of protracted delirium and corresponding long-term psychological sequelae.

Strategies designed to prevent and minimize the severity of delirium are therefore critical in the acute toxicology patient (see text written below – v.i. – Delirium). In considering the causes of psychological disturbance, the full panoply of organic comorbidities and the effects of their treatment must be considered in addition to the primary reason for admission. Recognition of and attendance to reversible causes of anxiety also should not be overlooked; alongside the pathophysiologic effects of poisoning, these patients equally can be in pain, experience cold, develop sepsis, have blocked catheters, suffer constipation, or be in alcohol or other drug withdrawal. With attunement to these issues, ICU staff may be able to manage some level of psychological disturbance without particular need for formal psychiatric input [104, 112].

Delirium

Delirium is common in ICU patients, especially for those with a period of mechanical ventilation; it is often undetected and is associated with a range of poor short-term outcomes. It is a syndromic condition associated with increased rates of morbidity and mortality, both from its serious underlying causes and from complications of its behavioral manifestations [113]. However, we know of no outcome studies specifically restricted to critical care toxicology patient populations and so must take some general guidance from the studies of all ICU patient populations, while studies of critically poisoned patients are awaited.

A recent systematic review of 42 studies (observational and clinical trials) reported delirium in 31.8% of critically ill patients. Patients with delirium had higher in-hospital mortality (RR 2.19, 94% CI 1.78–2.70); longer durations of mechanical ventilation (SMD 1.79 (95% CI 0.31–3.27); longer ICU lengths of stay (SMD 1.38, 95% CI 0.99–1.77); and longer hospital lengths of stay (SMD 0.97, 95% CI 0.61–1.33) [114]. It is important not to ignore these important outcome data, even though the majority of acute toxicology patients are both expected to

experience delirium by virtue of their intoxicants and expected to survive due to the particular characteristics of their critical illnesses. Optimal management of delirium depends upon the systematic detection thereof, along with a targeted approach to care that does not rely simply upon pharmacological interventions. Psychiatry identifies a state of delirium as being defined by the core features of disturbed attention and awareness along with impairment of least one other mental process referable to cerebrocortical function [115]. This fluctuating pathological state represents a relatively rapid change from baseline that cannot be better explained by a pre-existing condition but is driven by an underlying medical problem. Note that sensory disturbances and corresponding delusional misperceptions of reality can occur, but psychosis is not synonymous with delirium nor is it required for the diagnosis. This distinction is critical. If behavior disturbances in toxicology patients are too quickly attributed to underlying psychiatric problems or assumed to be “just part of the intoxication,” not only can other acute medical conditions go untreated, but the physical (e.g., restraints, catheters, respiratory tubes) and pharmacologic tools employed to control behavior can also, themselves, cause further harm.

Validated instruments for the detection of delirium in ICU populations are available if not consistently used and include: the Confusion Assessment Method (CAM), the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), the Intensive Care Delirium Screening Checklist (ICDSC), the Neelon and Champagne (NEECHAM) Confusion Scale, the Memorial Delirium Assessment Scale (MDAS), and the Delirium Rating Scale (DRS) [114]. An older systematic review of drug induced delirium (not restricted to critical care populations) recommended an integrated clinical approach: recognition, cessation or dose reduction of causative drug(s), reorientation strategies, and supportive medical care; with specific “antidotes” appropriate in some cases. Recommended pharmacological treatment aimed at sedation for specific indications, such as aggression, risk of harm to self or others, hallucinations, patient distress, and for compliance with procedures was limited

to some benzodiazepines (diazepam, lorazepam, midazolam) and/or haloperidol [116]. (Level II-2 recommendation) In the intervening years there has been the development of specific clinical implementation pathways using these general principles, although the content of specific programs can be quite different. The choice of possible medications to manage delirium and its associated behavioral manifestations has also expanded, although the evidence base for which drug (route of administration and dose) to choose, and for which clinical endpoint, remains lacking (v.i. Pharmacologic Management of Psychobehavioral Disturbance).

A recent systematic review of interventions (clinical implementation programs) to identify and treat ICU delirium identified 21 studies, 9 of which reported clinical outcomes. Meta-analyses showed reduced mortality and ICU length of stay for: implementation programs using six or more strategies; using an integrated framework of current evidence on pain, agitation, and delirium management (PAD) or using a strategy of early awakening, breathing, delirium screening, and early exercise (ABCDE bundle) [117]. (Level II-1 recommendation) A narrative review of ICU delirium expanded the management of delirium further to include the “triad” of pain, delirium, and agitation as being commonly linked; and thus indicating that sedative drugs should only be used when pain and delirium have first been addressed with the use of specific pharmacologic and nonpharmacologic strategies [118]. (Level III recommendation) Integrated clinical approaches or clinical guidelines to address these complex and interacting aspects have been developed and published in the public domain [119]; and although these approaches are not specific to toxicology populations, the use of a systematic approach within a given clinical unit has merit (Level III recommendation).

Nonpharmacologic Management of Psychobehavioral Disturbance

Guidelines for managing delirial signs without medications share common procedures. Many of

the principles for managing anxiety are similar to those for delirium [120], and recommendations for recognition, assessment, and treatment of anxiety in CCUs are also available [104]. There are a number of simple nonpharmacologic strategies advised for the critical care of all patients that can minimize psychosomatic stress to the acute toxicology patient. Fundamental to these environmental strategies are the goals of orientation and reassurance. (Level II-1 recommendation) Key supportive measures include minimizing noise and sleep disturbance, providing levels of stimulation matched to the time of day, arranging appropriate ambient lighting or proximity to natural light, and displaying personal objects and photographs of familiar faces. (Level II-2 recommendation) Minimizing sensory impairments (e.g., providing eyeglasses and hearing aides) is essential to the efficacy of some interventions. In addition, ensuring consistency of staff members; giving simple and repeated explanations; and facilitating communication with symbols, charts, writing boards, and pointing devices for intubated patients, all minimize medical trauma. (Level II-3 recommendation) One powerful evidence-based tool for preventing ICU trauma from leading to psychological sequelae is the use of medical diaries. (Level I recommendation) Helping patients to document and make sense of their ICU experiences reduces incident PTSD within the months following an episode of critical care by over 50% [121].

Flexible visitation schedules to facilitate family and social supports are also valuable in managing anxiety [104]. (Level II-3 recommendation) Where possible, relatives or significant others should be encouraged to participate in communication and reassurance. Their efforts can be vital in the coordinated treatment of a delirious patient, so caring for these caregivers is important. It is essential that ICUs have designated spaces for promoting effective communication with families – comfortable, nonthreatening places offering quiet and privacy, physically removed but not too distant from the unit. Attitudes of relatives are difficult to optimize in ICUs that lack appropriate places where relatives are able to speak with patients or staff. Relatives are frequently upset

and when upset are more likely to misinterpret communications with staff [93, 122]. They, too, experience medical trauma while enduring the critical illnesses of their loved ones. Symptoms of anxiety, depression, and PTSD are common and do not always abate even when patients have recovered and are ready for discharge [123], so psychiatric consultation to families of toxicology patients can be beneficial during the phase of ICU care and beyond (Level II-3 recommendation).

One aspect of critical care that can be particularly disturbing for patients' families is the appearance of a body invaded by tubes and wires and occasionally held down by restraints. Historically the use of physical restraint for management of behaviorally disturbed patients with delirium was more common than it is today [124]. Most mental health legislation and case law emphasize the principle of preference for the "least restrictive alternative" form of care. The American Psychiatric Association Task Force's report on seclusion and restraint has suggested possible indications for use, as follows: the prevention of imminent harm to self or others when other methods are ineffective; the prevention of substantial damage to the physical environment; the prevention of serious disruption to the treatment program; as a contingency in the treatment of dangerous behavior; to decrease stimulation; and at the patient's request [125]. Although these indications are not universally agreed upon and were outlined decades ago to apply in psychiatric treatment settings, they might be relevant to seriously poisoned patients now. (Level III recommendation) Restraints are not without their proponents and potential usefulness, although a balance between the benefits and risks in each case should be made in light of available evidence [126]. Perhaps the best indications for effectiveness are for the prevention of injury and reduction of agitation in inpatient psychiatric settings [126]. The usefulness of restraint for these purposes may not always translate to medical settings, and the indications may be less clear. Restraint may be deemed necessary when patients directly interfere with lifesaving treatments, but it is not without serious physical risk in itself. A

review of physical restraint in medical settings suggested there is a strong likelihood that deaths resulting from the practice are underreported, with severe injuries typically due to strangulation, circulatory compromise, or neuronal damage [127].

In addition to physical injuries, physical restraint has adverse psychological effects on patients [127] and staff [126]. Staff training in the prediction and prevention of violence may be valuable in reducing the rates of usage and resulting untoward effects of restraint [126, 128]. (Level II-3 recommendation) Physicians and patients in a psychiatric setting reportedly favored psychotropic medication over physical restraint [129]; it is our position that critical care toxicologists should agree with this perspective. There is a reported continuing decline in the use of physical restraint in CCUs in response to ethical and clinical concerns [124, 130], so unless the medical situation requires (e.g., a brain injured patient with dangerous behavior needs frequent neurologic reassessments), physicians with advanced expertise in pharmacology are encouraged to use the less traumatizing modality of medication for treating confusion and agitation (Level II-3 recommendation).

Pharmacologic Management of Psychobehavioral Disturbance

There is far from a consensus on the appropriate drug, dose, or route of administration to be used to address disturbed behavior, whether associated with delirium or other psychiatric condition. Few randomized controlled trials have been undertaken with clearly defined toxicology or DSP patient samples to guide choices, but there are reviews outlining medical and pharmacologic principles that should be followed [116, 120, 131]. The most important maxim is that medicine seeks the underlying causes of signs or symptoms and, when possible, treatments should be chosen that target etiologies. In some psychosomatic states, following this principle can be challenging, and since C-L psychiatry routinely contends with such complex cases, consultative input may help to choose management strategies and even assist

in the medical detective work involved in sorting out those multifactorial underlying causes of behavior disturbance [113]. There should be clearly defined indications for the use of medications in each case, because not all behaviorally disturbed patients may require them [116]. This point is critical, because choosing optimal pharmacologic interventions depends on the current state of neuropsychiatric functioning in addition to the attendant evolving toxicologic acuity and comorbid mental illness burden. (Level III recommendation) We therefore subdivide considerations for pharmacologic management into initial acute interventions for the new onset of agitation and subacute interventions for ongoing behavioral unrest.

Acute Treatment

A general algorithm for choosing medications for acute management of agitation is outlined in Fig. 2. Note that the first decision point involves determination of whether or not the observed psychobehavioral unrest is a reflection of delirium or the direct effects of an intoxicant. Assessment of the latter is addressed in other chapters of this text. Common tools available for identifying delirium (see text written above – *vide supra*. – Delirium) may take more time than is available in the care of an acutely poisoned patient and agitation may interfere with the process. A “micro-mental status examination” focused just on the individual’s orientation, attention, and short-term working memory may be better suited to the care of poisoned patients [132, 133] – with any gross deficit leading down the pathway that prioritizes delirium workup and management. (Level II-2 recommendation) Impairments in these basic cortical functions should never be ascribed merely to volition or mental illness with medications chosen to extinguish undesirable behavior.

Noting the short-term medical and long-term psychiatric dangers of delirium (v.s.), if direct treatment or a potentially beneficial antidote is available for a suspected cause, it should be administered. Examples include delivery of oxygen to a confused hypoxic patient and interventions to raise blood pressure in a patient with failing mental status from hypotension. Central

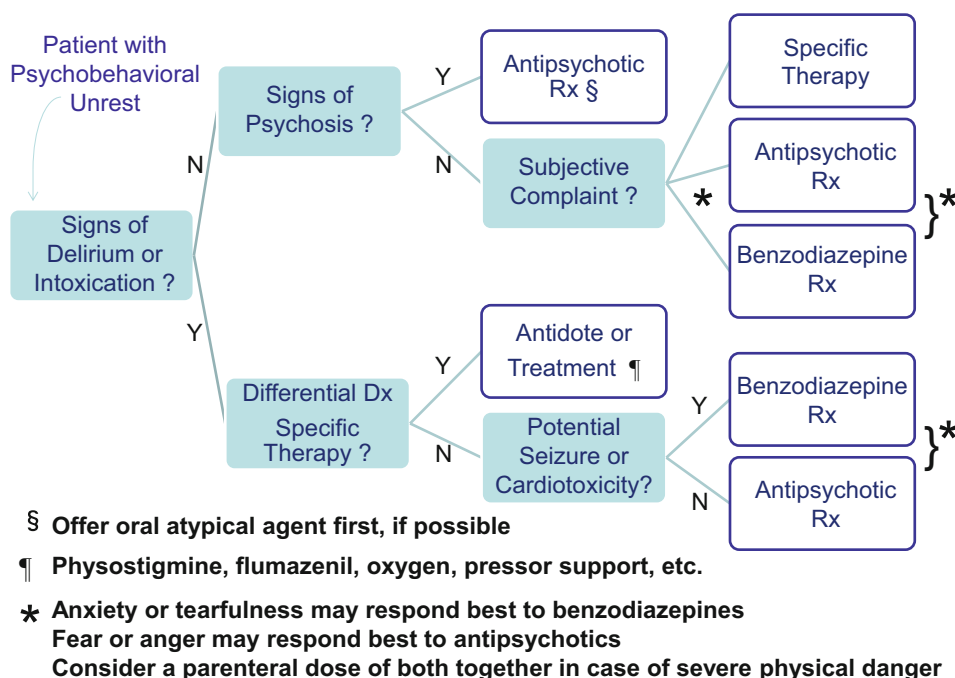


Fig. 2 Algorithm for pharmacologic management of acute agitation

nervous system antidotes also fall under this category. Naloxone is routinely employed to arouse patients from opioid-induced stupor. Flumazenil will reverse delirium from GABA-ergic toxins [134] and can be safely used in patients whose presentation is consistent with sedative toxicity (DSP or iatrogenic), even in the presence of comorbid neurologic and psychiatric illness, and in those who chronically take benzodiazepines [135]. (Level II-2 recommendation) Physostigmine is indicated to directly treat anticholinergic delirium and can be safely employed when cognitive impairment is suspected from a variety of compounds commonly involved in cases of DSP, including cyclic antidepressants [136]. (Level II-2 recommendation) Central nervous system antidotes help patients to assist in their own care and contribute vital information both about the causes of their distress and about other issues of medical and toxicologic import (e.g., sources of pain, focal dysfunction, toxic coingestion) (Level II-3 recommendation).

If such a specific intervention is not available and/or the underlying cause unclear after

assessment and use of antidotes, then one further question should be addressed. If the suspected differential diagnostic list of potential etiologies involves significant immediate risk of seizure or arrhythmia, then the initial medication choice for agitation should involve benzodiazepines; evidence supports their use alone or in combination with haloperidol [137]. (Level II-1 recommendation) If an adverse electrical event at the level of the heart or brain is not likely, then antipsychotic medication alone is safe and preferred to preserve cognition and avoid adverse effects of benzodiazepines [138–140]. (Level II-2 recommendation) The choice of a specific agent is complex and not clearly established in the literature, so local variation in practice is common. A consensus workgroup of emergency providers relying on meta-analytic review to outline best practices in evaluation and treatment of agitation (Project BETA) recommends atypical antipsychotics over butyrophenones [140] (Level II-3 recommendation), but it should be noted that the anticholinergic activity of certain agents (e.g., olanzapine, quetiapine) could worsen confusion in some

cases of toxic delirium. (Level III recommendation) Although there is concern about the potential for extrapyramidal reactions from haloperidol, the risk is vanishingly small in patients with delirium. Their cognitive impairments reflect functional CNS hypocholinergia (with impaired memory, attention, communication, and decision-making), so even robust dopamine blockade rarely causes imbalanced neurotransmission that results in movement side effects. Additionally, there is evidence for rapid cognitive improvement from intravenous haloperidol infusion through positive effects on hippocampal and frontal lobe function [141]. Such benefits support the recommended use of first generation antipsychotics (like haloperidol) for management of disinhibited agitation in alcohol intoxication [140], which can be exacerbated by GABA-ergic agents. (Level II-3 recommendation) Of course, all dopamine blockers must be avoided if antipsychotic medications are a suspected cause of a patient's delirium as a consequence of NMS.

Should delirium or severe intoxication not be present, medication choice largely turns on the presence or absence of psychosis. Psychobehavioral unrest driven by delusions and/or perceptual disturbances is best treated with antipsychotic medication. In this clinical scenario, Project BETA recommends the use of atypical agents that antagonize both dopamine and serotonin pathways based on data favoring better subjective patient experiences and milder side effect profiles [140]. Butyrophenones produce more dysphoria in nondelirious patients (Level II-3 recommendation), and the risk of extrapyramidal movement problems makes an oral offering of risperidone or olanzapine a more favorable option as well [140]. (Level II-2 recommendation) If delirium has just resolved or remains a significant risk, however, the antimuscarinic activity of olanzapine (or quetiapine) may be less desirable in the potentially complex pharmacologic situation of acute poisoning. Under such circumstances risperidone, ziprasidone, or a judicious dose of haloperidol may be best, avoiding cognitive impairment from anticholinergia. (Level III recommendation) If a patient is unwilling or unable to take medication in oral form, parenteral

options are available for ziprasidone, olanzapine, and aripiprazole – the latter is not recommended in the acutely poisoned patient due to a higher risk of akathisia (which may worsen agitation) and an array of effects on serotonin neurotransmission that can complicate toxicologic care [142] (Level II-3 recommendation).

In the agitated patient without delirium, psychosis, or intoxication, an effort should be made to engage in communication that will help to discern the underlying cause of distress so it may be addressed directly. (Level II-2 recommendation) If the subjective complaint is pain, analgesia may calm behavioral unrest. In patients with low distress tolerance who are hungry, thirsty, lonely, or overwhelmed, nonmedication solutions may be available. Some subjective upset can be calmed with medications – benzodiazepines are useful for anxiety or emotional anguish and atypical antipsychotics better address anger or fear [140]. (Level II-3 recommendation) If the patient cannot be engaged to discern a specific target for intervention and the physical threat from agitation is high, benzodiazepines and antipsychotics are the evidence-based options to ensure safety. Project BETA recommends oral offerings first, but parenteral delivery may be necessary. Clinical experience and some research suggest that when danger is very high and rapid tranquilization desirable, an injection of both haloperidol and lorazepam may be the best choice [137, 140]. (Level II-3 recommendation) (Note that most extrapyramidal reactions occur several hours after acute dopamine blockade, so despite being common in practice, the “prophylactic” use of parenteral anticholinergics along with haloperidol has little evidence and may impair cognition.) A randomized trial in potentially violent patients showed rapid efficacy with droperidol alone or in combination with midazolam, along with a superior physical side effect profile to midazolam alone [143]. (Level I recommendation) However, in some countries including the United States, this butyrophenone may be unavailable for use due to the impact of warnings, such as those from the Food and Drug Administration, about the potential for fatal arrhythmias. Such adverse events are rare, and a recent study demonstrated

minimal risk of repolarization anomalies with droperidol [144].

Very recently, intramuscular ketamine has been used for sedation of severely agitated patients as well. Caution should be exercised in the DSP population, however, as emergence reactions and persistent psychiatric symptoms related to the dissociative agent are more frequent in patients with mental illness and trauma histories – two common comorbidities in acute toxicology. (Level II-3 recommendation) Choosing high dose ketamine may also be complicated by the sympathomimesis and neuropathology of toxic states [145] along with pre-existing neurophysiologic vulnerabilities [146] for which benzodiazepines and dopamine blockers would be potentially safer.

Ongoing Treatment

Psychiatric consultants may not routinely be involved in the early course of behavioral management in toxicologic critical care when decisions about acute interventions are made. The principles outlined above are valuable throughout the course of treating DSP patients, even though some may appear to apply largely after the critical phase of toxicologic treatment has passed and mental health consultants are called to determine next steps in management and disposition. Even if C-L psychiatrists are involved earlier in the course, they may be less likely to contribute recommendations for maintenance of sedation and breakthrough agitation in the ICU, as such choices are viewed as the purview of critical care teams [147]. Noting the implications of delirium and complications from agitation, though, having a psychiatric perspective to augment a more comprehensive treatment plan may be worthwhile; practice guidelines are beginning to reflect this appreciation [148–150] (Level III recommendation).

Despite their utility and widespread use, benzodiazepines have long been a source of concern for psychiatric consultants who manage delirium in the acute care setting [120]. Continuous infusions of midazolam remain common practice with apparent benefits that fit with ICU nursing routines [151], even though interrupted regimens have been associated with decreased sedative

use, lower rates of delirium, fewer complications, and shorter lengths of stay; and thus appear in the most current practice guidelines for critical care [148]. When these agents must be employed, intermittent pro re nata dosing of a compound with reliable pharmacokinetics and without long-acting metabolites (e.g., lorazepam) can achieve desired results using less medication and shorter duration of treatment as demonstrated in the case of alcohol withdrawal [152]. (Level II-2 recommendation) Decreasing amount and duration of exposure to benzodiazepines is an important goal, since they yield an independent, dose-related risk of delirium [139]. Flumazenil can be used to reverse iatrogenic oversedation and delirium and support progress in recovery [135, 153]. (Level II-2 recommendation) Treatment of ICU patients with melatonin has been shown to help in maintaining circadian rhythms and promoting restful sleep with a concomitant decrease in sedative use [154] (Level I recommendation).

Even with these enhancements, escalating doses of sedative medications may still complicate the care of toxicology patients. The role of underlying substance use disorders is a fairly obvious but often neglected factor. Cross-tolerance between the agents chosen for sedation and drugs of abuse, including alcohol, may drive critical care teams to employ very large doses of benzodiazepines to control behavior – sometimes due to concern for emerging withdrawal in a ventilated patient. Although withdrawal can be problematic and severe, careful attention to neurologic examination and autonomic indices may help to identify when patients require withdrawal treatment and when patients' agitation can be safely managed with antipsychotic medications that circumvent cross-tolerance, minimize sedative use, and preserve cognition. (Level III recommendation) Nonaddictive agents like alpha-2 receptor agonists (e.g., clonidine, guanfacine, dexmedetomidine) may also be useful in toxicologic and withdrawal states to provide sympatholysis and calm without exacerbating delirium [155]. (Level II-1 recommendation) A number of studies suggest that managing withdrawal states and anxiety in addicted patients with medications like clonidine and

anticonvulsants (e.g., carbamazepine, valproic acid, gabapentin) that do not reinforce drug use correlates with much higher rates of pursuing sobriety after an acute episode of care [156]. (Level II-2 recommendation) Balancing good principles of toxicologic management with psychiatric guidance that helps to minimize cognitive dysfunction and negative impact on addictive diatheses is key to optimal management.

As an adjunct or alternative to benzodiazepines, opioids have gained wider use in ICU sedation regimens in recent years [148]. Noting that pain frequently accompanies critical illness states, the term “analgo-sedation” has been used to describe this practice. Since a large percentage of toxicology patients are not plagued with pain, however, the routine use of opioids for this subset of ICU patients comes into question, especially in light of the potential for adverse effects that can interfere with treatments (e.g., gastrointestinal slowing that complicates activated charcoal administration) and with patients’ cognition and behavior. Morphine may be particularly problematic due to the effects of delirigenic metabolites, especially in patients with renal impairment [148]. This added risk does not appear to be mediated by mu opioid activity, as naloxone is not a reliable antidote. Other opioids can be delirigenic, as well, with continuous infusions further increasing the likelihood of cognitive impairment [150]. (Level II-2 recommendation) Even though a dose relationship remains, the risk of delirium may be lower with fentanyl as compared to other opioids [148, 157, 158]. However, like the other phenylpiperidine opioid meperidine, fentanyl can contribute to serotonin toxicity and should be avoided in the ICU management of patients who may have been exposed to serotonergic agents [159]. (Level III recommendation) Noting the ubiquity of psychotropic drugs and abusable substances that enhance serotonin activity, the routine use of fentanyl for sedation in critical care toxicology cannot be recommended. Other opioids, including buprenorphine, may have a role if the issue of withdrawal from this class of agents is clearly complicating management [160] (Level II-3 recommendation).

In general, psychiatric perspectives on therapeutic sedation and management of delirium would likely advocate more frequent use of antipsychotic medication with corresponding decreases in the use of benzodiazepines and opioids. Cochrane reviews on pharmacologic interventions for delirium support this position [161, 162]. (Level II-2 recommendation) Data reviewed to guide care in the United Kingdom National Health Service are consistent as well [163]. (Level II-2 recommendation) Preservation of cognition in the face of acute, stressful illness is a central goal. While some critical care providers may believe it would be more desirable to sleep through the discomforts and confusion of critical illness, both short- and long-term measurable outcomes suggest otherwise [164, 165]. In addition, psychiatrists are attuned to the impact of reinforcing substances on health and behavior, so a C-L consultant will look to weigh risks against the benefits of using narcotic agents in the ICU – especially with patients who already struggle with addiction.

Psychiatry defines many of the ways in which toxicology patients differ from the average patient characteristics in ICU medicine. Although they tend to be younger and more physically resilient, toxicology patients have some unique issues and vulnerabilities to be considered in optimizing critical care. In addition to the pharmacologic concerns that accompany individuals with a predilection to self-exposure to toxins, underlying mental illness itself may impact responses to medications. Patients with obsessional personality traits and those who have experienced significant trauma more frequently react poorly to being maintained in states of partial awareness with sedative medications. Borderline personality disorder, a condition usually associated with trauma, carries a high likelihood of paradoxically agitated reactions to benzodiazepines [166]. Aggression is a more common after-effect of treatment with benzodiazepines than is regularly noted [167], and it may be more likely in those with high trait anxiety at baseline and those with antisocial personality disorder [166]. Atypical antipsychotic medications have the best evidence for achieving

desired effects of reduced anxiety and aggression in patients with Cluster B personality disorders while avoiding adverse physical and mood reactions [168–170]. These agents may be valuable adjuncts in the critical care phase of treatment of DSP patients, as such personality pathology is common in those who take purposeful overdoses (Level II-3 recommendation).

Legal and Ethical Issues

Psychopathology and the circumstances surrounding many acute toxicology cases give rise to unique legal concerns and produce moral distress in caregivers. The central goal should always be the best care of the patient, defined by professional standards of medicine and the ethics of care relationships. Legal standards sometimes support and other times impinge on ethical work in healthcare. By virtue of their specific training and experience with mental illnesses that may rob patients of insight and decision-making capacity, C-L psychiatrists can be helpful sorting out the proper course of action in the care of toxicology patients whose cases may be complicated in these ways. Familiarity with laws governing involuntary treatment is critical to psychiatric practice, as are expertise in assessing capacity for medical decision-making and the ability to mediate strained interpersonal interactions between and among patients, families, and treatment providers.

Consent to treatment requires that a patient understands the risks and benefits of proposed treatment and those of alternative treatments, including the option of no treatment [171]. Adult patients are presumed to be legally competent, and competent patients should give informed consent for *any* specific treatment; when a patient is deemed incompetent, an appointed guardian may give consent. A central issue is that many critically poisoned patients present for care with delirium that interferes with communication, information sharing, and the consent process. In this situation, presuming that patients would not want care simply on the basis of suspected DSP

and withholding treatment would be to err in at least two serious ways: (1) discounting the role of potentially treatable mental illness underlying the “suicidal” poisoning event and (2) disallowing the possibility that a patient’s perspective on living and dying may have changed. (Level III recommendation) The majority of patients with DSP do have psychiatric conditions driving suicidality that are amenable to intervention [46, 172] and do not frequently object to being treated or to having survived [24]. In the interest of survival, when a medical emergency exists in a delirious DSP patient, treatment may be delivered under the common law of implied consent [173]. (Level II-3 recommendation) In addition, there is the common-law principle of a duty of care to consider. Not all countries or provinces have an English common-law tradition. However, in those that do have such a tradition, a duty exists when a physician undertakes the care of a patient such that the physician must exercise a standard of care that would minimize risk of injury to the patient. The standard of care to be expected is that of a “reasonable person” possessing the special skills and knowledge of the professional involved [174].

The problem of adequately caring for patients with a variable degree of suicidal intent; patients who present with a deliberate, toxicologically serious poisoning requiring specific interventions; and patients who refuse to accept treatment is still a recurrent clinical and legal dilemma facing clinicians. Staff can be immobilized by the threat of litigation – of being found negligent for failing to treat a patient in need of but refusing treatment – or of assault – for treating a patient without consent. The available advice on how to proceed can seem conflicting. Legislation and common law may vary in different jurisdictions, and a clinician’s capacity to navigate the legal complexities may be inadequate. Treatment models that use psychiatric consultants and other staff or relatives to shore up the rationale for intervention and/or improve compliance with procedures may be useful to resolve conflicts [26]. (Level III recommendation) It is important to understand certain legal principles and precedents when determining an

approach to the treatment of a poisoned patient. A detailed examination of the clinical and legal standards for the care of suicidal patients in the United States is available [175].

One critical point to remember is that in medical emergencies, lifesaving care frequently proceeds without patients being aware or sufficiently cognizant of their circumstances to make decisions about what is done to or for them [176]. Although the patient's own actions (through DSP or drug misadventure) may be viewed as the cause of the toxicologic emergency at hand, the condition is still often just as critical, so as in other emergency situations in which lifesaving measures must be employed, physicians may institute treatment immediately without fear of incurring legal liability [171]. (Level II-3 recommendation) A review of the law in relation to suicide suggested that "it appears that there is a judicial assumption that there is a duty to take reasonable steps to prevent the suicide of a competent, informal (voluntary) patient in both psychiatric and ordinary health care settings" [177]. The common law recognizes that a reasonable person would want to receive treatment in a true medical emergency, even if his impaired awareness at the time of the emergency precludes giving informed consent. Practically this doctrine holds that the physician cannot be found legally liable for performing a procedure to which the patient has not consented, provided the situation is truly an emergency and the treatment itself is medically sound [173]. In most cases of drug misadventure, accidental poisoning, or unintended medication-related calamity, the forensic and philosophical calculus will be considerably less fraught due to decreasing levels of autonomous expression of lethal intent. Some cases are, of course, unclear and may have features suggesting a variety of causes and motivations behind the acute toxicologic presentation. Based on the logic, above, however, legal action taken against healthcare providers who intervene in the wake of self-poisoning rarely gains traction [178]. In this way, despite the potentially jarring and frustrating experience of caring for patient who is critically ill by his own hand, legal and ethical principles typically align in the majority of cases.

A degree of legal and ethical complexity does arise in rare cases when a patient with clear sensorium, who at least has the appearance of being a capacitated decision maker, actively resists lifesaving intervention. Examples include the relatively early presentation to hospital after ingestion of acetaminophen, lithium, warfarin, calcium channel blockers, and other potentially lethal agents with delayed impact on CNS function. An article from the United Kingdom outlining legal issues affecting the care of DSH patients emphasized the concept of competency as the principal determining factor in decisions concerning treatment; however, such a narrow "rights"-based view of competency in suicidal patients has been challenged in a review of case law in relation to suicidal actions [177]. It also has been suggested that because competency is a legal and not a clinical construct, clinicians are unable to apply such principles correctly [179]. Others have suggested that particular clinicians (e.g., psychiatrists) might be able to render an opinion as to a patient's competency and that psychiatrists are able to detect subtle forms of incompetency more readily than other physicians [171, 180, 181]. Although competency assessments usually involve cognitive criteria and processes, affective disorders [171, 182], paranoid states, and even anorexia nervosa also may affect a patient's competency [181]. Still, a medical opinion will be rendered about *capacity* for medical decision-making not *competency*. The former depends on the ability to understand one's condition, appreciate the consequences of various treatment options, weigh risks and benefits of each in a rational manner in light of one's goals and values, and make a consistent choice for a particular course of action [183]. Determination of capacity is always made for a particular decision or set of healthcare circumstances, whereas competency is judged as a more general state of ability for autonomous self-governance. Despite this distinction, courts do typically rule on a patient's competency in line with physicians' (especially psychiatrists') opinions on capacity [184].

The practical problem for a critical care toxicologist is the time it takes for such processes to render a guiding verdict. So, urgent psychiatric

consultation can be useful, but the backing of a judge will not come in time to allow delay of decision-making about lifesaving interventions. As a result, many toxicologists feel comfortable proceeding with a plan that entails compelling a patient to submit to care – a process that may involve physical restraints and forced medications – with or without the supporting input of a consultative psychiatrist. In such cases it is important to make a genuine assessment of the level of medical emergency involved to justify aggressive intervention. (Level II-3 recommendation) Self monitoring on the part of caregivers is also essential to avoid acting on the frustration engendered by resistant patients in ways that punish them or cause even more suffering – examples include the delivery of *N*-acetylcysteine in oral form when intravenous treatment would be adequate and more humane or the maintenance of physical restraints when pharmacologic treatment for agitation would provide relief and allow unbinding. Maintaining attention to patients' perspectives and experiences while navigating care relationships and crafting a treatment plan is advised. (Level III recommendation) It is useful to remember that many DSP attempts are carried out by individuals who feel as though their life events and emotions are both out of control and ingestions may, in part, represent a desperate attempt at mastery over them [185]. A purposeful ingestion may feel like the last available option to address overwhelming upset. Thus, taking away all control in the experience of toxicologic treatment can increase emotional distress and produce even greater conflict with caregivers. Preservation of a sense of autonomy with options, guided by psychiatric consultants if necessary, can more smoothly persuade ambivalent, distressed patients to accept lifesaving care (Level III recommendation).

Although rare, it is likely that a growing minority of patients will come to care with adamant resistance to treatment that is not merely a reflection of psychiatric distress. Most will not have sufficiently preserved CNS function to voice it in the moment, but they will have clearly articulated a desire to die in the context of sustained healthcare relationships. A relational,

contemplated, and consistently communicated desire for death is a key distinguishing factor in such cases. It is a core requirement in legally permitted pursuit of assisted suicide [186, 187], and it also supports the acceptable practice of foregoing life-sustaining interventions in terminal conditions like end stage renal disease and amyotrophic lateral sclerosis [188]. Still, in order to allow a critically ill patient to expire after deliberate poisoning, a physician cast in the caregiving role would have to be certain not only of intent but also of legality in the relevant jurisdiction. (Level III recommendation) Timetables of intervention in emergency departments and ICUs rarely allow for the necessary gathering of data. Ethical distress is virtually inevitable on some level for some portion of a medical team facing such a situation. The few cases documented thus far have been challenging and each unique in their own ways [189]. Not surprisingly, emotionally charged disagreements between and among family members can complicate matters, even though individual patient autonomy is the most prized bioethical principle in Western medicine, and assisted suicide laws are designed to enhance and defend it above other interests [190]. Urgent psychiatric consultation and, if available, medical ethics consultation are strongly advised to guide the course of action in these cases. (Level II-3 recommendation) It is also advised that hospitals make advanced preparations for how cases like these will be handled in light of local legal standards and practice guidelines crafted with input from the communities they serve (Level III recommendation).

One last category of even more complicated cases has recently highlighted the thorny convergence of these issues. For a number of years, advocates for better healthcare practices have encouraged patients to have proactive conversations with loved ones and treatment providers to outline wishes for interventions in various scenarios, particularly at the end of life. In the United States, the Physician Orders for Life-Sustaining Treatment (POLST) form is one common example of a simple document that comes out of such conversations and fairly informally guides providers within the health system in which it was

created [191]. Other patients have a clearly written, more legally binding set of advance directives. Patients with different kinds of healthcare documents have presented to acute toxicologic care with varying, unclear degrees of suicidal intent [192–194]. Intensivists have been reluctant either to honor or to ignore such directives when toxicology patients are critically ill. Some documents plainly state a desire not to be intubated or receive hemodialysis without qualification; despite that clear language, often the circumstances imagined that drive those firm written choices are those around terminal conditions in which such procedures merely prolong bodily integrity without the hope of restored health and function. However, intubation and hemodialysis have circumscribed utility that can prevent morbidity and mortality in cases of poisoning. Patients may be restored to full health with resuscitative care that must be instituted rapidly but is crucial to maintain for only a short time. Based on this rationale, and supported by precedent [195], some medical toxicologists are therefore more comfortable with overriding advance directives than with effectively participating in a patient's suicide plan that would be facilitated by such documents. This position is supported by a key analysis in the bioethics literature that recommends caution, consensus building, and the passage of time while critical care is maintained to gather data before considering the withdrawal of support – and considering withdrawal only if the same would be done in a case without suicidal overlay [196] (Level III recommendation).

At least one case has been published about a mentally ill individual who apparently crafted advance directives just days before an episode of DSP for the explicit purpose of making suicide completion more likely [197]. The 26-year-old patient ingested ethylene glycol, called an ambulance, and presented to hospital with her own self-prepared document in hand; she indicated that she desired to die on her own terms and insisted on comfort measures only. Despite longstanding depression and “untreatable” personality disorder, the patient was judged to have capacity to make these decisions and allowed to expire. The presence of interpersonal dysfunction tied directly to

the suicidal act and the absence of a legal sanction for assisted suicide in this case, however, would have led most psychiatric consultants to advise pursuit of all necessary lifesaving interventions. It is important not to merely assume that a suicide attempt automatically invalidates all advance directives, but following mandates of the most updated ethical analysis of the issues would lead to the same conclusion [198]. (Level III recommendation) As debates surrounding death with dignity evolve, POLST and other forms appear in the medical records of patients lacking capacity, and the threat of malpractice looms, the work of a critical care toxicologist in this arena will expand in complexity.

Vulnerable Populations

The majority of acute toxicology patients are young to middle-aged adults, but poisonings in other age groups are not uncommon. Unique issues accompany individuals at the extremes of age with which a psychiatric perspective can be helpful.

Adolescents and Children

Poisonings in young children, whether toxicologically significant or not, usually are “accidental,” in the sense of there being no deliberate intent on the part of the child to harm himself or herself. Most primary prevention programs aim to reduce the morbidity and mortality of these poisonings through educational initiatives and packaging modifications (e.g., child-resistant closures on containers of sublethal total doses). It has been suggested, however, that the factor most closely associated with childhood poisoning is the general level of psychological adjustment in the child and the family [199]. Perhaps 25% of all child patients repeat self-poisoning, and although few studies have focused on these populations, it would seem that child behavioral disturbance and family dysfunction are highly relevant [199]. In a series of clonidine poisonings reported in Australia, it was noted that the child's own

medication, for the treatment of a behavioral disorder, was the source of ingested medication [61]. There is a suggestion that rates of suicide attempt are increasing in younger children, especially those with mental illness and behavior disorders who are treated pharmacologically [200]. These findings suggest that psychiatric assessment in cases of all childhood poisoning cases may be worthwhile to identify possible remedial factors. (Level II-3 recommendation) We are not aware, however, of any consultation psychiatry studies or programs specifically directed at this population, and psychiatrists trained to care for children are often not available for acute hospital consultation.

Adolescent suicide, DSH, and DSP have been reported to be increasing in recent years [200, 201]. Drug and alcohol misuse has always been a major issue in adolescents, and increasing numbers of latency-aged children with recreational drug exposure resulting in treatment are being reported [202]. The assessment of the adolescent poisoned patient may present particular difficulties; staff from the psychiatric service may be able to provide consultation services for the patient and liaison services for the family and staff [122]. Psychiatric disorders are as common in child and adolescent suicide attempters as they are in adult patients, although the pattern of illness is different [203–206]. In addition to psychiatric disorders, self-poisoning patients frequently have difficulties in relationships with parents, boyfriends or girlfriends, school, work, or physical health [207]. Within the hospital setting, health professionals caring for children experience clinical and ethical problems similar to those of professionals involved in the care of poisoned adults, with some additional complexity. Parental psychopathology and relational conflicts with their adolescent children can stymie treatment plans. Assessment and care of the adolescent patient can be complicated by law. While parents and guardians remain the decision-makers for treatment (as long as they are deemed to have both capacity and the best interests of their children at the fore), many states enforce confidentiality in the substance use related care of teenagers [208, 209]. At the same time, work in psychotherapy with young people may

leave parents out of the details of the treatment, but suicidal risk is the recognized threshold for bringing in responsible adults [210]. The critical care of poisoned adolescents obviously can give rise to a complex mix of concerns along these lines. Staff from a psychiatric service may be able to address such difficulties, assisting with care relationships and legal logistics [122].

Delirium in children is often drug induced and is usually the result of accidental poisoning but occasionally may be deliberate or iatrogenic. Young age is a risk for unexpected and paradoxical reactions to compounds that affect the CNS [64]. A delirious child may interfere with intravenous lines and endotracheal tubes or even exhibit hostile behavior, and the psychiatric assessment and care of children at an early stage in delirium is recommended [211]. (Level III recommendation) Even when their ingestions are not intentional, children are often at risk for acute and chronic problems with adjustment after a poisoning event [212, 213]. In the ICU in particular, the presence of a parent may be one of the most useful interventions for reassurance and behavioral management [214] (Level III recommendation).

Other clinical scenarios with focus on parents require mention. Although uncommon, children are vulnerable to being victims of poisoning, and the responsible party in the majority of these cases is a parent. Sometimes the intent is not to cause harm but to exert behavioral control. In either case, however, protective services for the child (and any siblings) should be pursued. (Level II-3 recommendation) Some unfortunate situations may result from severe mood and psychotic illness in a parent, so psychiatric consultation may be indicated. Munchausen syndrome by proxy is a form of factitious disorder in which an adult presents another vulnerable individual (usually a child) for hospital treatment. The child may be gravely ill, particularly if a poisoning has engendered the clinical presentation [215]. Parental motivation is typically to receive attention as the attendant to the child, therefore interacting with caregivers in deceitful ways that obscure the true cause of sickness and prolong episodes of care is common [216]. A poisoning in this context is particularly stressful and warrants psychiatric

involvement as part of a multidisciplinary approach [217]. (Level III recommendation) Legal intervention for the safety of the child may be necessary, and notification of child protection services is mandatory. Considering the severe psychopathology in such parents (often in the form of Cluster B personality disorders), mental health intervention to prevent a reactive act of violence or self-injury may be required. Child and parental deaths have been known to occur in this curious syndrome.

Elderly Patients

Baseline cognitive deficits are the greatest source of toxicologic vulnerability in older individuals [113]. As already noted, medications that impact CNS function have a greater likelihood of serious consequences in those who already have neurologic impairment. The elderly also take more medications at the same time that diminished hepatic and renal function reduce clearance of those potential toxins. Medication errors at home in those with failing memory and/or eyesight are a major problem. As in the case of children, involvement with mental health services in the wake of a toxic event can help to reveal underlying problems in the individual and his psychosocial system to prevent recurrence. (Level II-3 recommendation) Studies have shown that psychiatric consultation in the acute medical setting is one of the most common methods by which dementias come to light in a way that leads to necessary outpatient interventions, so it is part of standard practice for psychiatrists to assess carefully for cognitive disorders in hospital consultations [218]. Even during the course of acute treatment, C-L psychiatry can help with strategies to prevent complications from delirium and manage expectations for CNS recovery (which takes longer in those of advanced age). (Level III recommendation) An episode of delirium comes with increased risk of cognitive impairment several months after hospital discharge in any patient [219], with older patients having a greater likelihood of not returning to premorbid mental functioning [54, 163].

Physical limitations add complexity to life circumstances in the elderly, as well, with dependence on caregivers and more general reliance on goodwill. This makes older patients with less resilience and independence more likely to suffer toxicologic problems at the hands of others. Patients of all ages with physical and intellectual disabilities are vulnerable in similar ways and are thus at elevated risk for abuse and neglect perpetrated by those charged with their care – a situation for which a toxic exposure may be the heralding event. The literature outlines in sad detail how the cognitively and physically challenged suffer abuse in professional care settings of various types, and an important proportion of those events is mediated by toxic exposures [220–222]. The elderly may be the most frequent victims of homicide by poisoning [223], but psychoactive substances can be used with malicious intent (e.g., sexual molestation, assault, robbery, abduction, and attempted murder) toward vulnerable individuals in any age group. History taking from multiple sources with an open but critical appraisal of information is essential to revealing the psychopathology behind such rare toxicological presentations. With their focus on detailed evaluation of relationships and systems surrounding an identified patient, psychiatrists may be instrumental in uncovering foul play.

Lastly, the problem of elder suicide is an important reason for presentation to critical toxicologic care. Mortality after suicide attempt is common in older individuals, with frequent use of lethal means, so a smaller fraction of elderly attempters reaches hospitals (Fig. 1). Those who do and survive demand special attention. DSP represents an opportunity to intervene in this portion of the population with the highest suicide rates [201]. Psychiatric consultation is a must in any older person presenting for acute hospital treatment who raises concern for suicidality, despite the fact that resistance to mental health care is common in this age group. (Level II-3 recommendation) The elderly may also receive psychiatric consultation at lower rates than younger patients due to physician biases [224]. However, identification of treatable mental illness in older people with interventions focused on safety – like mobilization of care relationships

and restriction of lethal means – is essential. Acute psychiatric hospitalization may be necessary, as well, but attention to other risk factors common to this group (e.g., pain, chronic physical illness and disability, isolation, loneliness) is even more critical to prevent an episode of DSP from being the sentinel event on a path to eventual suicide [225, 226] (Level II-2 recommendation).

Psychosomatic Interventions and Outcomes

Of the range of potential outcomes of DSP, there are three that are most important to discuss here: psychiatric treatment, repetition of poisoning, and subsequent suicide. Psychiatrists should have interest and a potential role in individual patient care along with public health initiatives around each of them. Psychiatric care also is important in other circumstances involving poisoned patients. Chronic neuropsychiatric sequelae sometimes can follow serious poisonings (e.g., with agents such as carbon monoxide [227] and organophosphates [228]). Patients with chronic illness states arguably attributable to various toxicities [229], such as “multiple chemical sensitivity” [230], also may benefit from psychiatric input to reframe expectations and plan a recovery-based model of care to restore function [231]. (Level II-3 recommendation) Occasionally an anxious or psychotic patient, believing himself or herself to be seriously poisoned, may enter the treatment system as a toxicology patient and present a clinical challenge [105]. Some chronic poisonings (e.g., carbon monoxide, lead, and mercury) may present with primarily psychiatric symptoms [232], and recognition of the toxicity may be delayed. A discussion of these specific examples is beyond the scope of this chapter.

Psychiatric Treatment

Psychiatric hospitalization may be the next intervention after physical recovery from an acute episode of DSP. It is common practice to keep patients under close observation, in opposition to

their desire to leave the hospital if necessary, until psychiatric consultation can be obtained to assess for safety and treatment needs. If an individual remains acutely suicidal, the required medical setting needs to be a secure environment with close observation. (Level III recommendation) A patient whose intentional ingestion does not result in a substantial change in mental status and/or level of consciousness may be at higher risk due to ongoing self-injurious urges from unmodulated psychiatric distress [24]. However, the vast majority of patients who experience delirium or coma from DSP do not have ongoing suicidal upset after recovery of CNS function [24]. For this reason (along with the reality of decreasing availability of inpatient psychiatric beds, at least in the United States), a growing percentage of DSP patients are not treated with the decades-old British Atkins Report recommendation for universal psychiatric hospitalization [233]. (Level II-2 recommendation) When mental health hospitalization is planned that involves transfer to an appropriate treatment center, patients’ somatic medical needs must be considered. As many facilities are now no longer connected to general hospitals, but free-standing (with little in the way of acute medical support), there may be some resistance to accepting patients for care who have physical treatment needs – or even benign laboratory abnormalities. A recent severe poisoning can raise concerns for receiving providers, as well, therefore having psychosomatic medical experts consulting on such cases can provide the necessary liaison for more efficient transfer to the next phase of care (Level III recommendation).

Mental health expertise can be helpful in determining the best use of care resources in the wake of DSP, drug misadventures, and toxicologic accidents, taking into account the specific factors involved in the acute presentation of each case in conjunction with the chronic conditions underlying them. Historically, the very act of DSP sufficient to require critical care led some psychiatric consultants to almost reflexively opine that judgment is impaired, risk is high, and the individual in question must be ill. Over time, however, psychosomatic medicine experts have emphasized looking beyond the severity of the poisoning

event to evaluate an individual's foregoing and subsequent states of mental health to determine what issues are amenable to intervention and in what form and setting [234]. (Level III recommendation) Psychiatric disorders [16], substance-related problems [235], and personality disorders in adults [21, 236, 237] and adolescents [238] are common in populations of DSP patients, although the patterns of illness may be different at different centers [46, 239]. In the absence of randomized controlled trials to clearly indicate which patients with which conditions should be psychiatrically hospitalized after DSP, studies of cohorts of patients suggest that the choice should depend on clinical factors psychiatrists use to determine the necessary level of care for other patients seen in acute consultation [234]. (Level II-2 recommendation) Hospitalization most commonly is instigated to protect a patient from imminent risk of self-harm, to reduce the risk of harm to others, to treat a psychiatric disorder or personality disorder, or for a combination of these reasons. It should always reflect a plan to address a condition that may be treated rather than a mere concern for the possibility of repeat suicidal behavior. (Level III recommendation) Following this principle may lead to a decision against admission of some DSP patients, and conversely an acute toxic episode may herald serious mental illness acuity that demands inpatient treatment even if the exposure was not deliberate or suicidal. Persisting psychotic symptoms or mood disturbance after a drug misadventure could also warrant inpatient mental health intervention. Not surprisingly, then, the rates of psychiatric admission directly after poisoning episodes are unclear and locally variable – for DSH, a range of 5–10% has been reported in the United Kingdom [16], whereas another study reported a rate of 28% in a US unit [19], and a Swedish study found a rate of 57% [240]. A study restricted to DSP patients in Australia reported 29% referred for psychiatric hospitalization, 18.3% on involuntary status [241]. It is to be hoped that because the majority of DSP patients frequently have a psychiatric disorder, have psychiatric symptoms, or at least are making a “cry for help,” appropriate aftercare can be provided. Studies of depressed and alcohol-

dependent patients who have made a suicide attempt suggest, however, that treatment before and after a suicide attempt is frequently inadequate [242, 243]. Attendance for psychiatric follow-up when offered after a poisoning episode has been reported to be as low as 16% [244]. A majority of adult victims of DSP have not historically made durable, sustaining connections to mental health services. Unfortunately, the same is true for young people who should, presumably, have invested family members involved to advocate and ensure participation in treatment [245, 246]. Important elements of care may include addressing potential sources of nonadherence, determining proper intensity of treatment, providing family psychoeducation, treating concurrent psychopathology, and remediating social skills and problem-solving deficits [247], all areas of expertise offered by a C-L psychiatrist (Level II-2 recommendation).

Impaired insight and associated effects on treatment adherence are a *sine qua non* of mental illness. However, the issue of coercion may play a role in patients' low rates of consistent follow-up after DSP and drug misadventures as well. Psychiatric hospitalization may be undertaken under voluntary or involuntary status. Even patients who voluntarily enter acute mental health treatment report experiencing a sense of coercion [248]. Study results are mixed, but being coerced into treatment as opposed to receiving clear communication of clinical rationale with fair assignment of voluntary versus involuntary status at the time of admission may be associated with poorer outcomes in the form of symptom change [249] and in maintenance of connection to mental health resources [250, 251] – particularly in patients from minority and disadvantaged backgrounds [252]. For this reason, clear communication in line with reasoned clinical assessment is superior to “bargaining” from a position of authority about admission versus discharge. (Level III recommendation) Issues around power and decision-making in care relationships can be challenging to navigate when balancing autonomy and beneficence, but it is recommended that sensitivity to these issues be maintained with the patient's best interest at the fore as disposition after critical

toxicologic care is planned [253]. The ethical values of law and medicine may come into conflict when the possibility of involuntary psychiatric treatment is concerned [254]. However, in the treatment of psychiatrically ill patients, initial imposition on autonomy can lead to greater freedom [254]; in other words, a greater benefit may accrue to the patient because of the insistence on legally applying appropriate psychiatric treatment.

For a patient with ongoing psychiatric acuity, accompanying imminent suicidal risk is a central issue when it comes to pursuing hospitalization even when the individual would prefer otherwise (v.i.). In a review of treatment standards for patients at risk of suicide in the United States, the authors noted that reasonable care must be shown by certain affirmative precautions, with standards equivalent to those prevailing in the community, and that the duty of care is proportionate to the patient's needs [255]. The most common legal action brought against psychiatrists is for the failure to protect patients from harming themselves, and courts impose much stricter standards on inpatient than on outpatient care [255]. Psychiatrists who follow the procedures of civil commitment laws are likely to have a broad protection from liability [256]. Patients who are willing to have acute psychiatric care after DSP may be disposed of by their medical teams to mental health facilities without such expertise from C-L psychiatry. But, having psychiatric consultants involved in all cases where there are conflicts between perspectives of care teams and patients regarding disposition can help to navigate the legal process effectively for critical care providers as well (Level III recommendation).

Specific legislation usually defines the circumstances in which a person may be detained involuntarily. Details vary among jurisdictions but typically the patient must be both "mentally ill" and dangerous to either self or others. This judgment involves a prediction concerning the likelihood of such dangerousness or harm and an accepted threshold for such a prediction [253]. The clinical task often involves an evaluation of the balance between civil liberty and

enforced protection and benevolence [257]. Some authors have suggested that the complexity of such evaluations, lack of reliable community psychosocial services, and fear of litigation from other parties down the line (e.g., family, victims of violence) may lead to some patients' being unnecessarily hospitalized under civil commitment justified by a perceived risk of violence [258, 259].

In 1983, "a model state law on civil commitment of the mentally ill" was proposed in the United States, suggesting four criteria necessary for involuntary commitment [260]. A later summary of commitment legislation suggested six common criteria (Table 2), which essentially still obtain [261]. An important focus of these developments was the need to place the patient's interests first, especially the need to address psychiatric conditions likely to respond to treatment and not to consider potential dangerousness as the only criterion for commitment [260]. (Level II-3 recommendation) Similar principles have been incorporated into mental health legislation in other countries [262–264]. In a review of all statutory requirements for involuntary hospitalization in the United States, it was found that each jurisdiction requires a person to have a mental illness and be dangerous to himself or herself, and 85% of jurisdictions require the dangerousness to be a result of the mental illness [265]. Only two jurisdictions require, however, that an attempt be made to involuntarily commit a person in imminent danger to himself or herself. These findings were similar to an older review [266].

Table 2 Eligibility for involuntary hospitalization from two studies

Stromberg and Stone [260]	Bednar et al. [261]
A severe mental disorder is present	Mental illness
Lacks the capacity to make a reasoned treatment decision	Danger to self or others or grave disability
Has a treatable condition	Refusal to consent
Likely to harm self or others	Treatable condition Lack of capacity to decide on treatment Use of the least restrictive treatment

It has been suggested that clinicians rely particularly on the “dangerousness” criterion in seeking a commitment while being sensitive to the patient’s need for treatment [267]. Noting the limitations of predicting imminently dangerous behavior in individuals and the rarity of completed suicide in general, more recent work in forensic psychiatry recommends a focus on respect and supports the right of persons to make decisions, rather than on perceived vulnerabilities and calculations of suicide risk [268]. (Level III recommendation) In the care of children or incompetent adults, parents, legally appointed guardians, or other responsible individuals serve as decision-makers with respect to treatment, so psychiatric hospitalization may be pursued voluntarily even if a patient does not assent. Rarely, it may be necessary to pursue involuntary treatment against the will of a parent or legal guardian on the basis of acutely dangerous mental illness. In general, however, the younger the patient, the less likely an inpatient psychiatric admission will be necessary or helpful, and the more likely a consultant will determine that ongoing safety can be assured by family and/or caregivers at home with guidance, where some interventions can take place alongside intensive outpatient programming (Level II-3 recommendation).

In recent decades, partly to address shrinking availability of inpatient mental health beds, a number of treatment programs have been created that can serve as a sufficient match for different levels of psychiatric acuity. Table 3 lists various forms of mental health care that may be pursued as an appropriate level of support after episodes of toxicologic critical illness. The recommended choice will generally depend upon an assessed risk of violence and/or self-harm with corresponding need for safety monitoring in conjunction with suitability of specific treatment offerings for a particular patient. Some individuals have conditions that may be expected to stabilize quickly, whereas others may be deemed to require longer-term treatment before being safe to return to care in the community. For others, a significant (even primary) focus on chemical dependency may be the key to recovery. Inevitably, some options will not be available in certain locales,

Table 3 Mental health treatment options after toxicologic care^a

1. Highest acuity locked facilities
a. State-sponsored long-term residential treatment program
b. Inpatient mental illness and/or chemical dependency program ^b
c. Acute crisis-stabilizing inpatient psychiatric unit
2. High acuity unlocked facilities
a. Intensive residential treatment program
b. Acute/residential chemical dependency program
c. Sub-acute stabilizing inpatient program ^c
3. Moderate acuity resources
a. Partial hospitalization program (“day treatment”) ^d
b. Intensive outpatient program
c. Community-based crisis housing program
4. Low acuity resources
a. Monitored/supportive residential placement
b. Assertive community treatment (ACT)
c. Structured group therapy program (e.g., dialectical behavior therapy)
d. Urgent access clinics
1. Psychopharmacology
2. Psychotherapy
3. Social services/intensive case management
e. Continuation of established outpatient treatment

^aMental health care resources are presented in decreasing level of acuity and corresponding capability of active safety monitoring. Within each numbered group, options are listed in decreasing order of resource intensity with a generally inverse relationship to the time necessary for placement in a given program

^bPrograms that combine treatment for addictions with other mental illnesses (i.e., MCD programs) are less commonly available but may offer better care of patients with these comorbid conditions

^cSome inpatient units are unlocked, but still offer a high level of intensive treatment. They are more common for particular illnesses and/or populations (e.g., primary mood disorders, eating disorders, adolescents)

^dPatients in partial hospitalization typically gather on units similar to inpatient settings for intensive treatment during most days of the week and return home each evening

and bed availability may also necessitate moving up or down from an initial recommended level of intervention; this unfortunate practical reality may be particularly relevant for patients at the extremes of age for whom a shortage of specialized services is the rule in most areas of the United States and United Kingdom, despite the appearance of growing demand [269–271].

As previously noted, an inpatient locked facility may indeed be necessary for a patient whose ongoing mental illness acuity is sufficiently high

to make further suicidal behavior imminently likely. Such units typically have a variety of services available (e.g., psychopharmacologic expertise, psychotherapy, and social services) and the ability to make detailed multidisciplinary assessments with referrals to ongoing care aimed at preventing recurrence of suicidal crises. Sometimes an inpatient stay makes for more efficient connection to long-term resources; hospitalization may even be required to meet eligibility for certain services. But patients may wait days or even weeks in some healthcare systems to access inpatient care. Having C-L Psychiatry actively involved to advocate for patients and their families can fulfill some requirements and, in some cases, expedite connection to services. Ongoing assessments can help to gauge when patients may safely transition to different levels of care that are available, as some patients who linger in hospital with sequelae of acute poisoning (e.g., receiving short-term hemodialysis until resolution of toxic renal failure) may be quite mentally stable once ready for medical discharge. Also, having C-L teams begin to deliver treatments after recovery from a poisoning event – first in the form of psychotherapy and when it is toxicologically safe, perhaps with medications as well – can help to stabilize mental illness and ready patients for disposition options other than acute psychiatric hospitalization.

Repeat Episodes of Poisoning

Much of the focus on the issue of psychiatric treatment relates to the hope that assertive after-care intervention will prevent recidivism. Repetition of DSH has been reported to have annual rates of 6–30% (median 16%) [16]. According to one Australian study, repeat DSP is quite common after an index medical encounter has ended; 4.5% of overdose patients present to hospital again within a month, 10% within 6 months, and 14% within a year [20]. It is not yet clear the extent to which particular models of service provision affect repetition rates. Hospital admission improves access to psychiatric services [26, 81], and studies suggest less favorable outcomes for

those discharged after emergency observation only [272, 273]. Therefore, admitting all DSP patients rather than making discharge decisions based on any of the complex analysis outlined above may have merit [16, 233, 274]. As previously discussed, however, such a practice policy is not clearly correlated with decreasing repeat DSP or suicide, is not in line with legal and ethical standards, nor is it feasible in most healthcare catchment areas (*vide supra*. Psychiatric Treatment). On the other hand, merely arranging for systematic follow-up with primary care medical providers after DSP is not sufficient to address mental illness acuity, reduce suicidality or hopelessness, or reduce rates of repeat attempts [275]. Therefore, efforts to provide for thorough psychiatric evaluation and treatment planning must be undertaken without reliance upon the option to transfer all DSP patients to an acute mental health facility. (Level II-2 recommendation) C-L Psychiatry presence in the acute medical setting may be helpful not only with that necessary evaluation but with making recommendations and arrangements for clinically meaningful interventions (Level III recommendation).

Certain DSP patients may be deemed suitable candidates for the few evidence-based interventions that may decrease the likelihood of repeating. In recent years, there have been a number of systematic reviews and meta-analyses reporting on interventions to prevent or reduce repetition of DSH. Although there have been no pharmacological interventions of clearly demonstrated effectiveness, there have been effective psychological and brief contact interventions for unselected adult hospital-treated DSH populations; effective psychological interventions for adults meeting diagnostic criteria for BPD; and effective psychological interventions for adolescent DSH populations. The two main outcomes of interest are: the binary outcome of any episode of repeat DSH and the number of repeat DSH events.

A recent Cochrane review of pharmacological interventions identified only seven relevant trials ($n = 546$ participants). There was no effect on any repeat DSH (including DSP) for: newer generation antidepressants, low-dose fluphenazine, mood stabilizers, or natural products. A

significant reduction in repetition of DSH was found in a single trial of flupenthixol (OR 0.09, 95% CI 0.02–0.50), although the quality of evidence was very low. There was no data available on adverse effects. Authors of the review concluded that it is not possible to make firm conclusions regarding pharmacological interventions because of the low quality of the available evidence and the small number of trials identified [276]. Specific focus on patients with the highest rates of repeat DSP/DSH has not been promising with respect to pharmacotherapy either. Meta-analysis of four trials of drug treatments showed that pharmacotherapy was ineffective in reducing repetition of DSH events in patients with BPD; while individual drug trials, valproate (one trial), olanzapine (two trials), and ziprasidone (one trial) also showed no benefit [277]. From the perspective of a medical toxicologist, especially noting these findings, reliance upon nonpharmacologic interventions for patients with high rates of DSP may be more prudent.

A recent systematic review of psychological and psychosocial interventions in unselected DSH populations identified 36 trials with suitable data available from 30. Meta-analysis showed a significant benefit for all psychological and psychosocial interventions combined for the outcome of any repeat DSH (RR 0.86; 95% CI 0.76–0.98), (NNT = 33) and significant effectiveness for the secondary outcomes of suicidal ideation severity, depressive symptoms, and hopelessness. For specific therapies, there was a statistically significant effect in favor of cognitive behavioral therapy (CBT) (4 trials: RR 0.80; 95% CI 0.66, 0.97) and a larger effect in favor of psychodynamic interpersonal psychotherapy (1 trial: RR 0.31; 95% CI 0.12, 0.78), (Level I recommendation) but no statistically significant effect for complex interventions with outreach, problem-solving interventions, or “other” interventions [278]. A recent systematic review of brief contact interventions without therapy (letters, postcards, electronic messages, and telephone calls) in unselected DSH patients identified 14 trials with suitable data available in 12. Brief contact interventions showed a nonsignificant reduction for any form of repeat self-harm (OR) 0.87; 95% CI

0.74–1.04) but a significant benefit for the number of repetitions per person (IRR = 0.66, 95% CI 0.54–0.80) [279]. (Level I recommendation) Thus, an episode of critical toxicologic care can provide an opportunity for meaningful intervention through a mechanism as simple as sending a postcard after discharge – a gesture whose impact may remain significant for a variety of DSP patients even years after an index self-poisoning event [280].

For the specific population of patients with a diagnosis of BPD, a recent clinical practice guideline has been published. These guidelines reported a meta-analysis of 10 trials of psychological treatments, which showed benefit in reducing the repetition of DSH events compared with treatment as usual. Five specific trials that showed a significant reduction in repeated DSH involved treatment with dialectical behavior therapy (DBT) [277]. This form of psychotherapy relies on principles of Eastern spiritual living in conjunction with skills training to cope with intensely disturbing emotions and urges [281]. It was created to address the inability of some personality disordered patients to benefit from a common treatment that focuses more narrowly on thoughts and actions that either perpetuate or aid recovery from mental illness – CBT. Mentalization based therapy (MBT) has a similar inspiration and purpose, focusing on understanding and managing mental processes and their impact on relationships between self and others [282]. Along with the thought-focused manual-assisted cognitive therapy (one trial), CBT (one trial) and MBT (one trial) were also associated with significant reductions in DSH events [277] (Level II-1 recommendation).

For the DSH population of children and adolescents, a recent Cochrane review identified 11 trials ($n = 1,126$ participants) all were psychosocial interventions. Only dialectical behavior therapy for adolescents (DBT-A) and group-based therapy had multiple trials, and all other interventions were reported in single trials. There was no data available on adverse effects. DBT-A was not effective for the binary outcome of any repeat DSH but was more effective than enhanced usual care for frequency of DSH events as well as

reductions in depression, hopelessness, and suicidal ideation. (Level I recommendation) Mentalization based therapy was effective for repetition of DSH based on the risk-taking and self-harm inventory, in a population with repeated DSH or personality disorder. (Level II-1 recommendation) Other interventions, group-based therapy, compliance enhancement, CBT, home-based family intervention and provision of an emergency card, were not effective for the binary outcome of any repeat DSH [283]. A recent systematic review restricted to adolescent populations identified 19 trials ($n = 2,176$ participants); only psychological and social interventions were identified and no pharmacological interventions. There was a significant beneficial effect for all therapies combined for any repeat DSH (28% vs. 33%), with the largest effect sizes for DBT, CBT, and MBT. The authors concluded that psychological therapies appear to be effective; however, independent replication of DBT, CBT, and MBT trials is a research priority [284]. Good outcomes in the longer term may be related in large part to improvements in home circumstances and in relationships with supportive and well-functioning adults [205].

It is critical to note that a basic level of structure and support fit to a particular patient's overall level of function is necessary to implement any of these specific evidence-based treatments. (Level III recommendation) This is the rationale for a number of the options listed in Table 3. Some patients simply will not abstain from DSH without fairly constant oversight in a structured setting. Others with severe and persistent mental illnesses (e.g., schizophrenia, bipolar disorder) may benefit from the support of a multidisciplinary assertive community treatment (ACT) team of providers to enhance overall functionality and prevent repeated hospitalizations [285]. Such facilities and teams can then help to increase adherence to protective treatments, including depot medications to prevent episodic illness decompensations and training like DBT to manage suicidal distress [286]. (Level II-3 recommendation) In and of themselves, these services may not specifically reduce DSP but serve a necessary function in the longitudinal care of mental illness and provide a

framework within which to deliver specific therapies outlined above.

Still, a significant minority of DSP patients will return with another episode of critical toxicologic illness. Repeaters may have a higher general burden of psychopathology [287], with greater co-occurrence of personality disorder, psychosis, traumatic brain injury, and/or early childhood disruption [288, 289]. A similar pattern of psychiatric and social problems is reported for adolescent repeaters [290]. Repetition also may constitute a behavioral response to stressful situations [21]. Psychiatric assessment of these patients seems warranted during repeat episodes to address psychological morbidity and current personal crises even when previous consultations may appear to have had no benefit, and an impact on subsequent suicidal behavior may appear unlikely. (Level III recommendation) A pattern of difficulty or a particular issue in need of intervention may be identified that was not evident during previous rounds of treatment. Furthermore, as implied above, patients may not receive an adequate level of care in a healthcare system short on resources until repeat episodes of acute distress and danger are documented and used to build a case for more intensive resource allocation. Although a potentially frustrating process for hospital based teams that deal with a stream of critical illness situations, advocacy of this type that takes the long view of patients' lives before and after ICU episodes of care is essential to prevent a subsequent episode from ending in death.

Suicide

Although most patients who come to medical care after an overdose survive a given DSP attempt, nearly 20% of Americans who die by their own hand do so by ingestion of toxic substances [291]. A review of 24 longitudinal cohort studies concluded that patients with an episode of DSH have a 1-year median rate of completed suicide of 1% (approximately 100 times the general population risk) [16], and the 5-year suicide mortality rate after an index episode of DSH is over 4%

[4]. Prospective longitudinal research suggests that mortality rates specific to suicide in those with an episode of DSP are over 10% within 10 years [292]. The suicide risk is highest in the 12 months after an episode of DSH but remains substantially elevated over the general population risk for more than a decade [16]. About a quarter of all suicides are treated at a hospital for DSH in the year before they die, making the critical care toxicology unit an important point of opportunity in a serious public health epidemic [293, 294].

An exhaustive review of evidence-based suicide prevention is beyond the scope of this chapter. However, in the short term, during an episode of suicidal mood disorder, electroconvulsive therapy (ECT) has the best evidence to prevent loss of life [295]. (Level II-1 recommendation) After acute toxicologic recovery, psychiatric consultation will provide the most efficient path to treatment with ECT for suitable patients. Along with DBT (discussed above regarding evidence for preventing repeat DSH) [277], (Level II-2 recommendation) other evidence-based interventions are based on the long term. Particular medications like clozapine and lithium may decrease rates of suicide in high-risk populations with an “anti-suicide” effect that is independent of their impact on core symptoms of mental illness [296]. (Level II-2 recommendation) Since suicide is a relatively rare and largely unpredictable event that shows its public health impact over time in large populations, conducting studies to identify specific interventions that will prevent self-killing is challenging. For this reason, some experts have advocated a public health approach to the problem of DSP that seeks to shift the emphasis away from liberal use of psychopharmacology without evidence of benefit, minimize the availability of poisoning agents to patients at risk, and provide chemical dependency treatment to decrease unhealthy relationships with substances in general [24].

Collaborative Research Areas

The opportunities for future research at the toxicology/psychiatry interface are as limitless as the possibilities for scientific evaluation of antidotes

for specific poisonings. Some questions are more important because of their relevance to the seriously poisoned patient.

1. *What is the optimal pharmacologic management of delirium? Are there particular opportunities to optimize the management and care experience of acutely poisoned patients with delirium?*

There is a need for randomized controlled trials, with clearly defined populations, that evaluate drug and dosage regimens and use standardized instruments relevant to the core features of delirium or attendant behavioral disturbances to measure outcomes. More sophisticated work could be done through collaboration by crafting specific assessments and targeted interventions for different kinds of delirial states based on underlying etiologies and psychosomatic patient characteristics. Longitudinal studies are necessary to determine the impact of an episode of toxicologic critical care and its treatment on long-term psychosomatic health [297].

2. *What are the optimal pharmacologic treatments of the toxidromes – neuroleptic malignant syndrome, serotonin syndrome, and anticholinergic syndrome?*

There is a need for randomized controlled multicenter trials for definitive progress in the care of these specific conditions. Along with coordinating practical expertise, it may be necessary to develop suitable instruments to evaluate treatment response. Although these conditions are potentially lethal, study measures will need to address other outcomes in addition to mortality, since death is rare, but psychiatric and cognitive sequelae are common [110, 219]. A number of other clinically meaningful results for patients should be tracked, as well as resource utilization and lengths of hospital stay.

3. *Can repetition of deliberate self-poisoning be reduced?*

The repetition of DSP is an important phenomenon for which the epidemiology is reasonably well described, at least in some countries and regions. Now that systematic

reviews have revealed some potentially effective mental health interventions, practical attempts at larger scale implementation must be undertaken with meaningful assessments of success or failure. Other initiatives involving multidisciplinary collaboration could focus on reducing amounts of medications given with each prescription and purchase, and coupling delivery of new pills with pharmacy based take-backs of the old. The role of comorbid addiction must be investigated as well.

4. ***Which critically poisoned patients are referred for particular levels of psychiatric treatment; which patients benefit from hospitalization as opposed to other dispositions of care?***

These are important questions and, perhaps surprisingly, have not been addressed adequately. In a world of increasing use of pharmacologic agents in mentally ill patients and a corresponding decrease in hospital-based psychiatric care, the issue of resource utilization is critical. There are considerable limitations because of ethical constraints and practical difficulties in recruiting subjects. A fruitful approach would involve prospective, long-term, naturalistic cohort studies of clinical populations referred for psychiatric hospitalization. Outcome measures should include suicide, repeat DSP, service utilization, disability, quality of life, and social function.

5. ***What opportunities are available for medical toxicologists to improve outcomes in addictive disorders?***

Those involved in toxicologic critical care bear witness to the growing problem of morbidity and mortality from abusable substances, particularly alcohol, opioids, and synthetic stimulants. Studies are needed to identify potential interventions during and in the wake of an ICU admission for poisoning that may have a positive impact on chronic problems with substance misuse. A recent publication demonstrated that an episode of acute care after drug misadventure is an opportunity to reduce morbidity by limiting prescription of potentially lethal agents to those who are unable to regulate their use [298]. Research

should include attention to medications given, along with safety education for both patients and prescribers. As highlighted in a forward-thinking editorial piece, investigating opportunities for acute hospital contact to improve access to treatment for addictions and to implement harm reduction practices is a vital clinical science endeavor as well [299].

Future Interdisciplinary Developments

There have been calls by the US surgeon general for a systematic public health approach at a national level to reduce the frequency of suicide and suicidal behavior [300]. It also has been suggested that a comprehensive strategy aimed at preventing suicidal behavior should include a national collection of information on DSP/DSH and interventions, improved services for dealing with persons with suicidal behavior or at high risk for such behavior, the provision of information to and training of professionals and the public, and the provision of special services to high-risk groups [301]. In the United States, initiatives have been launched with focus on the problem of suicide in military personnel, specifically [302], and a taskforce to coordinate research with clinical practical applicability, in general [303], but neither has recruited medical toxicologists in any substantive way. Having experts in the care of poisoned patients actively involved in large-scale initiatives for preventing behavior that produces the majority of critical toxicologic illness is long overdue.

Furthermore, restriction of these interests only to suicidal or DSP patients would be misguided, noting the enormous public health problem of death and disability from addictive substances. Substance use disorders bring a growing number of patients to emergency and intensive care where a toxicologist may function as a part of a patient's network of addiction specialists, filling key gaps in access to expertise and coordinating with mental health providers to better integrate treatment for a variety of neurobiologically interrelated symptoms [304]. Safe and humane treatment of agitation is an important issue in both psychiatry

and toxicology. The related concerns of medical trauma and the accompanying critical issue of delirium for all hospitalized patients should also be of interest to both disciplines. Generally speaking, the large majority of individuals who come to the attention of a critical care toxicologist are likely to benefit from a mental health care perspective as well. There is ample opportunity for future collaboration between medical toxicologists and psychiatrists on many aspects of the management of poisoned patients and those who may have unhealthy relationships with exogenous substances.

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It has been said that managing a pregnant patient involves managing two patients at once, the mother and the fetus. This dual management paradigm is often seen as a complex balancing act, benefits to the mother against risks to the fetus and vice versa. In the setting of poisoned patients, this takes on an even greater complexity, especially given the relative lack of literature to support or refute any given treatment recommendation. The higher acuity of the critically ill patient brings this situation to its sharpest point as the death of mother, fetus, or both becomes an ever more likely possibility. This chapter will discuss specific recommendations in greater detail, but as a general rule, the best approach to all poisoned pregnant patients is to treat the mother in the same way as if she were not pregnant. Improved maternal survival will typically lead to improved fetal survival.

As with other patients, poisoning in pregnancy can occur in several ways, including suicide attempt, and accidental exposures. Pregnancy adds additional concerns for poisonings more directly related to the fetus, namely exposure to abortifacients whether intentional by the mother or malicious by another person.

This chapter discusses poisoning in pregnancy in critically ill patients. Epidemiology, physiologic changes in pregnancy, gastrointestinal (GI) decontamination, general management, administration of antidotes, and abortifacients are discussed. Specific poisonings in pregnancy that are well described in the literature, some unique case reports, and the toxic effects of several obstetric medications are reviewed.

Epidemiology

In 2013, 7384 exposures in pregnant women were reported to US Poison Control Centers, representing 0.3% of all human exposures [1]. There were 31 pregnancy deaths reported to Poison Centers from 2000 through 2013; 27 of these were intentional. A 2012 survey estimated

that illicit drug use occurs in 5.9% of all pregnancies with higher rates in younger women [2]. In a study of nonnatural (homicide, suicide, accident, undetermined) deaths associated with pregnancy over a 6 year period, 52.5% had a positive toxicology report postmortem (includes caffeine), with drug toxicity as the cause of death in 13.2% [3].

A study through the Toxicology Investigators Consortium attempted to quantify the patterns of pregnant patients who are evaluated at the bedside by a toxicologist [4]. Of the 17,529 medical toxicology consultations recorded during the study period, 103 (0.6%) involved pregnant women. Of these, 88.7% involved pharmaceutical overdoses, 51.5% of which were intentional exposures. A total of 25.2% of these cases involved acetaminophen, followed by sedatives/hypnotics (18.4%) and opioids (16.5%). This study was limited in that it did not describe long-term pregnancy outcomes.

Most pregnant women who self-poison do so in the first trimester. According to a population-based prospective study by Czeizel and coworkers, 61% of suicide attempts occurred before completion of the first trimester. Many of these attempts (38%) were early in the first month, but most of these were in the third and fourth weeks [5]. The reported reasons for the suicide attempts were either unwanted pregnancies and related tension or crisis. Of the case study group, 22% had early fetal loss compared with pregnant women without overdose, matched by maternal and gestational age. Mortality was 0.36% in the study group compared with 0.0% in controls.

Knowledge of the outcome of these pregnancies after overdose is important because many of these women intend to harm the fetus. Flint and colleagues observed the results of pregnancy in 61 women who overdosed during pregnancy [6]. In this group, there was double the rate of miscarriages but no increased risk in congenital abnormalities or premature deliveries. Most of these women ingested acetaminophen, salicylates, psychotropics, or phenobarbital.

Teratology

Historically, the US Food and Drug Administration (FDA) has used a coding system for risk factors of possible teratogenicity to the fetus. Under this system, categories were assigned based on reliability of documentation and assessments of risks and benefits. As an example, category X (contraindicated in pregnancy) includes agents in which studies in humans or animals have demonstrated fetal abnormalities and/or there is a positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience and the risks involved in the use of the drug in pregnant women clearly outweighs potential benefits [7, 8] (Table 1). While it provides a simple reference point, the FDA categorization system has limitations and must be interpreted with caution. This is especially true of category C, which may indicate a paucity of data. Category C drugs can have animal data indicating abnormal fetal effects and

lack human data, or can lack both animal and human data. Unfortunately, in one study approximately 90% of drugs used in pregnancy were category C [8]. FDA pregnancy risk categories were assigned at the time a drug was approved by the FDA and rarely updated afterward. Similar systems are also in use in Sweden and Australia.

In December 2014, the FDA published a new Pregnancy and Lactation Labeling Rule which became effective in July 2015 [7]. This rule eliminates the letter categories described above in order to reduce confusion and improve the quality of information provided. The new labels will contain descriptive information on use of the medication in pregnancy (including labor and delivery), lactation, and in females and males of reproductive potential. Prescription drugs submitted to the FDA after the effective date will be required to use the new format, while older prescription drugs will be phased in gradually. The rule will not affect over-the-counter medications.

The fear of teratogenicity related to an acute drug overdose seems to be unwarranted in most cases according to two studies by Czeizel and colleagues [10, 11]. The first study evaluated 1399 cases over a 30-year period and found no increase in congenital abnormalities in women with a “semilethal” overdose, defined as patients who ingested an overdose amount sufficient to cause unconsciousness for 1 day [10]. A later study found no difference in teratogenicity in infants exposed to a drug overdose by the mother at 3–8 weeks of gestation [11]. Although the data are limited, it seems that the fetus in the “vulnerable phase” of 18–60 days of gestation either dies from the poisoning or survives without an increased risk for congenital abnormalities. These studies are based on a limited number of exposures; the potential for teratogenicity still must be considered for specific substances. This concern is further borne out by a later study by Petik and colleagues which showed an increased rate of mental retardation in children born after a maternal overdose on a combination insomnia treatment (amobarbital, glutethimide, and promethazine) but not with any of those drugs in isolation [12].

Chronic therapeutic use of pharmaceuticals more often will impact whether teratogenic effects

Table 1 Examples of drugs historically rated as pregnancy risk factor X by the US FDA

Amyl nitrite	Methotrexate
Atorvastatin	Methyltestosterone
Castor oil	Methysergide
Clomiphene	Mifepristone
Danazol	Misoprostol
Diethylstilbestrol	Oxymetholone
Ergotamine	Oxytocin
Estazolam	Podophyllum resin
Estrogens	Pravastatin
Conjugated	Prazepam
Esterified	Quazepam
Ethinyl estradiol	Quinine
Etretinate	Ribavirin
Finasteride	Simvastatin
Flurazepam	Stanozolol
Fluvastatin	Temazepam
Isoretinoin	Testosterone
Levonorgestrel	Thalidomide
Lorazepam	Thiethylperazine
Lovastatin	Triazolam
Megestrol acetate	Warfarin

Adapted from Leikin and Paloucek [9]

occur. The use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy are a current example of drugs being studied for their adverse effects. A recent multicenter study in the United States examined the National Birth Defects Prevention Study database to identify infants with or without birth defects [13]. They correlated this with maternal use of SSRIs 1 month before pregnancy and during the first 3 months and found some SSRIs were not associated with birth defects, while fluoxetine and paroxetine were associated with 2–3.5 times greater chance of birth defects. An earlier meta-analysis of 115 studies similarly found fluoxetine and paroxetine at increased risk for major malformations (odds ratios 1.14 and 1.29, respectively), while sertraline and citalopram were not associated with an increase [14].

When abusing recreational drugs, such as cocaine or alcohol, the pregnant woman may not be trying intentionally to harm herself or the fetus, but she still is putting her fetus at risk of intrauterine growth retardation, premature delivery, fetal demise, placental abruption, and fetal alcohol syndrome [15]. It also has been shown that women with a positive screen for substances of abuse are at increased risk for being physically abused [16].

For concerns about exposure to teratogens in pregnancy, it is useful to consult a medical toxicologist or a teratogen information service, if available.

Physiology of Pregnancy

Maternal Physiologic Changes

The physiologic changes in pregnancy can result in maternal exposures to toxins that are different from those of nonpregnant women at the same dose (Table 2). Gastrointestinal absorption is changed significantly by pregnancy. The hormonal effects of pregnancy cause delayed gastric emptying, decreased GI motility, and prolonged transit time. These changes lead to delayed but more complete absorption. These physiologic changes theoretically may make attempts at gastric decontamination more efficacious in overdose

Table 2 Physiologic changes of pregnancy

General physiologic changes
↑Body mass 25% by term
↑Body water 7–8 L
↑Body fat 20%
↑Temperature 0.5 °C
Specific systems
<i>Cardiovascular</i>
↑Cardiac output begins by 6 weeks
↑Cardiac output 35% by 10 week
↑Cardiac output 48% by 25 weeks
↑Heart rate 20%
↑Stroke volume10–32%
↓Peripheral vascular resistance
↑Peripheral flow
↓Oxygen extraction
↑Oxygen consumption
↓Blood pressure by second trimester (10–15 mmHg diastolic, 5–10 mmHg systolic)
<i>Respiratory</i>
↑Arterial PO ₂ 10 mmHg
↓Arterial PCO ₂ 10 mmHg
↑Minute volume 40–50%
↑Respiratory rate 0–15%
↑Tidal volume 40%
Vital capacity baseline
↓Functional residual capacity 20%
↓Expiratory reserve volume 20%
↓Residual volume 20%
↓Airway resistance 36%
<i>Gastrointestinal</i>
↑Nausea and vomiting
↓Lower esophageal sphincter tone
↑Gastroesophageal reflux disease
↓Mucus secretion
↓Gastric acidity and small-bowel motility
↑Stomach emptying time 0–160%
↑or ↓ Hepatic metabolism
↑Alkaline phosphatase secondary to placental production
Gallbladder emptying delayed
<i>Urogenital</i>
↑Weight of uterus 400% by 10 week
↑Weight of uterus 2000% by term
<i>Renal</i>
↓Urine concentration
Ureteral dilation secondary to hormonal
Relaxation or mechanical compression
↑Aldosterone
↑Antidiuretic hormone
↑Plasma volume 45–50% with 70% in volume of

(continued)

Table 2 (continued)

Extracellular fluid
↑Glomerular filtration rate
↓Serum creatinine, blood urea nitrogen
<i>Hematopoietic</i>
↑Blood volume 35–40%
↑Plasma volume 50%
↑Red blood cells 20%, volume 300–400 mL
↓Hematocrit 15%
↑Reticulocyte count (small increase)
↓Serum iron
↑White blood cells 66%
↓Total serum proteins 18% in third trimester
↓Serum albumin 15–30%
↑α-Globulin 0–20%
↑Fibrinogen 40–200%
↑Phospholipids, cholesterol, and free fatty acids
↓Leukocyte function in second trimester
↑Coagulation factors
↓Platelets (small decrease)
<i>Endocrine</i>
Hyperinsulinemia
Fasting hypoglycemia
Thyroid function baseline
<i>Neurologic</i>
↓Plasma cholinesterase 20%

during pregnancy. However, most studies in nonpregnant patients have not shown that attempts at GI decontamination in poisoned patients significantly affect their clinical course or outcome.

Because minute ventilation and tidal volume increase while residual capacity decreases, respiratory absorption of a poison can be increased in pregnancy. Inhalational exposures, such as those to carbon monoxide (CO), may be more serious in pregnant women because pregnant women also have less respiratory reserve to compensate for any respiratory insult.

The potential for dermal exposure is enhanced during pregnancy for two reasons. First, there is the increase in body surface area with increasing body mass and the gravid abdomen. Second, increased peripheral blood flow to the skin enhances the possibility of drug absorption. Neither of these changes has been definitively proven to be clinically relevant.

Toxicopharmacokinetics also changes during pregnancy. The volume of distribution of most substances increases because of the expanded plasma volume and body fat stores. The albumin level decreases and the cardiac output increases during pregnancy, allowing for more free drug to distribute to target organs, including the placenta.

Changes in serum pH at different times during pregnancy cause the ionization of some drugs, leading to changes in tissue penetration and elimination. Early in pregnancy, the fetal pH is elevated compared with the maternal pH. Weak acids, such as salicylates, phenobarbital, valproic acid (VPA), trimethadione, phenytoin, thalidomide, warfarin, and isotretinoin, pass through the placenta in an electrically neutral state, but in the relatively alkaline fetal fluids, they may become ion trapped [17]. Late in gestation, the fetus's blood becomes more acidic than the mother's, and weak bases likewise diffuse into and become trapped within the fetus.

Late in gestation, maternal free fatty acids increase, displacing protein-bound drugs, such as diazepam and VPA, from serum proteins [17]. This displacement results in potentially greater toxicity by reducing the natural "chelator" effect of these proteins. In contrast, the hyperdynamic state of the pregnant patient causes glomerular filtration rate increases, and more renally cleared substances potentially can be excreted in the urine.

Placental Factors

The placenta acts similar to an internal dialysis unit, which can increase or decrease the likelihood of fetal toxicity. It allows most drugs to pass by simple diffusion along the natural maternal-to-fetal concentration gradient. Substances weighing less than 1000 Da tend to have the capacity for passive diffusion across the placental membrane [18]. Drugs with small molecular weight, lipid solubility, neutral charge, and low protein binding are more apt to pass through the placenta. A common exception to this rule is iron, which enters the placenta by receptor-mediated endocytosis [19–21].

Another important exception to the aforementioned generalizations is acidic drugs such as valproic acid. These drugs are predominantly ionized at the mother's physiologic pH, but the small amount that remains nonpolar readily diffuses across the placental membrane [22]. The ionized and nonionized fractions tend to approach equilibrium in the maternal serum. The ionized fraction, which is made greater by placental removal of the nonionized, drives the equilibrium toward the neutral form in maternal serum. The latter can diffuse across the placenta. This maternal equilibrium process and the placental passive diffusion of the nonionized drug continue cycling, leading to enhanced concentrations in the fetal circulation.

Fetal Factors

The fetus has physiologic characteristics that can protect it from or make it more susceptible to the toxic effects of maternal poisoning. The fetal oxygen-hemoglobin dissociation curve lies to the left of the mother's [23]. This position allows the fetal hemoglobin to bind oxygen at a lower PO_2 . However, the hyperbolic shape of the fetal oxygen-hemoglobin curve also can be a disadvantage because fetal tissues are less able to extract oxygen from the hemoglobin. Also, because the curve is steep, a shift to the right because of acidemia results in decreased binding of fetal hemoglobin to oxygen at lower PO_2 .

The fetus also has a physiologic reflex response to hypoxia. This response consists of apnea, bradycardia, systolic hypertension, peripheral vasoconstriction, and lactate production. The vagally mediated response to hypoxia causes a direct negative inotropic response, which can be reversed with atropine. The peripheral vasoconstriction allows shunting of the blood to critical organs, such as the heart, brain, adrenals, and placenta. While beneficial for oxygenation, in a poisoned patient this reflex theoretically increases toxin delivery to vital tissues.

Treatment of Poisonings in Pregnancy

The same aggressive supportive care that one would render to a nonpregnant poisoned patient should be administered to a pregnant patient (Grade III). In general, if a toxin is causing seizures or hemodynamic instability in the mother, it also is having negative effects on the fetus. The optimal approach is to treat the mother; this is especially true in the critically poisoned patient. A remarkable report described a 27-year-old woman, 15 weeks pregnant, iatrogenically poisoned with intravenous lidocaine by the administration of a 1000-mg bolus (instead of 100 mg) for the treatment of bigeminy [23]. This patient developed multiple arrhythmias, including electromechanical dissociation, asystole, and ventricular tachycardia, and status epilepticus over 23 min. She was treated with supportive care and standard American Heart Association Advanced Cardiac Life Support (ACLS) recommendations for pulseless electrical activity and asystole. Fetal heart tones were not heard for 14 min during resuscitation, and remarkably both patients survived acute toxicity. The infant was born at 40 weeks' gestation without complication and showed no developmental delays at age 9 months.

Aggressive supportive care involves attention to airway, breathing, circulation, and neurologic disability. Maintenance of a patent airway, 100% oxygen administration, and if the patient is third trimester and is hypotensive, left lateral decubitus positioning along with two large-bore intravenous lines and aggressive fluid management are critical. Moving the patient to the left lateral decubitus position prevents the enlarged uterine fundus from compressing the inferior vena cava, which can decrease the central venous pressure 30–70%. If this position is not feasible, such as during chest compressions, manual leftward uterine displacement away from the inferior vena cava is also effective [24]. Cardiac drugs and unsynchronized cardioversion up to 300 J have not been found to be harmful to the fetus. The 2010 ACLS guidelines include an algorithm for pregnant cardiac arrest patients and specifically recommend using

typical ACLS drugs and doses [24, 25]. Open-chest cardiac massage has been suggested to reduce the required dose of epinephrine, which can cause vasoconstriction of the uteroplacental arteries [23, 26]. In contrast to most other instances of open-chest cardiac resuscitation, however, it is crucial not to cross-clamp the aorta because doing so would interrupt immediately uteroplacental blood flow.

If there is a change in mental status, dextrose, naloxone, and thiamine may diagnose and treat the related causes of central nervous system depression. The benefit of reversing a mother's respiratory depression and hypoxia from an opiate overdose far outweighs the risk of opiate withdrawal in the fetus. Fetal heart monitoring, which should be instituted during maternal stabilization, is an important factor if the fetus is of a gestational age at which it is potentially viable [27]. Emergent cesarean section may be necessary if there is fetal distress in the later stages of pregnancy. This therapy provides theoretical benefits to the mother by reducing circulatory load and to the fetus by removing it from a hypoxic/acidotic environment. A number of case reports have also described dramatic return of spontaneous circulation, after cardiac arrest in general, and recovery after perimortem cesarean section [24].

Decontamination

There is no approach to GI decontamination that could be applied empirically to all patients who overdose. Each patient must be assessed individually as to whether a particular method is indicated or contraindicated (see ► Chap. 3, "Therapeutic Approach to the Critically Poisoned Patient"). This approach applies to pregnant patients as well, with some additional considerations. As with most other pregnant poisoning topics, there has been no systematic evaluation of decontamination efficacy in pregnant patients.

Syrup of ipecac is contraindicated in pregnant patients because of increased abdominal and thoracic pressure with repeated emesis and may be

teratogenic [28, 29]. Currently, syrup of ipecac is essentially unavailable in the United States and should not be used in any poisoned patient (Grade III).

There are reports of gastric lavage in the pregnant patient. The indications and contraindications are the same as those for nonpregnant patients (see ► Chap. 3, "Therapeutic Approach to the Critically Poisoned Patient"). Because GI motility is slowed during pregnancy, delayed gastric lavage is theoretically attractive in the potentially life-threatening ingestion. However, the latest review of the literature related to nonpregnant patients, reenforced the principle that gastric lavage should not be routinely used in oral overdose, if at all [30] (Grade II-2-3). Gastric lavage is not a current, practical method of gastric decontamination and does not have a routine role in gastrointestinal decontamination of the pregnant patient, except in rare circumstances [31].

Activated charcoal can be an effective decontamination procedure, as it is in nonpregnant patients [32] (Grade II-2-3). AC itself is not absorbed and in theory should pose no direct harm to the fetus – in fact there have been no reports of fetal toxicity from AC. Similar to gastric lavage in pregnant patients, slowed gut motility may allow AC to be effective even if given more than 1–2 h after ingestion, in an awake, cooperative patient following a potentially lethal ingestion with no other effective antidote available. The activated charcoal dose for adolescents and older is 25–100 g [32]. Aspiration and bowel obstruction are the primary risks to the mother (Grade III). Although activated charcoal may decrease drug absorption if administered shortly after ingestion, there are no studies showing that its use alters the outcome of poisoned patients.

Cathartics, such as magnesium citrate and sorbitol, have no role in GI decontamination and should not be administered due to the potential for harmful outcome [33]. In most cases, one dose is safe, but with repetitive use, multiple doses can cause electrolyte abnormalities and possibly induce premature labor [28, 34]. Cathartics do

not add to the efficacy of AC. Many medical toxicologists prefer to administer AC as an aqueous suspension with no cathartics. This approach is not known to increase the likelihood of any charcoal-related adverse effects.

Whole-bowel irrigation (WBI) has been reported in pregnant patients [35, 36]. An iron overdose is one example in which this therapy may be used. In a report of an 18-year-old woman, 38 weeks pregnant, who ingested 55 tablets of prenatal iron, gastric lavage was attempted successfully, when the abdominal radiograph revealed tablets in the stomach. WBI with polyethylene glycol was started at 2 L/h and continued until the rectal effluent was clear. Deferoxamine therapy was also initiated. Fetal heart tones were in the range of 130–140 beats/min. The patient did well and had a normal delivery of a healthy infant in 5 weeks [35]. The indications and contraindications for WBI are the same for pregnant and nonpregnant patients [37] (see ► Chap. 3, “Therapeutic Approach to the Critically Poisoned Patient”).

Antidotes

There is minimal literature on the beneficial or harmful effects of antidotal therapy in pregnancy (Table 3). A small number of antidotes have had epidemiological studies for nonpoisoning indications [41]. Of these, atropine, calcium, and pyridoxine appear to be nonteratogenic. Ethanol and penicillamine are known teratogens, and both have alternative antidotes available. Methylene blue is a known teratogen in the setting of intra-amniotic injection for obstetric procedures, but its effects after intravenous administration in pregnancy are unknown. Based on the principle of improving maternal survival to improve fetal survival, giving a dose of methylene blue if indicated seems reasonable (Grade III) [41].

Aside from the above, only case reports or case series exist to provide insight on maternal-fetal effects or efficacy. These reports reveal little about the effect on the fetus but provide some observations about the effect on the mother. It is unlikely that a single exposure to antidotal therapy

would cause harm. There are well-documented cases of maternal and fetal mortality caused by withholding an antidote because of fear of inducing fetal teratogenicity [42, 43].

Enhanced Elimination

Although the supporting literature is limited, enhanced elimination with multiple-dose activated charcoal (MDAC) should be as effective and safe as single-dose AC in pregnant patients. As with single-dose AC, there is always the potential for aspiration. The few indications for possible MDAC therapy are the same as those in nonpregnant patients (e.g., ingestion of a potentially highly toxic amount of theophylline, phenobarbital, carbamazepine, dapsone, or quinine). MDAC for these drugs is supported in the literature because of effective “gut dialysis” or interruption of enterohepatic circulation in nonpregnant patients [44]. MDAC therapy is reviewed in detail in the ► Chap. 3, “Therapeutic Approach to the Critically Poisoned Patient”.

Hemodialysis in pregnancy is uncommon [45]. Most experience seems to be with patients with chronic renal failure or with acute renal failure from nontoxicologic causes [46–49]. In a study of 16 infants born to mothers on long-term hemodialysis with some residual renal function, it was found that none of the offspring had abnormalities, and all were delivered spontaneously at term [50].

The literature on extracorporeal therapies in pregnancy is limited to scant case reports. There is one case reported of use of hemodialysis in a pregnant patient at 11 weeks after a massive theophylline overdose [51]. In this case, hemodialysis was effective in increasing clearance of the drug and did not result in any appreciable complications for the mother. However, it is difficult to draw conclusions regarding fetal outcome as the mother elected to terminate her pregnancy 2 days after discharge. In another case report, a pregnant woman at 27 weeks gestation ingested paraquat in a suicide attempt [52]. After treatment with hemoperfusion, steroids, and cyclophosphamide pulse therapy, both she and the fetus survived, and

Table 3 Antidotes used in pregnancy [9]

Antidote	Historical pregnancy risk categories	Comments
Acetylcysteine [38]	B	Acetylcysteine can cross the human placenta
Ethyl alcohol	X	In chronic use, >2 g/kg/day in the first trimester two- to threefold higher risk for congenital malformations (about 10%)
	C	In acute therapy of toxic alcohol ingestion: use only if potential benefit outweighs the risks; ethanol crosses the placenta readily and enters fetal circulation
Amyl nitrite	X	
Antitoxin botulinum A, B, E	C	Use only if potential benefit outweighs the risks. It is unknown if the antitoxin antibodies cross the placenta
Antivenin (<i>Crotalidae</i>) polyvalent	C	Pregnancy is not a contraindication for antivenin therapy
Antivenin (<i>Micurus fulvius</i>) North American coral snake	C	Use only if potential benefit outweighs the risks. It is unknown if the antitoxin antibodies cross the placenta
Antivenin (<i>Crotalidae</i>) polyvalent (ovine) Fab	C	Pregnancy is not a contraindication for antivenin therapy
Atropine	C	Crosses the placenta; trace amounts appear in breast milk
Bromocriptine	C	Use only if potential benefit outweighs the risks
Calcium chloride	C	Crosses the placenta; appears in breast milk
Calcium gluconate	C	Crosses the placenta; appears in breast milk
Carboxypeptidase	C	
Charcoal	C	
Deferoxamine	C	Do not withhold chelation therapy for iron overdose solely due to pregnancy; has caused fetal abnormalities in animals
Digoxin immune Fab	C	No animal studies conducted
Dimercaprol	C	
Calcium EDTA	C	
Flumazenil	C	
Folic acid	A (C if dose exceeds RDA)	400 µg/day needed to prevent neural tube defects
Fomepizole	C	
Glucagon	B	
Hydroxycobalamin	C	
Insulin (R)	B	
Leucovorin	C	
Levocarnitine	B	
Lipid Emulsion [39, 40]	C	Recommended by Society for Obstetric Anesthesia and Perinatology for local anesthetic systemic toxicity at same doses as nonpregnant patients.
Methylene blue	C (D if injected intra-amniotically)	
Naloxone	B	
Octreotide	B	
Hyperbaric oxygen		Indicated for the treatment of pregnant patients when symptomatic or with a carboxyhemoglobin level >20%
Penicillamine	D	Correlated with cutis laxa in neonates
Physostigmine	C	

(continued)

Table 3 (continued)

Antidote	Historical pregnancy risk categories	Comments
Phytonadione	C (X if used in third trimester)	
Polyethylene glycol (high molecular weight)	C	
Pralidoxime	C	
Pyridoxine	A (C if dose exceeds RDA)	
Sodium bicarbonate	C	
Sodium nitrite	C	Has caused fetal death in humans and animals, avoid unless there is no other alternative (hydroxocobalamin)
Sodium thiosulfate	C	
Succimer	C	
Drugs of abuse	X	

EDTA ethylenediaminetetraacetic acid, *RDA* recommended daily allowance
Adapted from Leikin and Paloucek [9]

delivered successfully with no apparent complications at 5-year follow-up.

Based on the above case reports and increasing usage in nonpoisoned patients, it seems reasonable to consider use of dialysis in the poisoned pregnant patient. If dialysis would be indicated in a nonpregnant patient, it is indicated in a pregnant patient as well (Grade III).

Specific Agents

Abortifacients

An abortifacient is any agent that a pregnant woman may use in an attempt to terminate her pregnancy. Many different substances have been used historically, including lead and quinine [53, 54]. Currently, in addition to over-the-counter medicines such as acetaminophen, aspirin, and iron with perceived abortifacient effects, herbal preparations are being used. Different cultures have their own contributions to the list of herbal abortifacients. Some representatives are cottonroot bark from Mexico; pulsatilla from India; and rue, apiol, cohosh, sage, and pennyroyal oil from the United States (Table 4) [56, 57]. In the United States, these herbal preparations are protected from scrutiny by the Dietary

Supplement Health and Education Act of 1994, which designates herbal products as food. This allows them to be regulated in a less stringent fashion by the FDA than pharmaceuticals.

In a prospective observational study of 43 women who ingested known or perceived abortifacients, ingestions were most common in the first trimester (79%). Acetaminophen was the most common drug ingested (30.2%), and polysubstances were common (35%) [58]. Five patients picked specific substances because they knew they were abortifacients. Minor toxicity generally was observed (81%) except in a tricyclic antidepressant overdose and a bupropion overdose. Fetal demise was not reported in a limited 3-day follow-up.

It has been questioned why women are using medical abortifacients when abortion is legal and accessible in many countries. The answer is thought to be the general movement away from traditional health care and toward herbal remedies [56]. Because of barriers to health care and increasing cost, a progressively greater proportion of the population is willing to try “self-help” remedies first. The dangers to women are the toxic effects of the agent on themselves, teratogenic effects if the fetus is carried to term, and complications from delaying a physician-assisted abortion when the abortifacient fails.

Table 4 Abortifacients

Agent	Class/active compound	Toxidrome	Toxicity	Comments
Angelica root – <i>Angelica archangelica</i>	Essential oil	Hypotension/shock	>1 mL ingested	Activated charcoal; supportive therapy
Black cohosh – <i>Cimicifuga racemosa</i>	Alkaloids including methylcytosine and acetin	Bradycardia, dizziness, nausea, vomiting, tremors, headache	Not documented	Activated charcoal; supportive therapy
Blue cohosh – <i>Caulophyllum thalictroides</i>	Alkaloid methyl cystine	Similar to nicotine: nausea, vomiting, muscle paralysis, seizures, tachycardia, hypotension	Not documented. Roasting eliminates toxicity	Activated charcoal; supportive therapy
Buckthorn bark – <i>Rhamnus cathartica</i> , <i>R. frangula</i> , <i>R. alnifolia</i>	Frangulin (anthroquinone)	Nausea, vomiting, abdominal cramping, diarrhea, potential renal toxin in large doses	1-g berries, mild toxicity in children; 20 berries or chewing of bark is necessary for severe symptoms	Activated charcoal; supportive therapy
Diethylcarbamazine	Antihelminthic-antifilarial agent that kills the parasite in the adult stage	Anorexia, dizziness, abdominal cramping, nausea, vomiting	>1 g	Activated charcoal; betamethasone can be used for hypersensitivity reactions; supportive care, multiple-dose charcoal may be useful for enhanced elimination
Ergotamine	Alkaloid; α -blocker; directly stimulates vasculature to vasoconstrict; serotonin antagonist	Tachycardia, hypertension, vasospasm, headache, seizure, hypotension, bradycardia, shock, peripheral vascular effects, nausea, vomiting, diarrhea	>1 mg/kg dose toxic; serum levels >1.8 ng/mL are toxic	Activated charcoal; warm extremities; vasodilators; intraarterial phenolamine for vasospasm, aspirin for antiplatelet effect; prostaglandins; heparin for hypercoagulable state; hyperbaric oxygen for limb ischemia; cyproheptadine to reverse vasoconstriction; supportive care
Mifepristone; approved in France as an abortifacient (1988)	Antiprogesterin agent acts on deciduous progesterone receptors, causing release of prostaglandin in the endometrium, resulting in uterine bleeding, contraction, and cervical dilation	Syncope, headache, nausea, vomiting, uterine pain, bleeding, rupture	A 600-mg dose can cause abortion of fetus within 56 days of amenorrhea	Activated charcoal; transfusion and curettage may be required for uterine bleeding; supportive care

(continued)

Table 4 (continued)

Agent	Class/active compound	Toxidrome	Toxicity	Comments
Mistletoe – <i>Phoradendron falvescens</i> , <i>P. macrophyllum rubrum</i> , <i>P. serotinum</i> , <i>P. tomentosum</i> ; <i>Viscum album</i>	Unknown	Nausea, vomiting, diarrhea, abdominal pain, bradycardia, ataxia, hypotension, seizures, cardiovascular collapse	>2–3 berries, teas, and extracts are toxic	Activated charcoal; supportive care
Poison hemlock – <i>Conium maculatum</i>	Similar to nicotine; stimulation of autonomic ganglion, then depression	Nausea, vomiting, ataxia, burning sensation in throat, tachycardia followed by bradycardia, seizures, paralysis of skeletal muscles and diaphragm, rhabdomyolysis, renal failure	Ingestion of any part of the plant	Activated charcoal; supportive care
Sodium chloride 20% by transabdominal intra-amniotic injection	Causes fluid shift from intracellular to extracellular space, causing destruction of cells	Disseminated intravascular coagulation, renal necrosis, uterine and cervical lesions, pulmonary embolism, pneumonia, hemorrhage	Labor starts in 12–24 h after injection	Supportive care
Misoprostol	Prostaglandin E ₁ analogue	Hypertension, tachycardia, abdominal cramps, rhabdomyolysis, fever, tremor	3 mg – moderate; 6 mg – death	Activated charcoal; supportive therapy
Pennyroyal – <i>Mentha pulegium</i> / <i>Hedeoma pulegioides</i>	Essential oil, pugelone; 22–98% active compound	Confusion, delirium, seizures, hepatic necrosis, renal failure, disseminated intravascular coagulation	5 mL toxic; 10–15 mL lethal; 50–100 g leaves = 1 mg oil	Activated charcoal; supportive therapy; <i>N</i> -acetylcysteine may decrease hepatic damage
Windflower – <i>Anemone pulsatilla</i>	Ranunculin, metabolized protoanemonin	Mucosal irritation/ ulceration, dizziness, paralysis, abdominal pain, diarrhea, vomiting, hypersalivation, renal injury	20 mg/kg can cause CNS and cardiac effects	Activated charcoal; supportive therapy
Quinine	Alkaloid from cinchona bark	Cardiovascular toxicity the same as quinidine, within 8–24 h; tinnitus, deafness, visual field constriction, blindness, vomiting, abdominal pain	>2 g	Multidose activated charcoal; sodium bicarbonate for QRS widening; lidocaine for arrhythmias; avoid class IA–IC antiarrhythmics

(continued)

Table 4 (continued)

Agent	Class/active compound	Toxidrome	Toxicity	Comments
Rue – <i>Ruta graveolens</i>	Pilocarpine, 1.4% quinoline alkaloids, furocoumarins, psoralens	Miosis, cholinergic crisis, headache, nausea, rash, hypotension	Not documented	Activated charcoal; supportive therapy
Savin/juniper – <i>Juniperus sabina</i>	Oil of sabinol and other volatile oils	Agitation; one large dose can cause catharsis, but repeated small doses can cause personality changes and renal damage	Not documented	Activated charcoal; supportive therapy
Mandrake – <i>Podophyllum peltatum</i>	Green fruit, foliage, roots contain podophyllum. Ripe fruit is nontoxic	Diarrhea, headache, respiratory stimulation, lethargy, coma in 12–24 h	Not documented	Activated charcoal; supportive therapy
Tansy – <i>Tanacetum/Chrysanthemum vulgare</i>	Thujone, tanacetin, boneol, camphor	Catharsis, personality changes, renal damage	Not documented	Activated charcoal; supportive therapy
Syrian Rue (<i>Peganum harmala</i>) [55]	Herbaceous plant, quinazoline alkaloids (vasicine and casicinone) are most likely abortifacients. Also contains MAO-A inhibitors	Confusion, CNS depression, hallucinations, diffuse tremors, nausea/vomiting, bradycardia	Not documented	Activated charcoal, supportive therapy

CNS: Central Nervous System, MAO: Monoamine Oxidase

All women who present with an overdose with the ability to become pregnant should have a pregnancy test (Grade III). If the pregnancy test is positive, the possibility of abortifacient usage should be addressed. Women who present with vaginal bleeding and pregnancy also should be questioned as to whether the vaginal bleeding was self-induced by an abortifacient.

Acetaminophen

Pregnant patients have wide accessibility to acetaminophen because it is considered “safe” in pregnancy when taken in therapeutic doses. Acetaminophen is contained in many other over-the-counter preparations. As a result, the chance of acetaminophen toxicity is increased in a polydrug overdose.

Human and animal studies have shown that acetaminophen crosses the placenta [59–61]. The fetus is protected from acetaminophen toxicity in the first trimester by the immature cytochrome P-450 system, which is unable to form the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine. The fetus begins to have cytochrome P-450 activity at approximately 14 weeks of gestation [62]. The ability of 19-week and 22-week fetal liver tissue to form oxides verifies cytochrome P-450 activity at this age of development [63].

As with nonpregnant patients, *N*-acetylcysteine (NAC) is the prophylactic treatment for maternal acetaminophen overdose with possible hepatotoxicity. Pregnancy outcome is affected by time from ingestion until NAC administration. Spontaneous abortion was increased in pregnancies in which NAC was delayed in treating acetaminophen overdose [62]. One study in sheep showed that little NAC was able

to penetrate the placenta [64]. However, NAC later was shown to cross the placenta in rats. This discrepancy may be explained by the fact that sheep have a five-layer placenta and rats have a three-layered placenta similar to humans [38].

IV NAC has been detected in the umbilical cord blood both in poisoned and nonpoisoned patients. Fetal cord blood concentrations of NAC were measured in four newborns with mothers who overdosed on acetaminophen alone. The average NAC concentration was 9.4 $\mu\text{g/mL}$, within the therapeutic range in healthy volunteers [38, 65]. The use of intravenous NAC may be advantageous because oral NAC may induce emesis, and there is a greater maternal first-pass effect, which reduces the amount received by the fetus [64, 66]. However, there is no clinical evidence the route of NAC administration alters efficacy.

The outcomes of the mother and fetus are generally good after an acetaminophen overdose. Multiple case studies show that the outcomes of the fetus and mother are better in the first and second trimesters than in the third trimester [60, 67–73]. Even a massive 64-g ingestion at 15 weeks of gestation resulted in a good outcome [74], whereas in the third trimester fetal intratentorial hemorrhage, fetal demise, and maternal and fetal death have been documented [68–70]. Two large studies of women exposed to acetaminophen during all trimesters found no correlation between toxicity and malformations or miscarriages [75–77]. There appears to be no indication for a mother to terminate pregnancy if she overdosed on acetaminophen.

Although most acetaminophen ingestions result in recovery in the mother with a resultant normal delivery, heroic measures have been suggested in extreme cases of toxicity. Liver transplantation was attempted in one mother who developed fulminant hepatic failure after a repeat supratherapeutic overdose on acetaminophen at 19 weeks gestation [78]. Extensive measures were taken to tailor the patient's imaging and immune suppression to minimize risk to the fetus. The fetus appeared to do well immediately postoperative from the transplant. On postoperative day 14, the fetus began

developing rapidly progressive hydrocephalus and lateral herniation of the brain, leading to termination of the pregnancy.

Some authors advocate emergent delivery of the fetus in the third trimester if the mother has documented toxic levels of acetaminophen, but there is little to support this approach in the absence of hepatic failure [29]. Early vaginal or cesarean delivery may avoid potential complications if the mother becomes encephalopathic and coagulopathic. If there is fetal demise, emergent delivery also may be indicated if the fetus is retained and the mother has evidence of disseminated intravascular coagulation [68]. Exchange transfusion does not seem to be efficacious in the acetaminophen-poisoned neonate [60].

Treatment of pregnant patients for acetaminophen toxicity should be the same as that for nonpregnant patients, with some differences as noted previously (Grade III). See ► [Chap. 59, “Acetaminophen/Paracetamol”](#) for an in-depth discussion of acetaminophen toxicity.

Salicylates

Similar to acetaminophen, salicylates can be found in combination with other drugs in many preparations [79–81]. There is potential harm from salicylates taken therapeutically during pregnancy. Because of effects on neonatal coagulation and premature closure of the ductus arteriosus, salicylates are contraindicated in the third trimester of pregnancy [29]. Salicylates freely cross the placental membrane [82–85].

There are some variations from adult pharmacokinetics in the way the fetus reacts to the burden of a maternal salicylate overdose. Aspirin is hydrolyzed rapidly to salicylate. A small amount is excreted in the urine unchanged, whereas the remainder is metabolized to salicyluric acid, salicyl phenolic glucuronide, salicyl acyl glucuronide, and gentisic acid (Fig. 1). The largest fraction is converted to salicyluric acid, and the other pathways follow Michaelis-Menten kinetics. At low doses, salicylates are metabolized rapidly by first-order kinetics, whereas in higher doses,

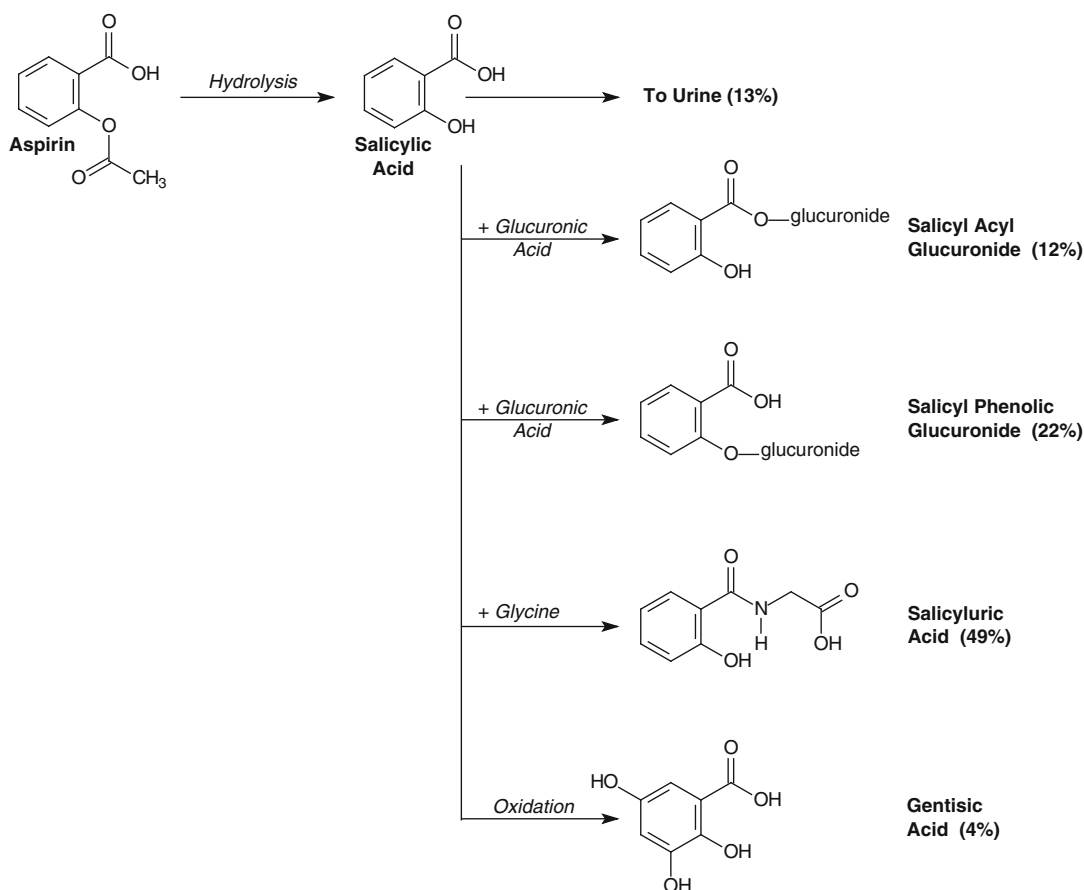


Fig. 1 Disposition of the primary metabolite of aspirin, salicylic acid, at a single dose of 4 g (54 mg/kg body weight) in a healthy adult. The percentage values refer to

the dose. Oxidation produces a mixture of *ortho*- and *para*- (relative to original OH group) isomers

metabolism slows after a switch to zero-order kinetics. The mother and the fetus metabolize salicylate at a decreased rate after overdose.

The metabolism of salicylate was studied in the newborn of a mother who ingested 6.5 g of aspirin daily for the entire pregnancy [82]. The neonate metabolized a relatively larger fraction to salicyluric and gentisic acids, with little glucuronidation. As a result, salicylate elimination by the infant was much slower than that in the adult. Although it was noted that the elimination was delayed in large overdoses, when the amount of ingestion is decreased to 7 mg/kg, the elimination increased to adult rates.

The fetus is especially vulnerable to salicylate toxicity in the third trimester of development. In

an overdose, the measured serum fetal salicylate level is greater than the maternal concentration [86]. A greater proportion of salicylate enters the fetal brain than the maternal central nervous system. The fetus also has decreased capacity to buffer salicylate-induced metabolic acidosis. Lastly, metabolism and excretion of salicylate are decreased in the fetus, as discussed earlier [29, 87]. Therefore, logic dictates that treatment of the mother should be initiated at lower serum salicylate concentrations than one would initiate for a nonpregnant patient (Grade III). Urinary alkalization therapy might be warranted when serum salicylate levels increase to greater than approximately 25 mg/dL (180 μ mol/L) to account for these differences in fetal salicylate levels

(Grade III). Similarly, hemodialysis may be indicated at lower serum salicylate levels, since neonatal toxicity and intrauterine fetal demise have both been documented with maternal salicylate levels in the 50–60 mg/dL (360–439 $\mu\text{mol/L}$) range [88, 89].

Salicylate ingestion just before delivery can lead to maternal and fetal platelet dysfunction. After delivery, these neonates can have petechiae, purpura, cephalohematoma, GI bleeding, and intracranial bleeding [90, 91]. Other effects on the fetus from maternal salicylate use are hyperbilirubinemia resulting from displacement from albumin, lower birth weight, and increased mortality [92]. Increased risk of congenital abnormalities and hypoglycemia are uncommon. It is believed that the antiprostaglandin effects of salicylates can cause complications in the mother as well [93]. The maternal effects of chronic salicylate ingestion include longer gestational periods, prolonged labor, increased risk of hemorrhage, and higher rates of cesarean [86].

Treatment of pregnant patients with salicylate toxicity should be the same as that for nonpregnant patients, with the caveat discussed previously (Grade III). In acute toxicity, GI decontamination should begin with AC, which is effective in binding salicylate. The total amount remains debatable, but at least a 1 g/kg dose up to a ratio of 10 g of activated charcoal: 1 g of salicylate, is recommended. Multiple determinations of serum concentrations of salicylate are needed to monitor for continued absorption and hence dictating the need for further activated charcoal. ► [Chapter 63, “Salicylates”](#) provides an in-depth discussion of the treatment of salicylate toxicity.

Because of the high toxicity of salicylate to the fetus, fetal monitoring may be needed to assist in the determination of the need for emergent delivery in a fetus of potentially viable gestational age. Emergent delivery is considered optimal treatment by some [29]. If the time of maternal overdose approximates the expected delivery date, the neonatologist should be alerted about the increased risk of platelet dysfunction.

Iron

Although accidental iron overdose has decreased substantially in the pediatric population because of changes in iron supplementation packaging, intentional overdose in the adult remains a serious ingestion. Iron is readily available to the pregnant woman because it is prescribed routinely during the prenatal period. As a result, it is a concern for potential overdose in pregnancy.

Iron toxicity injures the human body through multiple mechanisms: peroxidation of biologic membranes, inhibition of oxidative phosphorylation, and formation of free hydrogen ions as a by-product of the change from the ferrous to the ferric state, causing metabolic acidosis [94, 95]. Iron seems to have little direct toxicity to the fetus. It does not diffuse passively across biologic membranes but acts through a receptor-mediated endocytosis. A study of iron toxicity in pregnant sheep showed that elevated maternal serum iron concentrations are not reciprocated in the fetal circulation [21]. Human case reports also support this finding [42, 96]. Iron does not affect the fetus directly but does so indirectly through poisoning of the mother. The placenta provides an effective barrier to iron, leaving the fetus reliant on the well-being of the mother for its survival [97].

Two other components of general iron toxicity are present in pregnant patients. The peak serum iron concentration occurs in the range of 2–4 h, and using the total iron-binding capacity to predict the severity of poisoning is inaccurate [98]. Treatment must focus on the sum of many different data points to determine what is most appropriate. Greater than 60 mg/kg ingestion, hypotension, mental status depression, metabolic acidosis, GI bleeding, shock, and serum iron level greater than 500 $\mu\text{g/dL}$ (89 mmol/L) all are signs of a severe iron poisoning and are indications for deferoxamine administration (Grade III evidence).

GI decontamination after iron poisoning is controversial. Some authors support gastric lavage if a pregnant patient presents less than 1 h after ingesting a potentially toxic dose, but the proper equipment and training of staff has made

this technique largely unavailable, and should likely be avoided in most circumstances. Alternatively, WBI can be administered safely in the pregnant patient if significant quantities of iron-containing radiopacities are visualized on abdominal radiographs after recent ingestion. Activated charcoal may be used if a coingestant is suspected, but it does not adsorb iron itself. Ultrasound is the imaging modality of choice in pregnant patients because it causes no ionizing radiation, though its ability to identify pills in the setting of overdose remains in question [99, 100]. Pregnancy should not be a contraindication to a flat plate of the abdomen in the case of an iron overdose, overdose because of the very low dose of radiation and the benefits outweighing the risks. A kidney, ureter, and bladder film potentially could avoid toxicity for the mother and fetus by alerting the clinician to the diagnosis of iron toxicity while guiding decontamination therapy with WBI. Adverse side effects from the amount of radiation are trivial compared with the potential threat of fetal toxicity after a substantial iron ingestion.

Deferoxamine is the antidote for iron poisoning. It chelates free iron and is excreted by the kidneys. The indications were listed previously, but some clinicians take a more conservative approach and treat a pregnant patient with a serum iron concentration greater than 350 $\mu\text{g/dL}$ (62.5 mmol/L) [97]. The usual intravenous dose of 15 mg/kg/h with the upper limit of 6 g in 24 h is often quoted and still cited in the package insert [101]. The reason for this limit is to avoid hypotension and acute lung injury. A firm standard for the limits of deferoxamine therapy has yet to be shown in clinical trials.

Previously, deferoxamine was considered dangerous to give to the pregnant patient because of fears of teratogenicity. There have been reports of skeletal abnormalities in animals exposed to high doses of deferoxamine [96, 101]. In contrast, reviews of multiple case studies have shown no direct link between deferoxamine treatment in humans with iron toxicity and teratogenicity [102–105]. More reassurance of the safety of deferoxamine in pregnancy is provided by the fact that deferoxamine does not cross the placenta

in the ovine model [21]. The clinical pharmacology of deferoxamine is discussed in detail in ► Chap. 143, “Deferoxamine”.

It follows that if iron itself has difficulty passing the placenta and if deferoxamine does not penetrate the placenta well, neither iron nor deferoxamine directly contributes to fetal injury. In this overdose, the mother has more potential morbidity than the fetus. The primary concern is the mother’s clinical state. This constitutes a classic example of the dictum that the future of the mother and the fetus relies on optimal treatment of the mother. Iron toxicity is discussed in detail in the ► Chap. 67, “Iron”.

Carbon Monoxide

Carbon monoxide is an endogenous by-product of heme degradation in humans (75% hemoglobin + 25% other blood pigments) [106]. While no longer the leading cause of poisoning death in the United States, CO was still responsible for 14,289 calls to poison centers in 2013, with 60 of these cases being fatalities [1]. The clinical signs and symptoms of CO poisoning mimic the presentations of many illnesses, such as viral syndrome or gastroenteritis. The best way to diagnose CO poisoning is to consider it often in differential diagnoses. It cannot be overstated that one needs a high degree of suspicion to discover CO poisoning.

During a normal pregnancy, endogenous production of CO increases carboxyhemoglobin (COHb) 20–40% above normal levels [106, 107]. Of this increase in maternal COHb, 30–40% is from an increase in maternal erythrocyte load. The fetus contributes 15% of the COHb increase. The instigator of this increase is progesterone, which induces the catabolism of hemoglobin by hepatic microsomal enzymes. The minute ventilation also increases during pregnancy. The baseline increased burden of CO and the increased minute ventilation make the pregnant woman more susceptible to CO poisoning.

The pathogenesis of CO toxicity is twofold: CO generates oxidative stress, and it binds to

heme-containing proteins, such as hemoglobin, myoglobin, and cytochrome *aa3* [106]. CO has an affinity for hemoglobin 250, 25, and 1 time greater than oxygen for hemoglobin, myoglobin, and cytochrome *aa3*, respectively. This binding leads to systemic hypoxia and a shift of the oxygen-hemoglobin saturation curve to the left, with a transformation of the curve to a hyperbolic shape [107]. There may be direct toxicity to cardiac tissue as a result of the replacement of oxygen with CO in cardiac myocytes. Uncoupling of oxidative phosphorylation causes an increase in free hydrogen ions, leading to metabolic acidosis. Fetal hemoglobin complicates the situation because its oxygen binding curve is already hyperbola shaped and steep at low pressures of oxygen. Decreased ability of tissues to extract oxygen from the fetal hemoglobin and increased susceptibility to a precipitous drop in oxygen saturation result.

In acute maternal CO exposure, the CO slowly crosses the placenta by passive diffusion [108]. In humans, the fetal COHb concentration reaches maternal levels in 14–24 h and a state of equilibrium in 36–48 h, with percent fetal COHb 15–20% greater than the maternal percentage [106, 107, 109]. In acute exposure, death by anoxia occurs well before COHb concentrations increase [110]. In chronic CO exposure, the CO level in the fetus progressively increases, and the critical level is 60% [109]. The CO elimination half-life is 2 h in the mother and 7 h in the fetus.

The sum of the effects from fetal hemoglobin, prolonged elimination, delayed peak in fetal COHb concentration, and elevated concentration of COHb in the fetus places the fetus at greater risk for morbidity and mortality than the mother. There are multiple case reports of the mother's exhibiting minimal to no toxicity, with simultaneous significant adverse effects or death in the fetus [109–112]. Similar to the situation in nonpregnant patients, the CO level, expressed as percent COHb, does not correlate well with severity of toxicity. Fetal COHb levels are not realistically obtainable, making a history of exposure along with clinical signs and symptoms in the

mother the only guide for therapy. Multiple sources point out that maternal symptoms of altered mental status, neurologic deficits, seizures, and coma are better predictors of fetal toxicity than are COHb concentrations [108, 109, 113].

Teratogenicity varies with the timing of the exposure. Case reports suggest the possibility that exposure in the embryonic stage leads to neurologic, skeletal, and cleft palate deformities. During the fetal phase, anoxic encephalopathy and growth restriction may result. In the third trimester, prematurity delivery is reported and possibly decreased immunity, right-sided cardiomegaly, and delay in myelin formation [106, 114].

Primary treatment of CO toxicity involves removal of the mother from the source of exposure and starting therapy with 15 L of 100% oxygen via nonrebreather mask. HBO therapy has been advocated as the treatment of choice for pregnant patients exposed to CO [106, 115]. HBO therapy can reduce the elimination half-life of CO from 4 to 6 h on room air, to roughly 20 min. Normobaric oxygen and HBO therapy increases dissolved oxygen, accelerates dissociation of CO from hemoglobin, and shifts the oxygen-hemoglobin curve back to the right.

Nonetheless, the efficacy of HBO therapy in preventing neuropsychiatric sequelae from CO in the pregnant patient, which is the endpoint of the major studies, is unknown. As expected, pregnant patients have been excluded from HBO research as a therapy for CO poisoning. A Cochrane Review in 2011 found conflicting evidence in existing randomized controlled trials regarding HBO therapy for CO poisoning in nonpregnant patients [116]. Therefore, there are no evidence-based recommendations for HBO therapy for pregnant patients poisoned from CO, only opinions (Grade III).

Suggested indications for HBO therapy in the pregnant patient are a maternal COHb level greater than 15–20%, maternal neurologic signs or symptoms, and evidence of fetal compromise [117]. If maternal or fetal signs of CO toxicity persist 12 h after initial HBO therapy, a repeat session has been proposed [106, 118]. It has been recommended that 100% oxygen continue

five times longer in pregnant patients than standard treatment duration in nonpregnant patients to allow greater removal of CO from the fetal hemoglobin (Grade III) [108, 109, 113].

In addition, there are specific areas of concern for the fetus treated with HBO. High PO₂ is known to be teratogenic and to cause retinopathy, cardiovascular defects, and premature closure of the ductus arteriosus [118]. An animal study showed similar adverse effects [18].

Several human case reports and studies strongly advocate HBO therapy in pregnant patients [18, 108, 109, 113, 119, 120]. The safety of HBO therapy in pregnant patients was studied prospectively in 44 women, all of whom tolerated the procedure well, and no morbidity was seen in the mother or the fetus [121]. A prospective French series from 1983 to 2008 found no difference in early childhood development (as late as age 6 years) between those who received HBO for CO in utero and unexposed age matched controls, further emphasizing the apparent safety of HBO in pregnant patients [122].

In addition to the described standard therapy of CO poisoning, fetal heart monitoring is indicated in the late second and third trimesters. Poor variability and late decelerations are indications of fetal distress. One review article cautioned that immediate delivery of the fetus before HBO therapy carries a high risk of perinatal death. The authors concluded that HBO therapy should be considered before performing an emergency cesarean section [106]. This recommendation is based solely on theoretical considerations, however, and there are no data to support this from clinical trials.

Cyanide

Cyanide is a cellular asphyxiant that binds to and inhibits cytochrome oxidase at cytochrome a₃ in the mitochondria electron transport chain. It prevents the conversion of electron energy into the creation of ATP, leading to seizures, dysrhythmias and hypotension, metabolic acidosis and hyperlactatemia from anaerobic metabolism. The most probable exposure of the pregnant patient to

cyanide is in the gaseous form found in smoke inhalation, but ingestion of a cyanide salt, organic compound or nitroprusside infusion are possible as well.

Pregnant women exposed to cyanide from smoke inhalation or other sources are not well studied, leaving no guidance about this unique population. Roderique et al. report a case of a 32-year-old woman, G2P1, 36 weeks gestation, who was intubated and treated with 5 g of IV hydroxycobalamin after closed space smoke inhalation [123]. She was extubated after clinical improvement and delivered a healthy infant. The amniotic fluid and urine was noted to have the characteristic red color seen after hydroxycobalamin infusion, indicating placental transfer and fetal elimination of hydroxycobalamin. There was no long-term follow-up.

Nitroprusside contains cyanide molecules that are released as the drug is metabolized. This can cause cyanide toxicity if the infusion exceeds 2 mcg/kg/min or continued for a prolonged time period. Because nitroprusside crosses the ewe placenta, this animal model was used to determine if prophylactic sodium thiosulfate could prevent cyanide toxicity in the pregnant ewe. There was successful reduction in uptake of cyanide in RBCs in the mother and the fetus, despite a follow-up study revealing sodium thiosulfate does not cross the ewe placenta [124, 125].

Hydroxycobalamin, sodium nitrite, and sodium thiosulfate are antidotes available for the treatment of cyanide toxicity in the pregnant patient (Grade III) and are considered category C in pregnancy. Amyl nitrite is not recommended especially with more efficacious and safer pharmaceuticals like hydroxycobalamin and sodium thiosulfate. See the ► Chap. 97, “Cyanide: Hydrogen Cyanide, Inorganic Cyanide Salts, and Nitriles” chapter for further information on cyanide toxicity.

Cocaine

Cocaine is a common drug of abuse in women of childbearing age [126]. One study found that 17% of urban women enrolled in prenatal care admitted

to using cocaine once during their pregnancy [127]. Smoking crack cocaine is the most common route of exposure, and most pregnant women who use this substance do not receive any prenatal care [128, 129]. Some women do not realize they are pregnant, whereas others surmise the pregnancy is lost and decide to continue using cocaine [130]. Still others falsely think that cocaine speeds labor. Cocaine can increase the length of labor, however, and exacerbates pain sensation [131].

The manifestations of cocaine toxicity are the same as those in any nonpregnant patient. Hyperthermia, hypertension, tachycardia, agitation, seizures, stroke, myocardial infarction, intracerebral hemorrhage, and aortic dissection are possible results of cocaine use. The unique complications associated with cocaine use in pregnancy are abruptio placentae, decreased fetal growth, preterm labor, urinary congenital abnormalities, neurobehavioral abnormalities, and fetal demise [132–134].

The pregnant patient theoretically is at enhanced susceptibility to cocaine poisoning due to reduced cholinesterase levels [135], causing her to have decreased ability to metabolize cocaine. The fetus also has reduced levels of cholinesterase, but the placenta has sufficient activity to allow metabolism of some of the cocaine before it crosses the placenta and affects the fetus [136]. Cocaine administered to the pregnant ewe caused increased vascular resistance, decreased uterine flow, increased fetal heart rate and blood pressure, and lower fetal oxygen content [137]. Progesterone may increase cocaine's cardiovascular toxicity in the pregnant patient [138].

Benzodiazepines are the medication of choice to treat the agitated, seizing, or tachycardic patient who is manifesting signs of cocaine toxicity. Diazepam and lorazepam are often considered contraindicated in pregnancy out of concern for teratogenic risks. Despite this warning, in the case of a pregnant woman with cocaine toxicity who presents with seizures, agitation, and hyperthermia, benzodiazepines are effective at diffusing cocaine toxicity and may decrease morbidity and mortality [139]. The teratogenic risk of benzodiazepines is likely minimal except for a small association with oral clefts [140]. Further, mothers

who attempt suicide by single large benzodiazepine overdose show no increase in congenital abnormalities [141]. There may be respiratory depression on delivery of a fetus from a mother recently treated with benzodiazepines, but the benefits outweigh the risks. If efforts to halt seizures are refractory to benzodiazepines, phenobarbital is preferred over phenytoin owing to the latter's known teratogenic effects on the fetus (Grade III). Antihypertensives, such as nitroglycerin, may be used for hypertension, and rapid external cooling for hyperthermia is essential. If chest pain is present, investigation and treatment of possible myocardial ischemia are warranted. Cocaine toxicity is discussed in greater detail in ► Chap. 75, "Cocaine."

Opioids

The epidemic of opioid abuse has been well recorded and described previously [142]. This epidemic is also seen among pregnant patients, where 0.1% of pregnant women report having used heroin, 1% report nonmedical use of opioid pain medications, and 2.6% of pregnant women in one urban teaching hospital tested positive for opioids [143]. Some opioids, particularly codeine, have been associated with birth defects including congenital heart defects [143]. Chronic heroin risk has been associated with a variety of poor fetal outcomes including fetal growth restriction, preterm labor, and fetal death. In the case of heroin, there is a theory that these effects are from both repeated exposure and repeated withdrawal.

The treatment of opioid withdrawal creates a concern regarding naloxone use in pregnancy. While opioid withdrawal is typically not life threatening, it can precipitate preterm labor and fetal distress, so we recommend that naloxone be used only in the case of maternal overdose with hypoxia and potential airway compromise in order to save the mother's life (Grade III) [143]. Similarly, pregnant patients who may be dependent on opioids should be observed for signs and symptoms of withdrawal and managed as needed to prevent fetal distress (Grade III).

Other Intoxications

There have been many reports of other poisonings and toxic syndromes in pregnancy. Some of these cases are summarized in Table 5. All recommendations are Grade III.

Toxicity of Pregnancy-Related Medications

Magnesium Sulfate

The magnesium cation is involved in many physiologic reactions and regulation of ion channels. Most is stored in bone, leaving only 1% free in the serum. Magnesium sulfate is used as an anticonvulsant in pregnant patients with eclampsia or severe preeclampsia. In most cases, magnesium sulfate has been shown to be safe and effective [159–161].

The true mechanism of magnesium's action is not documented clearly. It affects many different systems, which may contribute to the antiepileptic properties of this medication. Magnesium is a calcium antagonist and causes systemic and cerebral vasodilation. It increases cyclic guanosine monophosphate levels, which may act as a vasodilator by increasing nitric oxide levels and decreasing endothelin-1. Magnesium can slow conduction through the myocardium and decrease inotropy in high doses. It also can protect neuronal tissues from injury by blocking calcium channels directly in *N*-methyl-D-aspartate receptors. Finally, magnesium can decrease acetylcholine release from the presynaptic neuron onto the motor endplate, by blocking influx of presynaptic calcium. The major importance of this effect is loss of diaphragm function [159, 161, 162].

The toxicity of magnesium probably depends more on its rate of administration than the duration or the total dose, except in extreme circumstances. When magnesium administration exceeds its rate of renal clearance, its serum concentrations increase and may result in toxicity. There are many different regimens used in pregnancy, including regimens involving the intravenous and intramuscular routes with different

target serum magnesium concentrations. At levels of 3.8–5 mmol/L, the patient may have flushing, headaches, blurred vision, nausea, nystagmus, lethargy, hypothermia, urinary retention, loss of the patellar reflex, or ileus. Respiratory muscle paralysis may occur at concentrations of 5–6.5 mmol/L. Cardiac conduction disturbances occur at magnesium serum concentrations of 7.5 mmol/L, and cardiac arrest may ensue at levels of approximately 12.5 mmol/L [162].

Magnesium toxicity affects the mother and the fetus. For the mother, this toxicity typically occurs by an error in the rate of administration [163]. In a case report of a 23-year-old woman at 32 weeks' gestation, the patient had a cardiopulmonary arrest after 25 g had been administered instead of 1 g/min for a total dose of 4 g [164]. The mother also is in danger when magnesium therapy is combined with polarizing and nondepolarizing agents because of prolonged respiratory paralysis [162]. Hypotension can be a complication when magnesium is used with epidural blocks. Because of their calcium channel-blocking properties, magnesium combined with nifedipine can lead to profound hypotension [162].

The effect of magnesium on the fetus is variable. The classic result in the neonate is hypotonicity, which may affect diaphragmatic function. In a retrospective cohort analysis of more than 6600 women with preeclampsia treated with magnesium, 6% of the infants were diagnosed with hypotonia [165]. Magnesium toxicity in the mother also increases the rate of perinatal mortality, even when there is little effect on the mother [166]. Magnesium therapy may be detrimental to the fetus in the scenario of maternal hemorrhage. A study of pregnant ewes at 123 days' gestation found increased mortality in the fetuses whose mothers were treated with magnesium therapy during maternal hemorrhage compared with saline therapy. The magnesium may have inhibited the natural response to hypoxemia in the fetus [167]. Another study in pregnant sheep found that magnesium did not impair cardiac output, however, or increase fetal death during maternal hemorrhage [168].

The treatment of magnesium toxicity involves attention to airway, breathing, and cardiovascular

Table 5 Poisonings in pregnant patients

Toxin	Clinical course/treatment	Outcome	Recommendations
Methanol [144]			
Editorial: 1. Freely crosses the placenta 2. Alcohol dehydrogenase activity 10% in wk 10–16	See ► Chap. 88, “Methanol and Formaldehyde”	?	1. Caution alcohol known teratogen 2. Blockade of alcohol dehydrogenase with ethanol and hemodialysis 3. Published before fomepizole 4. Emergent delivery if fetal distress
Ergotamine [145]			
Case report: 17-year-old G ₁ P ₀ , 35 weeks gestation, ingested 20 mg of ergotamine 3 h PTA and presented confused with normal vital signs	1. Gastric lavage 2. FHT 170 beats/min; NST 2 h after arrival was reactive but unsatisfactory 3. Uterine contractions once/min	1. 8 h later, fetal death and mother had myocardial ischemia 2. Fetal death presumed from uterine contractions and arterial spasm	1. Fetal death presumed from uterine contractions and arterial spasm 2. Early delivery because of deleterious fetal effects without morbidity to mother
Neuroleptic malignant syndrome [146]			
Case report: Multitpara 25 {6/7} weeks was in ICU for respiratory failure and pneumonia. She was treated with increasing doses of haloperidol for agitation	1. Haloperidol discontinued 2. Bromocriptine 2.5 mg tid 3. Dantrolene 40 mg pid 4. The above medications were discontinued in 12 days 5. Biweekly NST and weekly amniotic fluid tests	1. 4 weeks after admission the patient was discharged 2. Healthy female infant born at 38 {4/7} wk	1. Correct fluid, electrolytes, and fever 2. Bromocriptine is safe to use in pregnancy 3. Limited experience with dantrolene in the literature, but no neonatal effects noted in this case
Carbamazepine [147]			
Case report: Term breast-fed boy born to a mother on carbamazepine for epilepsy with asphyxia at birth and hepatic dysfunction in the first week of life. After recovery, at the fifth week of life, cholestatic hepatitis	1. Ruled out nontoxic etiologies 2. Liver biopsy showed bile duct lymphocytic infiltrates, hepatocellular cholestasis, and microvesicular fatty changes 3. Maternal carbamazepine level 12.4 mg/L 4. Fetal carbamazepine level 0.5 mg/L	No specific details of outcome	Consider drug-induced cholestatic hepatitis in a mother on carbamazepine during pregnancy and nursing
Snake envenomation			
Prospective observational study in Sri Lanka [148] 1. 39 pregnant women 62% snakes identified	26% received antivenom	1. 55.5% had adverse reactions (one patient required epinephrine) 2. No maternal deaths 3. 29% abortions and one malformation (all abortions occurred <18 weeks gestation)	1. Snake bite in first trimester with systemic envenomation results in a poor outcome (second trimester is better, and third trimester is the best outcome) 2. Did not find snake antivenom to be a risk factor for fetal death

(continued)

Table 5 (continued)

Toxin	Clinical course/treatment	Outcome	Recommendations
Case series of three patients envenomated by <i>Trimeresurus stejnegeri</i> (Habu) while pregnant [149]	2/3 received equine-derived Fab2 antivenom	All mothers and children alive and well 6–10 years post envenomation and treatment without apparent abnormality	Antivenom administration did not appear to significantly worsen fetal outcome
<i>Amanita phalloides</i> [150]			
Case report: 22-year-old, 11 week gestation, ate mushrooms and 10 h later gastrointestinal symptoms 36 h AST/ALT = 663/607 U/L Peak AST/ALT = 4127/2903 U/L Factors V, II, VII, X decreased by 20%, 24%, 23%, 13%, respectively	1. Silybinin 20 mg/kg q 6 h 2. Activated charcoal 3. NAC IV per protocol 4. Abdominal ultrasound 5. Fetal movements and cardiac activity monitored	1. Day 9 discharged 2. 38 weeks delivered healthy infant 3. 2-year follow-up both patients doing well	1. During first trimester, invasive prenatal tests must be avoided 2. The therapy mentioned may be of benefit 3. Abortion is not recommended 4. Pregnancy is not a contraindication for transplant
Phenytoin [151]			
Case report: 18-year-old, eighth month of pregnancy, took 22 g of phenytoin and 2.4 g of phenobarbital Presented alert with stable vital signs	1. Intubation 2. Gastric lavage 3. Hemodialysis 138 h postingestion	Mother and infant did well	1. Hemodialysis did not seem to change clinical scenario 2. Questionable how much phenytoin or phenobarbital crosses the placenta
Vaginally administered cocaine [152]			
Case report: 21-year-old G ₂ P ₁₀₀₁ , 16 weeks gestation, presented unresponsive after boyfriend inserted 1.5 g of cocaine into vagina	1. 0 pulse, 0 BP: intubation, CPR, dopamine 2. Seizure: phenobarbital 3. Cocaine and benzylecgonine positive in urine and vaginal wash 4. Head CT: edema 5. Neonate delivered at 33 weeks by cesarean section: betamethasone given, Apgar 1 and 4 at 1 and 5 min, respectively, hydrocephaly and no brainstem on brain CT	1. Mother died 8 months after admission 2. Fetus died on 10th day of life	1. Treatment of acidosis and seizures is a priority 2. Fatal dose in 70-kg person is 1.4 g intranasally, 750–800 mg SC, IV, or inhaled
Misoprostol – PO [153]			
Case report: 19-year-old G ₃ P ₁₀₁₁ , 31 week gestation, ingested 30 tablets of misoprostol, 200 µg, and 4 tablets of trifluoperazine, 2 mg, 2 h PTA	1. Gastric lavage and activated charcoal 2. 1 h PTA no fetal movement by ultrasound 3. Uterine tetany, acidosis, hyperthermia, tachycardia, hypertension, hypoxemia treated with supportive care 4. Dead fetus delivered 2 h postpresentation 5. CPK peaked at 5849 U/L 25 h postingestion	1. Fetal death, autopsy remarkable for diffuse head and upper-body bruising 2. Maternal survival	1. Rapid onset of symptoms and resolution <12 h consistent with misoprostol pharmacokinetics 2. 400 µg of misoprostol q 4 h is the most administered to induce labor; ingestion of 6000 µg most likely led to fetal death. Uterine contractions and placental dysfunction probably led to death, but direct toxicity cannot be ruled out

(continued)

Table 5 (continued)

Toxin	Clinical course/treatment	Outcome	Recommendations
Misoprostol – vaginal [154]			
Case report: 25-year-old G ₃ P ₀₀₂₀ , 36 weeks gestation, intravaginally administered 6000 µg of misoprostol and ingested 600 µg, 3 h PTA	<ol style="list-style-type: none"> 1. Rapid chills, cramping, emesis, confusion, uterine contractions 2. 3.5 h postingestion temperature 106 °F, systolic BP 80 mmHg 3. Ultrasound 3.5 h postingestion, no fetal movement 4. Nonviable fetus delivered by cesarean section 5. Treatment of mother was supportive, including intubation with a paralytic to control agitation and hyperthermia 	<ol style="list-style-type: none"> 1. Fetal death, with normal anatomy and partial placental abruption 2. Maternal recovery in 16 h 	<ol style="list-style-type: none"> 1. Activated charcoal if oral ingestion 2. Vaginal lavage with saline 3. Supportive care with benzodiazepines, fluids, cooling, paralysis
Diazinon [155]			
Case report: 42-year-old G4P0 at 26 weeks was unintentionally exposed to diazinon while cleaning a small unaired bathroom	Treated with atropine and pralidoxime, recovered within 7 days	Healthy child delivered at term 12 weeks later	Treat organophosphate exposures in pregnant patients similarly to nonpregnant patients
Diphenhydramine [156]			
Case report: 19-year-old gravida 1, 26 weeks gestation, ingested 35 25-mg diphenhydramine tablets, and acetaminophen	<ol style="list-style-type: none"> 1. Hypertension, tachycardia treated supportively 2. 6-mg bolus followed by 3 mg/h IV magnesium sulfate halted the uterine contractions 	<ol style="list-style-type: none"> 1. No comment on future delivery of the fetus, but no morbidity or mortality during monitoring in this case 2. Maternal recovery 	<ol style="list-style-type: none"> 1. Supportive care 2. IV tocolysis
Chemotherapy [157]			
84 children who were exposed in utero to various chemotherapy regimens for maternal hematological malignancies, many during the 1st trimester	No significant change was made to any of the treatment regimens to account for maternal pregnancy	All children were born without apparent abnormality with follow-up of 6–29 years. 12 second generation children were also without abnormality	Full dose chemotherapy for aggressive hematological malignancies is reasonable, including in the first trimester
Paraquat [52]			
Case report: 27-year-old G5P4A1 at 27 weeks drank 40 mL of 24% paraquat in a suicide attempt and presented within 2 h	Received activated charcoal, magnesium citrate, hemoperfusion x2, cyclophosphamide pulse therapy, steroids	Mother and fetus survived. Child born at term, no abnormalities noted by age 5 years	Cyclophosphamide, steroids, and hemoperfusion should be considered in third trimester

(continued)

Table 5 (continued)

Toxin	Clinical course/treatment	Outcome	Recommendations
Brodifacoum [158]			
Case report: 19-year-old, 22 weeks gestation, ingested a box of brodifacoum 8 days prior	<ol style="list-style-type: none"> 1. Brodifacoum level of 220 ng/mL 2. PT >60 s, INR >20 3. Transfusion of 2 U PRBCs, total of 70 mg phytonadione IV and 625 mg orally 4. FHT 150 beats/min 	<ol style="list-style-type: none"> 1. Discharged on hospital day 12 (21 days postingestion) 2. Fetus delivered term, no fetal hemorrhage, no abruption, no problems at 1-year follow-up 	<ol style="list-style-type: none"> 1. No fetal hemorrhagic or teratogenic effects noted 2. Treatment supportive

AST/ALT aspartate aminotransferase/alanine aminotransferase, *BP* blood pressure, *CPK* creatine phosphokinase, *CPR* cardiopulmonary resuscitation, *CT* computed tomography, *FHT* fetal heart tones, *ICU* intensive care unit, *INR* international normalized ratio, *IV* intravenous, *NAC* N-acetylcysteine, *NST* nonstress test, *PRBCs* packed red blood cells, *PT* prothrombin time, *PTA* prior to arrival, *SC* subcutaneous(ly)

status. Intubation and vasopressors with aggressive supportive care are the mainstays of treatment. Intravenous calcium may serve as an antidote to the effects of magnesium toxicity. Maintaining a urine output of at least 100 mL/4 h also can ensure elimination of the magnesium [162] (Grade III evidence). Maternal hemodialysis may be indicated in cases of severe hypermagnesemia.

Methotrexate

Methotrexate (MTX) is used to abort ectopic pregnancies and to treat gestational trophoblastic disease. MTX destroys actively dividing cells because it acts as an analogue of folate (Fig. 2). MTX replaces folate at its binding site on dihydrofolate reductase and thymidylate synthetase (Fig. 3). The end result is inhibition of DNA synthesis, leading to cell death. MTX exhibits profound dose-dependent toxicity. It may cause nausea, vomiting, mucositis, pleuritis, pericarditis, peritonitis, liver injury, renal failure, anemia, and leucopenia at therapeutic doses [169–171].

MTX overdose has followed intravenous, oral, and intrathecal routes. Multiple doses of AC may be effective in lowering the serum MTX concentrations [172]. Urinary alkalinization may ion-trap MTX in the renal tubules and enhance its elimination (Grade II-3 recommendation). Leucovorin is the antidote of choice for MTX overdose (Grade II-3 recommendation). Its dosage depends on the

serum MTX concentration. The standard dose is 10 mg/m² intravenously or orally every 6 h. This antidote should not be delayed while waiting for an MTX level. Intrathecal MTX overdoses may be treated by cerebrospinal fluid drainage, exchange, or transfusion [173]. Carboxypeptidase is a antidote that directly deactivates MTX. In a severe overdose, granulocyte-macrophage colony-stimulating factor has been used to treat pancytopenia with apparent success [174]. MTX toxicity is described in detail in ► Chap. 60, “Methotrexate.”

Vagotonics/Tocolytics

Vagotonics are medications used to increase contractions of the uterus. Methylergonovine in overdose can cause hypertension, chest pain, myocardial infarction, headache, vertigo, nausea, vomiting, and blurred vision. Fetal bradycardia may occur and may be treated with terbutaline [9]. Standard treatment for possible myocardial infarction and stroke is the same as that for a nontoxic cause.

Oxytocin can cause fetal toxicity manifested by bradycardia, brain damage, neonatal jaundice, retinal hemorrhage, hypoxia, and death. In the mother, cardiac arrhythmias, hypertension, seizures, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) have been reported [9]. Treatments for oxytocin toxicity include ritodrine to reverse oxytocin-induced labor and benzodiazepines for seizures. Because of the

Fig. 2 Chemical structures of folic acid (a) and methotrexate (b). The positions at which methotrexate differs from folic acid are shaded

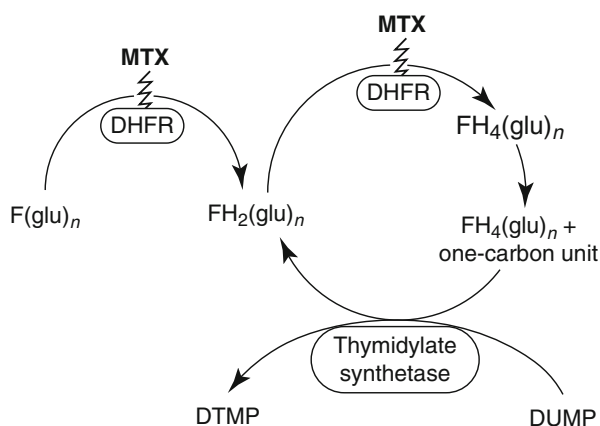
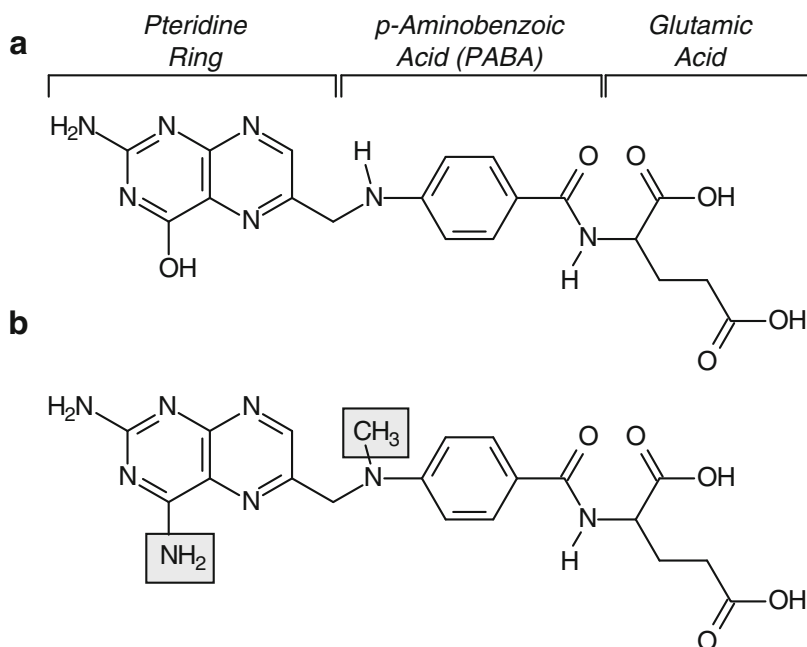


Fig. 3 Simplified diagram of the action of methotrexate (MTX) on thymidylate synthesis. Tetrahydrofolate polyglutamate [FH₄(glu)_n] functions as a carrier of a one-carbon unit, providing the methyl group necessary for the conversion of 2'-deoxyuridylylate (DUMP) to 2'-deoxythymidylylate (DTMP) by thymidylate synthetase.

This one-carbon transfer results in the oxidation of FH₄(glu)_n to the dihydrofolate form FH₂(glu)_n. DHFR, dihydrofolate reductase (From Rang HP, Dale MM, Ritter JM, Gardner P: Pharmacology, 4th ed. New York, Churchill Livingstone, 2001, p 676 – with permission)

possibility of SIADH, serum sodium should be monitored.

Prostaglandins can cause tachycardia, hypertension, hyperthermia, chills, cramping, and possibly hypotension. In a case report, a 31-year-old woman of 35 weeks' gestation was administered 40 mg, instead of 1–5 mg, of prostaglandin F_{2α}

inadvertently by intramyometrial injection to improve the contractility of the lower segment of the uterus after oxytocin failed to stop uterine bleeding. Three to four minutes after injection, she had no palpable blood pressure but was resuscitated successfully with intravenous fluids, red blood cells, and dopamine [175].

Tocolytics are medications that are used to relax the uterus. These agents include magnesium, terbutaline, nifedipine, ritodrine, and indomethacin. Excluding magnesium, terbutaline is one of the more toxic agents in overdose. When comparing ritodrine, hexaprenaline, betamethasone, and terbutaline in mongrel dogs, terbutaline was found to be the most toxic [176]. Terbutaline overdose can lead to tremor, dizziness, palpitations, myocardial ischemia, and blood pressure changes [177]. Propranolol has been advocated as an antidote in a single case report but has not been studied formally [178]. Terbutaline can cross the placenta and cause injury to the fetus. Three out of the four newborns in a quadruplet pregnancy developed bradycardia, metabolic acidosis, poor tissue perfusion, and decreased urine output after 50 days of terbutaline therapy (total of 200 mg) to prevent labor [179]. It was suggested that the β_2 -receptors were downregulated by the prolonged therapy. All three neonates responded well to dobutamine administration.

Calcium channel antagonists are used widely for control of hypertension and tocolysis. The long-acting preparations seem to be safe and effective when used in these settings. When nifedipine has been administered with magnesium, however, severe hypotension has been described [180]. This association between magnesium and short-acting calcium channel blockers also has been studied in rhesus monkeys and Sprague–Dawley rats. The results support the findings in the human case reports [181, 182]. Treatment of calcium channel antagonist toxicity is described in detail in the chapter on these agents.

Ritodrine shares a similar toxicity with terbutaline because of its β_2 -agonist properties, and ritodrine toxicity is treated in a similar fashion. Indomethacin may cause gastric irritation, ulcers, heartburn, and GI bleeding in the mother. In the fetus, it may cause premature closure of the ductus arteriosus, neonatal anuria, and bowel perforation [183]. There is a case report of maternal toxic epidermal necrosis after treatment with ritodrine, indomethacin, and betamethasone [184]. Treatment of the mother after indomethacin toxicity is

supportive, whereas the treatment of the fetus is primarily preventive.

Indications for ICU Admission

- For any given poisoning, the indications for ICU admission do not substantially change with pregnancy and should be based on the mother's hemodynamic parameters.
- Physiologic changes in pregnancy, such as tachycardia and dilutional anemia, should be accounted for when making level of care triage decisions. Prenatal care records, when available, can be helpful in establishing the patient's baseline during this pregnancy.

Key Points

- When treating pregnant patients, both mother and fetus must be considered.
- In general, the best treatment for the mother will also be the best treatment for the fetus.
- The risk of teratogenicity from any acute overdose or antidotal therapy is likely very low.
- The literature on poisonings in pregnancy is sparse at best, typically based on case reports.
- After acetaminophen overdose the fetal liver may not produce significant quantities of NAPQI due to immature hepatic enzymes. However, to prevent maternal toxicity oral or IV NAC should be started, ideally within 8 h of ingestion.
- The fetus is more vulnerable and unable to eliminate salicylates as well as the mother so aggressive enhancement of elimination is warranted at potentially lower maternal serum salicylate concentrations.
- Do not hesitate to administer deferoxamine because of fears of teratogenicity in the pregnant patient. The benefits of maternal survival outweigh the risks of fetal injury.
- Treat the pregnant patient with CO poisoning longer with normobaric oxygen than would

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be indicated for a nonpregnant patient. The role of hyperbaric oxygen therapy is inconclusive. Consultation with a medical toxicologist or, if one is not available, with a poison control center is warranted.

- Hydroxycobalamin is the current treatment of choice for cyanide poisoning in the pregnant patient.
- The benefit of treating seizures from cocaine toxicity with benzodiazepines outweighs the risk of teratogenicity.
- Use the lowest effective dose of naloxone, and titrate as needed, to reverse respiratory depression and hypoxia and avoid withdrawal symptoms.

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In 2010, it was estimated that approximately 13% of the US population was older than age 65 years [1, 2]. This age group is considered the fastest growing population in the United States and is expected to increase to 21% by 2040 [3]. In the United States, 81% of patients over the age of 65 take at least one prescription medication, 42% take at least one over-the-counter medication, and 29% take five or more prescription medications [4]. The number of drugs prescribed per patient is related to the number of the patient's chronic medical conditions, which directly relates to age of the patient [4]. With each new drug an elderly patient uses, the opportunity for untoward events increases [5].

Data collected for the year 2014 by the American Association of Poison Control Centers' National Poison Data System (NPDS) for human exposures to pharmaceutical and nonpharmaceutical agents showed that although exposures occurring in individuals 60 years old or older represented only 8% of the approximately two million exposures reported for the year, the poisoning fatality rate within this age group accounted for 25.8% of the total fatalities reported [6]. These findings are similar to those reported previously regarding the epidemiology of poisoning in the elderly [7, 8]. Of the 302 fatalities reported for the older age group, 25% were deemed to have resulted from suicidal exposure, whereas more than half were attributed to poisoning by one or more pharmaceutical agents [6]. Of 249 deaths that occurred in this age group linked

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to pharmaceutical agents, 18% were judged to have occurred as a result of therapeutic error or as an adverse reaction to therapy. It is likely that the NPDS data profoundly underestimate the morbidity and mortality of adverse drug effects in this age group.

It is conventional medical wisdom that the frequency of adverse drug-related events (ADEs) in the elderly, including medication errors and adverse drug reactions, is a function of the number of medications used per patient [9]. In a study of patients presenting to ambulatory care settings, 13.5 million ADE-related visits occurred during the 2-year study period, and a notably positive exposure–effect relationship was observed between number of medications taken and frequency of ADEs [10]. Approximately 0.5% of all ambulatory care visits were ADE related, with patients over age 65 at the highest risk. Medications most frequently associated with ADEs were nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, anticoagulants, diuretics, hypoglycemics, β -blockers, calcium channel blockers, or chemotherapeutic agents. A relationship also has been observed between the number of drugs prescribed and the number of diseases per patient and rate of hospitalization.

General Themes in Geriatric Pharmacology and Toxicology

The elderly have:

1. Age-related changes in physiologic/pharmacologic parameters
2. A high prevalence of chronic medical disorders
3. Frequent polypharmacy, associated with medication errors, adverse effects, and drug interactions

Drug-related problems in hospitalized patients, many of whom are elderly, are associated with increases in patient morbidity, length of hospital stay, and economic costs. The costs of medication errors alone have been estimated at greater than \$3500 per adverse drug event in community hospitals, with an average associated increase in

length of hospital stay of approximately 3.1 days [11].

Pharmacology and Pathophysiology

The impact of advanced age on risk of toxic pharmaceutical or nonpharmaceutical exposure may be characterized in terms of several categories of determinants: (1) physiologic factors, such as age-related alteration in drug absorption or effect on myocardial function; (2) interactions among pharmaceutical and nonpharmaceutical agents resulting from the use of multiple medications for multiple medical problems; and (3) extrinsic, social, and behavioral factors, such as physician prescribing practice and patient compliance. The pharmacologic or toxicologic effects of exposure to a drug or other substance commonly are distinguished on the basis of whether they concern (1) the pharmacokinetic or toxicokinetic response to exposure (i.e., the disposition of that substance as a function of its absorption, distribution, metabolism, and elimination) or (2) the pharmacodynamic or toxicodynamic response (i.e., organ/system effects that result from the actions of a drug or other exogenous substance at tissue/organ effectors (e.g., cell membrane receptors, enzymes, or other components with cell signaling functions)).

The combination of age-related pharmacokinetic and pharmacodynamic changes and inappropriate exposure to drugs or other substances results in an increase in the incidence of untoward exposure events in older individuals. This increase is particularly true of pharmaceutical agents with narrow therapeutic indices (i.e., low therapeutic-to-toxic ratios), such as aminoglycosides, digoxin, lithium, metformin, phenytoin, salicylates, and theophylline. For many of these agents, their already low therapeutic index is reduced further by physiologic changes in the geriatric population. For example, older patients are at heightened risk of developing lithium toxicity with therapeutic use because their natural decline in renal function reduces their ability to excrete the drug. Iatrogenic events have a prominent causal role in mortality and

Table 1 Types of drug-related iatrogenic disease

Predictable effects of a medication based on the known pharmacologic action (e.g., tardive dyskinesia with metoclopramide)
Hypersensitivity reactions (e.g., penicillin-induced anaphylaxis)
Idiosyncratic (non-dose related) reactions (e.g., NSAID-induced aseptic meningitis)
Overlapping pharmacology (e.g., anticholinergic toxicity from concomitant use of antihistamines and antidepressants)
Adverse effects related to metabolites (e.g., myoclonus and seizures secondary to accumulation of the meperidine metabolite normeperidine)
Drug interactions (e.g., inhibition of theophylline metabolism by cimetidine)
Inappropriate dosing (e.g., failure to adjust aminoglycoside maintenance dose for age-related decline in renal function)
Medication error (e.g., dispensing error based on similarity of drug names such as Celexa (citalopram) and Celebrex (celecoxib))

morbidity from pharmaceutical exposure in all populations, but particularly in the elderly. Some types and examples of iatrogenic-poisoning occurrences are listed in Table 1. For the reasons already described, the elderly population is at increased risk for all of these errors.

Pharmacokinetic Considerations

Much of the published data regarding pharmacokinetic characteristics of various drugs are based on volunteer studies in young, healthy individuals. Age-related physiologic changes may alter drug disposition significantly in elderly patients (Table 2) and should be considered in the prevention and treatment of toxicologic illness in elderly patients.

Several well-known, age-related changes within the gastrointestinal tract have been described. Increases in gastric pH and gastric emptying time have been observed along with decreases in gastrointestinal blood flow and mucosal absorptive surface area [12]. Despite these alterations, the extent of drug absorption typically does not change; however, there may be a significant decrease in the rate of absorption

Table 2 Pharmacokinetic considerations in the elderly

Parameter	Age-related change	Impact
Absorption		
Gastric pH	Increased	Reduced absorption (e.g., itraconazole)
Gastric emptying	Reduced	Reduced rate of absorption
Distribution		
Body fat	Increased	Increased Vd for lipophilic agents (e.g., diazepam)
Body water	Reduced	Reduced Vd for hydrophilic agents (e.g., lithium)
Plasma protein		
Albumin	Reduced	Increased free fraction (e.g., phenytoin)
α -Glycoprotein	Increased (illness)	Reduced free fraction (e.g., lidocaine)
Metabolism		
Hepatic mass/blood flow	Reduced	Reduced clearance (e.g., lidocaine)
Phase I enzyme activity	Reduced	Reduced clearance (e.g., diazepam, meperidine)
Elimination		
Liver metabolism	Reduced	Reduced elimination rate
Renal excretion GFR	Reduced	Reduced elimination rate

GFR glomerular filtration rate, Vd volume of distribution

of some drugs. The net effect of these changes is hard to predict and does not allow for broad generalization, but with slowed absorption, there may be a slower onset of action for some drugs. This effect is particularly important for agents such as analgesics or sedatives, in which a rapid onset of drug effect is desirable. In addition, drugs that require an acidic environment for dissolution and absorption, such as ketoconazole or itraconazole, may be less bioavailable in the elderly.

Age-related changes in chemical, drug, or toxin distribution result from several factors. Reduction in body water and muscle mass along with an increase in body fat results in reduced volume of distribution (Vd) for substances that primarily distribute in water or lean body mass,

such as digoxin and ethanol, whereas V_d is expanded for substances that distribute primarily in fat, such as diazepam. The time interval from first administration to attainment of steady state and the elimination half-life of a substance may be increased or reduced in elderly individuals depending on whether the substance is lipid soluble or water soluble. In elderly individuals started on regular doses of a fat-soluble drug such as diazepam, the onset of toxic effects may be delayed, and their duration prolonged.

Serum albumin levels decline as a result of aging, disease, debilitation, and poor nutrition [1]. This change results in an increase in active, unbound fractions of drugs with characteristically high binding affinity to plasma proteins (e.g., salicylate, diazepam, warfarin, phenytoin, quinidine, theophylline), and an increase in the V_d . Under conditions of increased physiologic stress (e.g., acute myocardial infarction), the production and plasma content of α -acid glycoprotein (α AG), an acute-phase reactant, may be increased. The effect of an increase in α AG level in plasma is opposite to that of hypoalbuminemia (i.e., reduction in free drug fraction and amount of drug (e.g., lidocaine) available for target organ effect). These effects do not offset each other, however, because the drugs that bind to albumin frequently are different from the drugs that bind to α AG. Other disease states that are relatively common in elderly patients (e.g., sepsis) are associated with increased capillary permeability. This physiologic action may result in a dramatic increase in V_d of substances (e.g., gentamicin) that distribute into extracellular body water, requiring increased doses to maintain therapeutic blood levels.

The metabolism of a pharmaceutical or nonpharmaceutical compound may inactivate it (e.g., lidocaine), activate it (e.g., enalapril and several other angiotensin-converting enzyme inhibitor prodrugs), or prolong its activity (e.g., diazepam's conversion to its longer-acting metabolite nordiazepam). The body's clearance of some drugs (e.g., lidocaine, propranolol) greatly depends on hepatic metabolism and on hepatic blood flow or enzyme activity. Aging-related declines in liver mass and cardiac output are associated with reduction in hepatic blood flow by

50% in individuals older than age 65, resulting in slowed metabolism of perfusion-dependent drugs (e.g., lidocaine) [10]. Diseases such as congestive heart failure may compromise hepatic blood flow and clearance of perfusion-dependent drugs further.

Although experimental evidence suggests that their role, independent of other risk factors, in reduced drug clearance in elderly patients is relatively minor [11], oxidative (phase I) enzymes that make lipid-soluble drugs more water soluble for excretion by the kidney may have reduced activity in the elderly. This reduced activity may result in reduced metabolism of active parent compounds (e.g., diazepam) and, in some instances, their active metabolites (e.g., nordiazepam). Age-related reduction in phase I enzyme activity may be compounded further by non-age-related genetic variation and exogenous influences, such as drugs (e.g., erythromycin) and dietary sources (e.g., grapefruit juice), that inhibit enzyme activity. Phase II reactions, involving attachment of large polar groups (e.g., glucuronide moiety) to drugs (e.g., lorazepam), inactivating them, and further facilitating their excretion, seem to be affected minimally by aging. Drugs that normally are highly protein bound (e.g., phenytoin) may be subject to increased metabolism in the elderly as a result of the age-related decline in production of albumin and resultant increase in free drug available to the liver to be metabolized.

Perhaps the most important age-related physiologic determinant of ADEs is decline in renal clearance. Progressive diminution in renal perfusion, glomerular filtration, and tubular function commonly results in reduced clearance rates and potentially toxic accumulation of drugs or other exogenous substances. Most notable are agents that are highly dependent on renal elimination (e.g., lithium, digoxin, metformin, baclofen, normeperidine, aminoglycosides, penicillin). Serum creatinine levels may remain normal as creatinine production declines because of age-related reduction in muscle mass in parallel with decline in renal function. Estimates of renal function in elderly individuals that are based on serum creatinine level, including estimates that take age, weight, and gender into account, should

be viewed with caution and not overly relied on to assess renal-dependent drug clearance [13].

Important Geriatric Pharmacokinetic and Pharmacodynamic Characteristics

The elderly have:

1. Altered drug/toxin distribution (increase or decrease in volume of distribution) of drugs depending on fat and water solubility and protein-binding affinity
2. Reduced hepatic clearance of perfusion-dependent and phase I enzyme-metabolized substances
3. Reduced elimination of drugs predominantly cleared by the kidney
4. Increased sensitivity to target organ/tissue effects
5. Reduced ability to compensate for the pathophysiologic effects of toxic exposure (age-related blunting of homeostatic control mechanisms or pathology associated with concurrent disease or both)

Pharmacodynamic Factors

Many pharmacodynamic factors are thought to influence the elderly individual's response to exposure to pharmaceutical and nonpharmaceutical agents. These factors include age-related changes in receptor tissue density, reduced capacity for compensatory response to physiologic change or stress, blunted homeostatic control (e.g., thermoregulatory and baroreceptor) mechanisms, and altered sensitivity to the effects of various agents, independent of their pharmacokinetic characteristics [14]. Data from experimental and clinical studies show significant age-dependent reduction in β -adrenergic receptor responsiveness to agonists and antagonists [1, 4]. In general, however, elderly patients seem to be more sensitive than younger individuals to developing the adverse effects of various medications, including cognitive dysfunction (e.g., sedative agents), respiratory depression (e.g., opioid analgesics), dysrhythmia or conduction

disturbance (e.g., digoxin, calcium channel blockers), postural hypotension (e.g., tricyclic antidepressants), gastrointestinal bleeding (e.g., NSAIDs), constipation (e.g., opioid analgesics), urinary retention (e.g., antihistamines), hyponatremia or hypokalemia (e.g., thiazide diuretics), hyperkalemia (e.g., trimethoprim), hypoglycemia (e.g., ethanol), renal failure (e.g., NSAIDs), and coagulopathy (e.g., warfarin).

Preexisting or comorbid medical conditions frequently amplify the elderly patient's sensitivity to the effects of various pharmaceutical and nonpharmaceutical agents. This familiar observation is well supported by marked age-related increases in the prevalence of medical disorders such as various types of senile dementia, Parkinson's disease, hypertension, coronary artery disease, sick sinus syndrome, atrophic gastritis, prostatic hypertrophy, diabetes mellitus, hypothyroidism, malnutrition, sepsis, various malignant neoplastic diseases, and glaucoma.

Drug-Drug, Drug-Food, and Drug-Lifestyle Interactions

Toxic pharmacokinetic and pharmacodynamic interactions among various pharmaceutical and nonpharmaceutical (e.g., dietary) agents may be more likely to occur in elderly individuals, given their tendency to use multiple medications and their increased sensitivity to the effects of many agents. A vigilant posture should be assumed in regard to rapid onset, life-threatening drug-drug interactions that may occur in hospitalized elderly patients with multisystemic illness for which multiple medications may seem indicated [15].

Undesirable reduction in bioavailability of some drugs may occur in response to altered gastrointestinal pH or cation content or induction of phase I enzyme activity responsible for drug metabolism. The absorption of imidazole antifungal drugs (e.g., ketoconazole) is reduced when coadministered with drugs that raise gastrointestinal pH, such as antacids or proton-pump inhibitors, whereas the presence of increased gastrointestinal concentrations of cations (e.g., Fe^{++} , Ca^{++} , Mg^{++}) associated with consumption

of iron supplements, milk, or antacids interferes with the absorption of some antibiotics (e.g., fluoroquinolones, tetracyclines). Another familiar example of a pharmacokinetic drug interaction is that involving cigarette smoking and theophylline; induction of a phase I isoenzyme involved in theophylline metabolism, cytochrome P-450 (CYP) 1A2, by polycyclic aromatic hydrocarbons in tobacco smoke is believed to be responsible for the increased clearance of theophylline observed in individuals who smoke while taking theophylline.

Increased levels and prolonged effects of drugs metabolized by hepatic phase I enzymes (e.g., warfarin by CYP 2C9 and diltiazem by CYP 3A4) may occur in response to administration of drugs (e.g., amiodarone) or consumption of foods (e.g., grapefruit juice) that inhibit the activity of these enzymes. Other mechanisms responsible for toxic drug interactions include displacement of protein-bound drug (e.g., salicylate) by other drugs with high protein-binding affinity (e.g., warfarin), impaired renal elimination (e.g., NSAID-induced, angiotensin-converting enzyme, inhibitor-induced, or thiazide-induced reduction in lithium clearance), and additive pharmacodynamic effects, such as those produced by central nervous system depressant medications (e.g., sedatives and opioid analgesics). The reader is referred to frequently updated reference sources for drug–drug interactions [16, 17].

Social and Behavioral Factors

The increased prevalence of medical disorders in older individuals predisposes them to social, behavioral, and pharmacokinetic and pharmacodynamic risks of adverse exposure to pharmaceutical and nonpharmaceutical compounds. As previously noted, ADEs in this age group are related to individuals' tendency to use multiple medications. The causal basis for polypharmacy in the geriatric population seems to be multifactorial, involving not only an increased number of diagnoses but also deficiencies in health-care professionals' education, attitudes (e.g., neglect), and prescribing practices (e.g., off-site management of

nursing home patients, “standing” and “continuation” medication orders, tendency to add “blindly” to list of medications prescribed by other providers).

Iatrogenic medication errors (improper prescription, distribution, or administration) are an important cause of ADEs in all populations, but especially the elderly. The rates of medication error-related adverse drug events have been reported to range from 4.4% to 8.5% [18, 19]. The potential for therapeutic misadventure is compounded further by patient noncompliance, which may be intentional (e.g., on the basis of affective disturbance) or unintentional (e.g., on the basis of cognitive or perceptual dysfunction), resulting in subtherapeutic and supratherapeutic dosing.

Studies have shown up to 50% of elderly patients receive potentially inappropriate medications, with benzodiazepines, NSAIDs, diuretics, antidiabetic medications, theophylline, opioids, and aspirin among commonly prescribed high-risk medications [20, 21]. Inappropriate prescribing contributed to hospital admissions in 27% of patients and was associated with an increased risk of falls and fractures [20].

Clinical Presentation

Health-care providers must be alert to the possibility that poisoning in the elderly individual may present in a manner that is chronic or subacute, subtle (e.g., mild sleep disturbance or intermittent decline in sensorium), indirect (e.g., fall or motor vehicle accident), or atypical compared with that seen in younger healthy individuals (e.g., focal neurologic abnormality). Obtaining an accurate history, with particular attention to prescribed, recently administered, or available medications or other health supplements, is paramount in making an accurate diagnosis and embarking on effective treatment for elderly individuals. The clinician's index of suspicion for a toxicologic basis for the presenting sign and symptom complex should be raised by the documented or suggested use of medications with low therapeutic indices (e.g., digoxin), preexisting disorders (e.g.,

dementia, depression, alcoholism, renal insufficiency), or history suggesting toxic exposure to nonpharmaceutical agents (e.g., ethanol, pesticides, carbon monoxide).

Key Points in the Clinical Presentation of Geriatric Poisoning

1. Poisoning in a geriatric patient is often chronic, subacute, or subtle.
2. Neurobehavioral dysfunction is common.
3. Also relatively commonly occurring or life-threatening are cardiac dysrhythmia/conduction disturbance, postural hypotension, respiratory failure, pulmonary edema, gastrointestinal dysmotility, urinary retention, hypoglycemia, or bleeding diathesis.

Elderly individuals are particularly vulnerable to the neurobehavioral effects of a broad array of pharmaceutical agents (Table 3; refer to specific chapters on relevant drug class (e.g., antihistamine) or toxic syndrome (e.g., anticholinergic poisoning) for detailed descriptions of the neurobehavioral and other systemic effects of the pharmaceutical agents of interest) [22]. Cognitive disturbance is a common presentation for poisoning in older patients. Delirium occurs in up to 40% of hospitalized elderly patients [23]. Medications, especially benzodiazepines or neuroleptics, are highly associated with increased delirium risk.

Evaluating health-care providers should examine elderly patients with altered mental status for relatively common toxic syndromes. Anticholinergic poisoning (see ► Chap. 23, “Anticholinergic Syndrome”) is associated with the use of many prescription and nonprescription medications, including tricyclic antidepressants, first-generation antihistamines, some antiarrhythmics, antiparkinsonian agents, antipsychotics, and muscle relaxants. Alcohol or sedative-hypnotic drug intoxication or withdrawal also produces mental status changes. A high index of suspicion for chronic salicylism should be maintained in elderly individuals who present with altered sensorium and a characteristic mixed acid–base disturbance (see ► Chap. 63, “Salicylates”). Delay in diagnosis of geriatric

Table 3 Examples of drug classes/drugs that may induce neurobehavioral dysfunction^a in the elderly

Class	Specific drugs
Antiarrhythmics	Digoxin, lidocaine, procainamide
Anticonvulsants	Phenytoin, carbamazepine, valproic acid
Antidepressants	Amitriptyline, fluoxetine
Antiemetics	Promethazine, metoclopramide
Antihypertensives	Clonidine, propranolol, verapamil
Antimicrobials	Penicillin, ciprofloxacin, isoniazid
Antiparkinsonians	Levodopa, amantadine
Antipsychotics	Thioridazine
Bronchodilators	Theophylline
Antineoplastics	Methotrexate, vincristine, procarbazine, cytarabine
Histamine receptor (H ₁ -, H ₂ -) antagonists	Diphenhydramine, cimetidine
Immunosuppressants	Corticosteroids, cyclosporine
Mood stabilizers	Lithium
Muscle relaxants	Carisoprodol, cyclobenzaprine, orphenadrine
Nonsteroidal anti-inflammatory drugs	Salicylate, mefenamic acid
Opioid analgesics	Meperidine/normeperidine
Sedative–hypnotics	Diazepam, phenobarbital, meprobamate

^aRefer to specific chapters on relevant drug class (e.g., antihistamine) or toxic syndrome (e.g., anticholinergic poisoning) for detailed descriptions of the neurobehavioral and other systemic effects of the pharmaceutical agents of interest

salicylate poisoning is common, in part, because of its similarity to other disease processes [7]. Preexisting chronic or acute drug (e.g., NSAID induced) renal insufficiency may be an important contributing factor to the development of neurotoxicity, including seizures, from renally eliminated drugs, such as lithium and certain antibiotics particularly among the fluoroquinolone (e.g., ciprofloxacin) and β -lactam antibacterials (e.g., penicillin, imipenem, cefazolin) [24].

Clinicians also should recognize that elderly individuals with underlying disorders such as atherosclerotic cerebrovascular disease may be more sensitive to insults such as sulfonyleurea-induced

or alcohol-induced hypoglycemia [25]. Acute-onset focal neurologic deficits may be more likely in elderly patients than in younger healthy individuals to represent the potentially reversible effects of a toxic insult, as opposed to progression of the primary disease process.

Although they are nonspecific, vital sign abnormalities that are more likely to occur in elderly individuals in response to a toxic insult include hyperthermia and hypothermia, orthostatic hypotension, and bradycardia. The reported prevalence of orthostatic hypotension in the geriatric population is up to 32% [26] and frequently is associated with the use of medications such as diuretics, calcium channel blockers, β -blockers, angiotensin-converting enzyme inhibitors, nitrates, antidepressants, and antipsychotics.

Presyncopal dizziness or frank syncope may reflect cardiac rhythm or conduction disturbance as an acute or chronic toxic effect of administration of drugs that directly (e.g., β -blockers, calcium channel blockers) or indirectly (e.g., digoxin) prolong atrioventricular nodal conduction, increase automaticity (e.g., digoxin), or cause repolarization abnormalities such as QT interval prolongation (e.g., type IA antidysrhythmics, tricyclic antidepressants, piperidine antipsychotics such as thioridazine and mesoridazine, and the newer atypical neuroleptics). Extracardiac manifestations of digoxin toxicity, such as anorexia, nausea, visual disturbance, and confusion, may support the diagnosis further but are so prevalent and nonspecific that their presence may not enhance clinical recognition [27].

Pulmonary edema is more likely to occur in elderly individuals as a consequence of drug-induced negative inotropy combined with limited cardiac functional reserve capacity. An acute respiratory distress syndrome may be a manifestation of poisoning (e.g., chronic salicylism) and may not be associated with the presence of jugulovenous distention or S_3 gallop, typical features of cardiac failure. Gastrointestinal dysmotility disorders (e.g., constipation, adynamic ileus) and genitourinary dysfunction (e.g., urinary distention) are relatively common clinical presentations in the elderly for toxicity from drugs

with narcotic (e.g., opioid analgesics) or anticholinergic (e.g., antihistamines) actions. The presence of a bleeding diathesis should suggest the possibility of warfarin-induced coagulopathy in individuals who have indications for or are known to be on anticoagulant treatment.

Diagnosis

Although there is no substitute for a thorough and accurate history in making a timely diagnosis of poisoning in an elderly individual, the clinical laboratory can be of invaluable assistance to the clinician dealing with initially scant or unobtainable historical information. The limitations and caveats that apply to toxicologic analyses in general apply to their role in the diagnosis and management of geriatric poisoning. Correlations between drug levels and the occurrence of toxicity may be even more limited in elderly patients, given their propensity to present well into the post-distribution phase after chronic, cumulative exposure to potentially toxic agents (e.g., salicylate, theophylline, digoxin, lithium) and their aging-altered drug distribution (e.g., increased free phenytoin fraction).

Routine clinical laboratory monitoring of serum electrolytes, glucose, and indices of renal function may be essential to the diagnosis and further prevention of untoward medication effects (e.g., digoxin-induced arrhythmia) in high-risk elderly patients, such as patients on diuretic or oral hypoglycemic therapy. Clinically significant abnormalities of serum sodium and potassium are particularly common among elderly individuals taking thiazide diuretics (hyponatremia, hypokalemia), whereas angiotensin-converting enzyme inhibitors, potassium-sparing diuretics, and trimethoprim may cause hyperkalemia [28, 29]. As previously discussed, methods used to estimate drug clearance by the kidney that are based on serum creatinine should take into account age-related changes in muscle mass and creatinine excretion and otherwise be employed with caution.

In contrast to serum chemistry indices of renal function, quantitative serum values of hepatic

enzymes (e.g., transaminases) and liver function tests (e.g., prothrombin time) are of little predictive value with regard to drug clearance. These analyses are used mainly to detect and monitor toxic hepatocellular injury (e.g., acetaminophen-induced hepatic necrosis) and effects on hepatic synthetic function (e.g., inhibition of vitamin K-dependent clotting factors by warfarin or salicylate). Quantitative serum drug assays are generally indicated if there is any clinical suspicion in elderly patients of salicylate or acetaminophen poisoning or for therapeutic monitoring of drug therapy involving agents with narrow therapeutic indices (e.g., digoxin, theophylline, lithium, aminoglycosides). Apart from routinely obtaining admission electrocardiograms and chest radiographs on all elderly patients requiring hospitalization for management of poisoning, indications for other diagnostic tests, such as abdominal radiographs and blood lead level, depend on the specific exposure.

Treatment and Prevention

Treatment of acute and chronic poisoning in elderly patients should be approached in much the same manner as for other age groups, with many added caveats that pertain to age-related pharmacokinetic and pharmacodynamic differences. Special attention should be directed at the potentially greater need for aggressive ventilatory support and for caution in fluid volume resuscitation in elderly individuals, given their greater sensitivity to the central depressant effects of some agents, greater likelihood of cardiac inotropic or chronotropic compromise, and tendency to develop life-threatening complications of such therapy (e.g., acute pulmonary edema). Clinicians also should recognize in older patients with chronic medical conditions the importance of considering blunted homeostatic (e.g., thermoregulatory) mechanisms, endocrine dysfunction (thyroid, adrenal), and nutritional deficiencies (e.g., limited vitamin and glucose stores) and address these with appropriate supportive measures (e.g., body warming or cooling, empirical thiamine administration). Although it may seem

obvious, a frequently overlooked step in the initial management that may be of significant short-term or long-term benefit is temporary discontinuation of previously prescribed medications, particularly medications with narrow therapeutic indices or medications considered likely offenders (e.g., lithium, warfarin, digoxin, NSAIDs, anticholinergics, and serotonergic drugs).

Hemodialysis as a method of enhanced elimination of drugs and toxins (see ► [Chap. 12, “Extracorporeal Substance Removal”](#)) plays an important role in the management of geriatric poisoning, particularly in instances in which the offending agent is of low molecular weight, low Vd, and low protein-binding affinity and undergoes predominantly renal elimination (e.g., lithium, salicylate, phenobarbital). The greater likelihood of impaired renal drug clearance and susceptibility to complications from aggressive sodium and fluid loading in this age group provides a compelling argument in support of hemodialysis when it is indicated for toxicologic reasons.

Key Points in the Management of Geriatric Poisoning

1. Medication history should be reviewed carefully for evidence of medication error, adverse effect, or drug interaction, and potentially offending medications should be discontinued.
2. Extra caution should be exercised during administration of supportive and antidotal therapy, urinary pH manipulation, and gastrointestinal decontamination.
3. Hemodialysis as a means of enhancing elimination may be warranted further in poisoned elderly individuals, given their age-related reduction in renal clearance or increased risks of other therapy.

In older individuals, caution also should be exercised in the administration of antidotal agents such as physostigmine for anticholinergic poisoning in individuals at risk for cardiac conduction disturbance, antidigoxin antibodies for digitalis poisoning in patients with preexisting rapid atrial

fibrillation, β -adrenergic antagonists for theophylline-induced tachydysrhythmias in individuals who may have underlying coronary artery or obstructive airway disease, and flumazenil for suspected benzodiazepine-induced central nervous system depression in individuals at risk for acute withdrawal from the latter agents. Antidotal agents that are cleared primarily by the kidney (e.g., the heavy metal chelator calcium sodium ethylenediamine tetraacetic acid) may be ineffective or contraindicated in individuals with renal insufficiency. Similarly, the dosing of medications used to treat complicating or concurrent illness that is eliminated primarily via the renal route (e.g., aminoglycoside antibiotics meperidine/normeperidine) should be adjusted for renal insufficiency. Although the administration of an antidote in many of these circumstances still may be warranted, consultation with a medical toxicologist is recommended.

Prevention of toxic exposure in hospitalized elderly patients may be enhanced further through improved health-care provider education, limited use or avoidance of certain pharmaceutical agents, computerized physician entry of medication orders, and pharmacy surveillance (computerized or on-site, pharmacist staffed) [22, 30, 31].

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Epidemiology

According to the National Poison Data System (NPDS) of the American Association of Poison Control Centers, in 2014 poisoning in children under the age of 20 accounted for 61% of calls to poison centers in the United States [1]. The proportion of those cases that required referral to a health care facility (HCF) varied. 12.7% of children ≤ 5 years and only 16.5% of children between 6 and 12 years were managed in an HCF compared to 61.1% of teenagers (13–19 years). The proportion of children described as having a “Major Effect” rose from 0.07% in the under 5 age group to 1.65% in teenagers. The fatality rate was highest in the teen group (0.05%), where more than one half of ingestions are intentional versus the under 5 age group ($<0.002\%$) where 99.5% of exposures are unintentional. The number of pediatric deaths among cases reported to US poison centers was 88. These figures have remained consistent over the past several years.

While the number of patients requiring pediatric intensive care unit (PICU) admission is unclear, in a European study 1.5% of patients seen for poisoning in an emergency department (ED) were admitted to the PICU [2]. In a Canadian study, 6.3% of patients seen in a metropolitan pediatric ED with poisoning were admitted to the

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PICU [3]. This represented 3.1% of all PICU admissions to that institution over the 3-year study period. In a US retrospective study, 8% of all PICU admissions to an academic center represented poisonings [4]. According to NPDS, 127 children received hemodialysis, 2336 received mechanical ventilation, 509 received vasopressors, and 21 received extracorporeal membrane oxygenation (ECMO) in the USA in 2014.

It should be noted that the number of poisoning exposures and the number of deaths described in NPDS underrepresent the actual nationwide numbers as not all cases are reported to poison centers.

Admission to the PICU

Critically ill pediatric patients should be cared for in a PICU where there are specially trained personnel and equipment tailored to the needs of children. If there is no PICU, unless clinical effects are mild to moderate, and the expected duration of illness is short, arrangements should be made to transfer the patient to a PICU for care. Most tertiary care programs, and some smaller ones, have dedicated pediatric transport teams for the movement of patients. These teams may have various compositions and may include pediatric nurses, respiratory therapists, and physicians. They typically use specially outfitted ambulances that contain pediatric equipment and are equipped to handle emergencies during transport. It is likewise important to have the expertise of a consultant medical toxicologist ideally on site, or through the regional poison center.

Indications for admission to the PICU are given in Table 1. In the triage of patients with few, or no, clinical manifestations of their poisonings, it is important to carefully consider the time of exposure and the pharmacokinetics of the agent in question so patients can be observed in the critical care setting until the risk of serious compromise has passed. Finally, patients at high risk of suicide may be admitted to the PICU if no other closely monitored area is available.

General Pediatric Intensive Care Unit Treatment

The usual mechanism of admission to the PICU is either through the ED or via transfer from another institution. Decontamination, if any, is typically initiated in the referring facility prior to transfer. In most cases, the time elapsed prior to PICU admission renders further decontamination efforts relatively useless after admission. Potential exceptions include techniques such as whole bowel irrigation for selected toxins, such as controlled-release products, iron, lithium, and potassium, or in body packers [5]. Multiple dose activated charcoal may also be considered in certain toxic ingestions (see “► Chap. 3, “[Therapeutic Approach to the Critically Poisoned Patient](#)” for detailed discussion) [6]. Whole bowel irrigation and multiple dose activated charcoal should be administered with caution, or not at all, in patients with ileus or circulatory shock.

The mainstay of the ICU management of a poisoned pediatric patient is supportive care. The general ICU care of most poisoned patients is not any different from the care received by other ICU patients with a comparable level of severity and similar symptoms [7, 8]. All PICU patients should have continuous monitoring of heart rate, respiratory rate, and pulse oximetry. The frequency of nursing assessment and vital signs monitoring depends on the stability of the patient and the problems present or anticipated. The frequency of assessment may vary from every few minutes to every 4 h and should be appropriate for the patient and the circumstances.

Any patient admitted to an ICU should have stable intravenous access. Whether a peripheral intravenous catheter or a central line is required depends on the stability of the patient and the problems anticipated. If major organ system instability is present or likely, central access or multiple peripheral intravenous lines generally should be obtained. A single peripheral intravenous line is not adequate for a severely ill patient who may require lifesaving therapies. Central lines can be placed in subclavian, internal jugular, or femoral vessels. In newborns, the umbilical vein may also

Table 1 Indications for pediatric ICU admission relevant to toxic exposures

1. Acute respiratory failure as manifested by one or more of the following:
a. Need for mechanical ventilation or emergency tracheostomy
b. Marked respiratory compromise as indicated by
(1) RR ≤ 20 or ≥ 60 for infants ≤ 1 year old
(2) RR ≤ 12 or ≥ 60 for patients > 1 year old
(3) SpO ₂ $\leq 92\%$ on 100% oxygen by nonrebreather mask or tracheostomy collar
(4) PaO ₂ < 80 mmHg on 100% oxygen by nonrebreather mask
c. Rapidly progressive deterioration in respiratory status
d. Respiratory acidosis with PaCO ₂ > 60 mmHg and pH < 7.25
e. Airway obstruction
g. Apnea
h. Anaphylaxis
2. Hemodynamic instability or circulatory failure as manifested by one or more of the following:
a. Shock as indicated by
(1) Capillary refill > 4 s
(2) Nonpalpable distal or proximal pulses
(3) Systolic blood pressure $<$ lower limit for age and/or MAP < 50 mmHg (neonates < 40 mmHg)
(4) Acute metabolic acidosis with pH < 7.25 , base deficit > -10 or serum bicarbonate ≤ 10 mEq/L
(5) Need for invasive hemodynamic monitoring
b. Unstable or new cardiac dysrhythmia
c. Need for continuous infusion of vasoactive drugs
d. ECG showing changes consistent with ischemia
e. Acute congestive heart failure
f. Unstable vascular volume as indicated by
(1) Need for > 40 mL/kg fluid bolus
(2) Hemoglobin < 8 g/dL in a bleeding or hemolyzing patient
(3) Platelet count $< 20,000$ with active bleeding
(4) INR > 2 with active bleeding
g. Need for cardioversion
h. Malignant hypertension
3. Neurologic instability as manifested by one or more of the following:
a. Acute neurologic deterioration as indicated by
(1) Glasgow Coma Scale score ≤ 10
(2) Severe irritability
(3) Hallucinations
(4) Posturing
b. Intracranial hemorrhage
c. Evidence of increased ICP
d. Seizures
e. Delirium
4. Metabolic derangements placing patients at risk of serious complications as evidenced by one or more of the following:
a. Serum sodium < 125 mmol/L or > 160 mmol/L
b. Serum potassium < 3 mmol/L or > 6.5 mmol/L (nonhemolyzed)
c. Blood glucose < 30 mg/dL or > 400 mg/dL (1.7 mmol/L or 22.2 mmol/L)
d. Ionized calcium < 0.8 mEq/L
e. Base deficit > -10
5. Other patients displaying evidence of acute or developing failure of an essential organ system
6. Patients with a toxic exposure in which none of the above are present but in which
a. One of the above admission criteria can be expected to develop within a few hours based on the nature of the exposure
b. The patient is suicidal, and no other safe area of medical and psychiatric observation exists

ECG electrocardiogram, ICP intracranial pressure, INR international normalized ratio, MAP mean arterial blood pressure, PaO₂ arterial oxygen partial pressure, PaCO₂ arterial carbon dioxide partial pressure, RBC red blood cell, RR respiratory rate, SpO₂ arterial oxygen saturation

be available and can be used. If lines are properly placed in either the superior or the inferior vena cava, they may be transduced to provide central venous pressure measurement. Because improperly placed lines can give incorrect and misleading information, placement should be verified by radiograph before the lines are transduced. Arterial catheters for arterial blood sampling and continuous blood pressure monitoring should be inserted in any patient with significant cardiovascular dysfunction secondary to a toxic exposure and in patients intubated because of central nervous system (CNS) depression.

The use of laboratory monitoring, including arterial blood gas measurements, should be dictated by the status of the patient, the initial values obtained, and the anticipated problems. Sequential measurement of drug or toxin levels may be valuable in selected cases as either a marker of therapeutic efficacy or a predictor of likely toxic effects.

Neurologic Toxicity

Derangement of neurologic function associated with intoxication is a common reason for PICU admission. Common neurologic changes resulting from intoxication include a depressed level of consciousness, agitation and delirium, or seizures, sometimes in combination. A detailed discussion of these topics is beyond the scope of this chapter, but some basic issues of critical care assessment and initial management strategies are discussed. For greater detail see ► [Chap. 19, “Toxicant-Induced Alterations in Consciousness.”](#)

A diminished level of consciousness may result from a number of causes, such as intoxication, metabolic derangements, and structural neurologic insults such as trauma, intracranial hemorrhage, focal ischemic injury or stroke, infection, or psychiatric disorders. Sometimes more than one of these categories simultaneously may be responsible for mental status change, as in a patient with ethanol toxicity accompanied by hypoglycemia or a trauma patient under the influence of drugs or ethanol.

Altered mental status resulting from toxic and metabolic causes differs from mental status alteration from other causes in that brain structure is not altered, and neurologic pathways are intact. Clouding of consciousness usually is not associated with focal neurologic findings and is reflective of global encephalopathic change. Altered mental status may occur in combination with CNS depression, as in the case of benzodiazepine, opiate, or barbiturate ingestion, or with agitation and delirium, as is seen in dextromethorphan intoxication. Alternatively, agitation and delirium may occur without alteration in consciousness, as seen in anticholinergic and hallucinogenic drug ingestions, and *Centruroides* envenomation.

Physical findings on neurologic examination after ingestion of a CNS depressant (e.g., benzodiazepine, opioid, or barbiturate) usually include diminution in the magnitude of response rather than loss of response, unless the overdose is large enough to induce coma. Pupillary response generally is preserved, although commonly it is sluggish and diminished in intensity. An exception is the ingestion of antimuscarinics in which pupillary response may be absent. Toxic or metabolic encephalopathy also may result in diminution of control of brainstem functions, such as respiratory drive, resulting in hypoventilation or apnea, or control of peripheral vascular tone, resulting in vasodilation and hypotension. Loss of motor tone in skeletal musculature may result in bulbar and hypopharyngeal muscle dysfunction, causing upper airway obstruction and loss of airway protective reflexes, or may result in a decrease in respiratory muscle function, with resulting hypoventilation.

Alternatively, patients may present with altered mental status in combination with agitation, hallucinosis, and even seizures. The list of drugs that can manifest in this manner is long and includes *Centruroides* scorpion stings, antimuscarinics, amphetamines, cocaine, synthetic cannabinoids, lysergic acid diethylamide, ketamine, phencyclidine, “bath salts,” and huffing of solvents. These patients may present with hyperthermia, tachycardia, and hypertension. Motor tone is frequently increased, with associated hyperreflexia and abnormal motor movements.

The assessment of a patient with neurotoxicity includes a detailed history and physical examination to exclude other causes of neurologic deterioration. Localizing findings strongly suggest a cause other than intoxication. Computed tomography (CT) or magnetic resonance imaging of the brain may be indicated to exclude hemorrhage, stroke, global ischemic injury, or cerebral edema. Fever in the presence of depressed mental status may warrant the performance of a lumbar puncture to rule out infection, although this may represent an anticholinergic syndrome for which a trial of physostigmine may aid in making the distinction. An electroencephalogram may be warranted to rule out nonconvulsive status epilepticus.

In the child with a depressed level of consciousness, the first priority is to ensure adequate airway, breathing, and circulation. Once these have been assured, point of care measurement of blood glucose is indicated with correction of hypoglycemia if warranted. Empiric administration of naloxone is indicated. The pediatric starting dose is 0.01 mg/kg. Thiamine, although commonly administered in adults because of the relatively high incidence of deficiency associated with alcoholism or malnutrition, is not routinely indicated in children, although it may be considered in the older child where a history of alcoholism cannot be excluded.

Seizures

Seizures are a common finding in intoxication with drugs that affect the central nervous system. A detailed discussion of the neuropharmacology of seizures in poisoned patients is beyond the scope of this chapter (see ► [Chap. 20, “Toxicant-Induced Seizures”](#)). Seizure control is a primary issue in the management of a poisoned child in the PICU, however, and is addressed briefly here.

Seizures associated with ingestion of toxins may be difficult to control and may be recurrent or persistent, resulting in status epilepticus. Status epilepticus is associated with an increase in cerebral metabolic demand [9] for oxygen and may cause a decrease in respiratory effort, upsetting the

balance between cerebral oxygen demand and delivery, resulting in cerebral ischemia. Aggressive management of seizures associated with poisoning is crucial to unimpaired recovery.

The first priority in management of seizures is prompt attention to the adequacy of airway patency, respiratory effort, and oxygenation, to ensure oxygen delivery to the brain. Administration of supplemental oxygen, positioning to avoid airway obstruction, and attention to the adequacy of spontaneous respirations, with aggressive intervention in patients with marginal respiratory status, is critically important. Assessment and correction of hypoglycemia and electrolyte disturbances should also be promptly performed.

Anticonvulsant management of toxicant-induced seizures can typically be achieved with benzodiazepines. Lorazepam and diazepam appear to be equally efficacious at terminating status epilepticus in children [10] although lorazepam may have a lower rate of seizure recurrence after treatment [11, 12]. If benzodiazepines are insufficient, phenobarbital, propofol, and valproic acid are useful additional agents for seizure control. Phenytoin is unlikely to be efficacious in the treatment of toxin-induced seizures [13].

A particular cause of seizures likely to be unresponsive to traditional anticonvulsant therapy is ingestion of the antituberculous drug isoniazid and similar hydrazine compounds. Seizures in this instance result from depletion of pyridoxine and are generally responsive only to pyridoxine replacement. This specific ingestion is discussed in detail in ► [Chap. 65, “Isoniazid and Related Hydrazines.”](#)

Cardiovascular Toxicity

Cardiovascular compromise resulting from intoxication is a serious complication of poisoning that requires prompt critical care management and monitoring. A thorough understanding of the derangements produced by individual toxins and a sophisticated understanding of cardiovascular assessment, supportive care, and monitoring techniques are essential for successful treatment of

these critically ill patients. Cardiovascular function is the end result of a complex interaction between the heart and the peripheral vascular system. When functioning properly, this interaction provides for adequate cardiac output and appropriate distribution of cardiac output to specific organs and tissues to ensure optimal function. Cardiac function is regulated by specific neural and hormonal feedback mechanisms that monitor and modulate cardiac rate and contractility, peripheral vascular resistance and venous capacitance, and specific organ and tissue blood flows. A toxin may harm the heart or vascular smooth muscle directly; have neurogenic effects on the sympathetic or parasympathetic regulation of heart rate, contractility, or vascular resistance; or cause changes in intravascular volume, metabolic disturbances such as hypoglycemia, or electrolyte disturbances.

Evaluation of an intoxicated child at risk for cardiovascular compromise requires a thorough physical examination. Assessment of vital signs and autonomic findings, such as pupillary dilation or constriction, skin flushing or pallor, lacrimation, and salivation, provides useful information regarding cardiovascular status and may aid in identifying the type of intoxication. Evaluation of intravascular volume, performed by assessment of jugular venous distention, skin turgor, moistness of mucous membranes, and liver size, informs initial resuscitative management.

The adequacy of cardiac output can be assessed indirectly by the assessment of organ and tissue function. The patient's mental status, depth and frequency of respirations (increased in metabolic acidosis), volume of urine output, and estimation of peripheral perfusion (via palpation of central and peripheral pulses, capillary refill time, and peripheral warmth and skin color) reflect cardiac output. After initial assessment, reexamination at frequent intervals identifies changes in cardiovascular stability, directing further resuscitative care. Continuous cerebral and somatic oximetry using near infrared spectroscopy can provide assessment of the adequacy of cardiac output, as can serial measurement of arterial or mixed-venous lactate concentrations or mixed-venous oxygen saturation.

In addition to assessment of volume status and cardiac output, laboratory abnormalities should be addressed. Evaluation of acid–base status with arterial blood gases; measurement of electrolytes, including calcium, magnesium, and glucose; and baseline assessment of hepatic and renal function provide a basis for correction of metabolic derangements. Current technology allows for bedside evaluation of these parameters. In addition, if the intoxicant is known, plasma or serum concentrations of the intoxicating agent in selected cases may provide information regarding the severity of intoxication and aid in treatment decisions. Electrocardiography and echocardiography may also be indicated to guide therapy in cases of suspected intoxication with cardiovascular instability.

Patients requiring ICU admission for significant hemodynamic compromise and patients with a known ingestion with the potential for cardiovascular effects need cardiovascular monitoring. Critical care monitoring frequently includes placement of an arterial catheter for continuous direct measurement of blood pressure. The arterial catheter also allows painless arterial blood sampling for blood gases, enabling frequent monitoring of acid–base status and cardiorespiratory function. Placement of a central venous catheter may provide additional information about central venous filling pressures, which may be useful in decisions regarding fluid resuscitation and the use of inotropic agents. Central venous access provides for the reliable administration of cardioactive agents, such as inotropes, vasoconstrictors, and vasodilators, as needed.

Initial management of cardiovascular dysfunction is focused on restoration of cardiac output and organ system perfusion and correction of metabolic and electrolyte disturbances. Early in the course of cardiovascular instability, compensatory mechanisms may keep vital signs relatively normal. These mechanisms are an increase in sympathetic tone, resulting in an increase in heart rate, and peripheral vascular resistance may minimize changes in blood pressure, at the expense of cardiac output. Hypotension results only when the capacity of compensatory mechanisms is exceeded or when the intoxicating substance directly interferes with these mechanisms. One

example is tricyclic antidepressant intoxication, in which α -adrenergic receptor blockade interferes with peripheral vasoconstriction, while the direct cardiovascular effects diminish cardiac output. Similarly, beta blockers may blunt the tachycardic response normally seen with hypotension, similarly diminishing cardiac output.

Initial correction of inadequate cardiac output can usually be accomplished in the absence of identification of an intoxicating substance. Identification of an intoxicating substance may simplify management if the intoxicant's common effects are known, allowing specific intervention for these effects. In the absence of this knowledge, initial resuscitation involves administration of intravenous fluids to ensure adequate intravascular volume. Initial rapid administration of isotonic fluids, usually crystalloid, such as normal saline or Ringer's lactate, in increments of 20 mL/kg body weight given over 10–15 min, is used to reestablish sufficient intravascular volume. After initial fluid administration, reassessment of vital signs and physical examination are performed, and additional fluids are administered if reestablishment of intravascular volume is incomplete. Repletion of intravascular volume may result in restoration of vital signs and tissue perfusion, with improvement in mentation, urine output, and peripheral pulses. In patients in whom intrinsic cardiac function is impaired, overly vigorous expansion of intravascular volume may result in fluid overload, with an increase in liver size, evidence of pulmonary edema, jugular venous distention, or an increase in heart size on chest radiograph, without improvement in vital signs and tissue perfusion. In these patients, the addition of an inotropic agent may be necessary to improve cardiac function and tissue oxygen delivery. Bedside echocardiography may be valuable in helping to decide between the administration of additional fluid and the addition of a cardiovascular agent. The choice of inotrope or pressor for a given circumstance depends on the cardiovascular derangements present. Cardiovascular drug effects depend on the drug's site of action (e.g., α -adrenergic versus β -adrenergic effects, vasopressin receptor effects), and choosing a specific agent depends on matching the expected effects of

a drug to the hemodynamic derangement requiring correction. Although almost any agent may be administered temporarily through a peripheral intravenous catheter, the central venous route is preferred because of the risk of extravasation, particularly in infants in whom intravenous infiltration is not uncommon. Since epinephrine is commonly administered subcutaneously or intramuscularly for other indications with little in the way of local deleterious effects, it may be a good choice of initial adrenergic agent to use peripherally, particularly if the vein is small, until more reliable access can be established as it might be safer in the case of extravasation. This topic is discussed in greater detail in ► [Chap. 14, "The Assessment and Management of Hypotension and Shock in the Poisoned Patient."](#)

Dysrhythmias

A common complication of poisoning with cardiovascular agents is the development of dysrhythmias. Dysrhythmogenic drugs may produce their actions by directly affecting the electrical conduction system of the heart, by changing the electrical potential of individual myocardial cells, by indirectly influencing the cardiac conduction system via the autonomic nervous system or CNS, or by inducing electrolyte and metabolic disturbances that affect electrical activity within the heart. Table 3 lists drugs commonly associated with dysrhythmias in pediatric patients (Table 2).

Bradydysrhythmias occur as a result of agents that decrease sympathetic outflow from the CNS, such as opioids, benzodiazepines, and barbiturates, and as a result of drugs that decrease the chronotropic activity of the conduction system, including agents such as beta blockers, nondihydropyridine calcium channel blockers, and class I antidysrhythmic drugs. Severe overdose of any of these agents may result in asystole and cardiac arrest.

Treatment of bradydysrhythmia resulting from an unknown ingestant is supportive. Administration of atropine or inotropic agents with positive chronotropic effects (e.g., epinephrine) may be corrective. If the causative agent of the ingestion

Table 2 Agents producing dysrhythmias

Bradydysrhythmias
α_2 -Adrenergic agonists
Aconitine
Antidysrhythmics
β -Adrenergic blockers
Calcium channel blockers
Carbamates
Cocaine (late)
Cholinomimetics
Digoxin
Jin bu huan
Opioids
Organophosphates
Plants containing cardiac glycosides (foxglove, lily of the valley, oleander, yew)
Sedative-hypnotics
Tricyclic antidepressants (late or massive ingestion)
Tachydysrhythmias
α -Adrenergic agonists
Aluminum phosphide
Amantadine
Antidysrhythmics
Anticholinergics
Antihistamines
Astemizole
β -Adrenergic agonists
Carbamazepine
Cisapride
Chloral hydrate
Chloroquine
Cholinomimetics
Digitalis glycosides
Hydrocarbons/solvents – “huffing”
Inhalational anesthetics
Ecstasy (3,4-methylene- dioxymethamphetamine)
Orphenadrine
Pentamidine
Plants containing cardiac glycosides (foxglove, lily of the valley, oleander, yew)
Phenothiazines
Phosphodiesterase inhibitors (methyl xanthines, amrinone, milrinone)
Propoxyphene
Scorpion envenomation
Selenium – “gun blue”
Snake envenomation
Sympathomimetics (amphetamines, cocaine, phencyclidine)
Terfenadine
Theophylline
Tricyclic antidepressants

Table 3 Indications for endotracheal intubation

1. Upper airway obstruction nonresponsive to positioning or less invasive device
2. Depressed level of consciousness
a. Absence of gag and cough reflexes
b. Apnea/hypoventilation
3. Actual or impending respiratory failure
a. Hypoxic ($\text{PaO}_2 < 60$ mmHg or oxygen saturation $< 90\%$ on $\text{FiO}_2 > 0.6$)
b. Hypercarbic ($\text{PaCO}_2 > 50$ mmHg with $\text{pH} < 7.30$)
4. Cardiovascular instability with hypotension, inadequate cardiac output, metabolic acidosis
5. Excessive airway secretions inadequately cleared with cough/pharyngeal suctioning
6. Treatment of pulmonary hypertension
FiO_2 fractional concentration of oxygen in inspired gas, ICP intracranial pressure, PaO_2 arterial oxygen partial pressure, PaCO_2 arterial carbon dioxide partial pressure

is known, therapies directed at antagonism of the toxic effects (e.g., calcium chloride administration for calcium channel blocker overdose) may be beneficial. In severe cases of bradydysrhythmia or heart block unresponsive to pharmacologic therapy, direct transthoracic pacing or transvenous pacing may be necessary (see subsequent section).

Tachydysrhythmias are commonly seen after poisoning. Sinus tachycardia may occur as a result of increased sympathetic tone after ingestion of CNS stimulants, as a result of ingestion of agents that block catecholamine reuptake at sympathetic nerve terminals (e.g., methamphetamine, cocaine), or as a result of ingestion of drugs with anticholinergic properties. Halogenated hydrocarbons, such as chloral hydrate, may sensitize the myocardium to the effects of endogenous catecholamines, increasing the risk of tachydysrhythmias, including supraventricular and ventricular tachycardia [29, 30]. Overdose with antidysrhythmic agents, particularly class Ia agents, may result in supraventricular or ventricular tachycardia. Tricyclic antidepressants, carbamazepine, and diphenhydramine, all of which share structural similarities and have cell membrane effects similar to quinidine and other class Ia antidysrhythmics, have propensities to develop wide-complex ventricular dysrhythmias.

Torsades de pointes is a unique form of ventricular tachycardia that can be seen with certain overdoses and adverse drug reactions during therapeutic use. Torsades de pointes may occur after ingestion of any drug associated with ventricular tachycardia, such as the class Ia and class Ic antidysrhythmics. This dysrhythmia is discussed in greater detail in ► [Chap. 22, “Toxicant-Induced Torsade de Pointes.”](#)

Treatment of tachydysrhythmias associated with poisoning is generally the same as in other circumstances, with some unique exceptions. The treatment of dysrhythmias associated with a specific antidysrhythmic or class of antidysrhythmic agents should avoid using another drug in the same class. For example, the use of procainamide to treat dysrhythmias associated with quinidine overdose is contraindicated. Treatment of supraventricular tachycardia of hemodynamic significance may be benefited by the use of adenosine, although the short half-life of adenosine and the persistent presence of a dysrhythmogenic toxin make the utility of short-acting agents uncertain. The use of drugs of general utility, such as lidocaine and amiodarone, may be preferred in this setting, unless it is contraindicated on electrophysiologic grounds in specific intoxications.

A unique circumstance is seen in dysrhythmias associated with overdose of tricyclic antidepressants and other agents with sodium channel activity, such as class Ia antidysrhythmic drugs. Numerous studies have investigated the antidysrhythmic effects of sodium bicarbonate in these life-threatening overdoses. Sodium bicarbonate has been shown to consistently reverse wide-complex tachydysrhythmias associated with tricyclic antidepressant poisoning [14–16]. Studies suggest that the beneficial effects are due to both sodium loading and alkalinization [17]. Similar but less consistent reversal of dysrhythmias has occurred with sodium bicarbonate in the treatment of dysrhythmias associated with quinidine and other class Ia antidysrhythmics [18]. This topic is discussed in greater detail in ► [Chap. 39, “Sodium Channel-Blocking Antidysrhythmics.”](#)

Treatment of a pediatric patient with torsades de pointes associated with overdose is similar to that seen with torsades de pointes in any other circumstance. Correction of electrolyte and other metabolic disturbances is crucial, followed by administration of magnesium sulfate [19]. Electrical cardioversion frequently is unsuccessful in converting torsades de pointes. Magnesium sulfate is also the treatment of choice for drug-induced prolonged QT interval, although there is considerable variation among providers in determining threshold at which treatment should be given [20]. This topic is discussed in greater detail in ► [Chap. 22, “Toxicant-Induced Torsade de Pointes.”](#)

In pediatric patients with massive overdose with a cardiotoxic agent, dysrhythmias may be unresponsive to pharmacologic therapy, and electrical cardioversion may be unsuccessful or only temporarily successful in converting the patient back to a sinus rhythm. For these patients, temporary pacing may be attempted. Available methods of pacing include transcutaneous pacing, transvenous pacing, and transesophageal pacing. Transcutaneous pacing, although uncomfortable in a conscious patient, is the most readily available modality for cardiac pacing. This approach may be lifesaving while alternative therapies are initiated, such as transvenous pacing, initiation of additional pharmacologic measures, or cannulation for ECMO. Sedation and analgesia may be beneficial in alleviating the discomfort associated with external pacing.

Transvenous pacing, utilizing a catheter placed into the heart via central venous access, is an alternative to transcutaneous pacing. This modality is more technically difficult, especially in the infant or small child, requiring availability of fluoroscopic guidance for effective catheter placement, and requires more time in its placement. Adverse effects are minimal when the catheter is placed appropriately, and the transvenous approach is tolerated better by the patient and may be used for a longer time than transcutaneous pacing.

Transesophageal pacing may be useful for overdrive pacing of patients with atrial tachydysrhythmias and may also be attempted in cases of

severe symptomatic sinus bradycardia not responsive to other modalities. It generally requires anesthesia or deep sedation as well as consultation from a pediatric cardiologist experienced in the procedure. Although there are case reports of successful ventricular pacing via this method [21], transesophageal pacing cannot be relied upon in the case of AV block.

Respiratory Support

Respiratory distress and the potential for respiratory failure are common reasons for ICU admission of children after intoxication. Respiratory insufficiency may be neurologic or pulmonary in origin.

Impaired respiratory drive leading to hypoventilation or apnea may develop as a result of ingestion of CNS depressant drugs. Alternatively, other drugs may stimulate respiration by increasing central respiratory drive (e.g., salicylates, theophylline), inducing a respiratory alkalosis. Patients ingesting such drugs are at risk for eventual respiratory failure if excessive respiratory drive results in respiratory muscle exhaustion.

Central nervous system depressants also may impair the function of pharyngeal and hypopharyngeal musculature, resulting in obstruction of the upper airway by the tongue or other pharyngeal structures. A number of devices including nasopharyngeal or oropharyngeal airways may be sufficient to alleviate obstruction in these patients. Upper airway obstruction also may occur after exposure to agents (e.g., organophosphates, carbamates, scorpion envenomation) that increase pharyngeal and tracheobronchial secretions, obstructing either the hypopharynx, the glottic apparatus, or the tracheobronchial tree with secretions. Caustic agents and thermal injuries to the airway may cause airway obstruction due to the development of airway edema. The pediatric airway, with the characteristic narrowing that occurs in the subglottic region, is at great risk for obstruction from airway edema or increased airway secretions.

Respiratory failure also may occur owing to a wide variety of problems involving the lower

respiratory tract. Airway obstruction may occur secondary to increased tracheobronchial secretions or the development of bronchospasm due to the effects of airway irritants on bronchial smooth muscle. Aspiration of asphyxiant gases (e.g., volatile hydrocarbons, carbon dioxide) may interfere with oxygenation, with resulting CNS and organ system hypoxia.

Aspiration, inhalation, parenteral injection, or ingestion of a broad range of intoxicants may be responsible for parenchymal lung injury. A variety of trigger events, including hydrocarbon aspiration, inhalation of smoke or toxic gases, drowning, and a broad range of nonpulmonary triggers such as narcotic overdose, have been associated with the development of noncardiogenic pulmonary edema. Loss of integrity of the alveolar capillary permeability barrier allows leakage of proteinaceous fluid from alveolar capillaries into the alveolar airspaces, leading to the clinical manifestations of acute respiratory distress syndrome (ARDS): hypoxemia, radiographic opacities, decreased lung compliance and functional residual capacity, and increased dead space. The risk factors for the development of ARDS are similar to those in adults. Key elements in the criteria for the diagnosis of PARDS are summarized in Fig. 1.

Approximately 10% of children admitted to the PICU for poisoning may require endotracheal intubation [4]. Criteria for endotracheal intubation are found in Table 3.

Provision of sedation and analgesia and the use of a neuromuscular blocking agent to allow complete muscle relaxation before intubation are desirable in most patients to minimize the risk of traumatic intubation. The use of neuromuscular blocking agents, which by necessity result in apnea and complete loss of airway protective reflexes, requires that the airway manager have excellent airway skills to ensure that prompt intubation occurs without complications. Table 4 lists drugs commonly used for endotracheal intubation in children. Succinylcholine is now rarely used in children. Although it is listed here for reference, the routine use of atropine in pediatric intubation is not recommended but it can be considered in patients where there is bradycardia or increased risk of its development. Also, the new Pediatric

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	Non Invasive mechanical ventilation	Invasive mechanical ventilation		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥ 5 cm H ₂ O PF ratio ≤ 300 SF ratio ≤ 264	$4 \leq \text{OI} < 8$ $5 \leq \text{OSI} < 7.5$	$8 \leq \text{OI} < 16$ $7.5 \leq \text{OSI} < 12.3$	$\text{OI} \geq 16$ $\text{OSI} \geq 12.3$
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease.			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Fig. 1 Pediatric acute respiratory distress syndrome (PARDS) definition. Use Pa_{O_2} -based metric when available. If Pa_{O_2} is not available, wean F_{IO_2} to maintain $\text{Sp}_{\text{O}_2} \leq 97\%$ to calculate oxygen saturation index (OSI; $[\text{F}_{\text{IO}_2} \text{ A} \sim \text{mean airway pressure A} \sim 100]/\text{Sp}_{\text{O}_2}$) or $\text{Sp}_{\text{O}_2}:\text{F}_{\text{IO}_2}$ (SF) ratio. For nonintubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation,

see Figure 2 for “at-risk” criteria. Acute respiratory distress syndrome severity groups stratified by oxygenation index (OI; $[\text{F}_{\text{IO}_2} \text{ A} \sim \text{mean airway pressure A} \sim 100]/\text{Pa}_{\text{O}_2}$) or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic congenital heart disease. CPAP = continuous positive airway pressure, PF = $\text{Pa}_{\text{O}_2}:\text{F}_{\text{IO}_2}$.

Table 4 Pharmacologic agents for endotracheal intubation

Drug	Dose	Duration of effect
Sedation/Anesthesia		
Midazolam	0.1–0.2 mg/kg	45–90 min
Ketamine	0.5–2 mg/kg	15–30 min
Fentanyl	2–5 $\mu\text{g}/\text{kg}$	30–60 min
Neuromuscular blockers		
Rocuronium	0.5–1 mg/kg	15–30 min
Vecuronium	0.1–0.2 mg/kg	30–60 min
Anticholinergic		
Atropine	0.02 mg/kg	2–3 h

Advanced Life Support guidelines no longer recommend a minimum dose for atropine [22].

A broad range of equipment is necessary to allow for the wide range of patient size. A selection of both straight and curved blades should be available. Capnography should be available to assist in confirming endotracheal tube placement

in the airway. The recommended endotracheal tube sizes based on average childhood size appear in Table 5. A rough rule of thumb for endotracheal tube size is $(\text{age in years} + 16)/4$ and the insertion depth is three times the endotracheal tube (ETT) size (e.g., a 4 mm ETT would be inserted to a depth of 12 cm). Proper placement should always be verified by radiography. A cuffed endotracheal tube is appropriate for all but the smallest patients and can help to facilitate effective mechanical ventilation in patients with poor lung compliance.

Mechanical Ventilation

After endotracheal intubation, appropriate ventilatory assistance is required. The choice of ventilator, mode of ventilation, and assisted breathing rate depends on the age and size of the patient and the clinical circumstances. Patients in whom the

Table 5 Equipment for endotracheal intubation

Age	ETT size ^a	ETT insertion depth (CM) ^b
Newborn (>2 kg)	3.5	9–10
1–6 months	3.5	10–11
1 year	4.0	12–13
2–3 years	4.5	13–14
4–5 years	5.0	14–16
6–7 years	5.5	16–18
8–9 years	6.0	17–19
10–11 year	6.5	18–20
12–13 years	7.0	19–21
14–15 years	7.5	20–22

^aExternal diameter of a cuffed ETT is equivalent to an uncuffed ETT a half-size larger (e.g., 5.0 cuffed = 5.5 uncuffed)

^bETT insertion depths are for oral insertion in a child of normal size for age, measured from the lip to the tip of the endotracheal tube

ETT endotracheal tube, NG nasogastric

lungs are functionally normal and who are intubated for airway protection or the provision of hyperventilation are managed much differently than patients with hydrocarbon aspiration and evolving ARDS. Although detailed discussion of ventilator management is beyond the scope of this chapter, some general issues are discussed here.

The goal of mechanical ventilation is to provide sufficient exchange of oxygen and carbon dioxide to provide for the metabolic needs of a patient with a minimum of adverse effects. In patients intubated primarily for airway protection and in whom the lungs are essentially normal, minimal ventilatory assistance is required. Little resistance to air entry exists, and compliance is normal, allowing air to enter and escape from the lungs with minimal ventilator pressure. No barrier to gas exchange exists, and oxygen crosses the alveolar epithelial and pulmonary capillary membranes easily.

If interstitial edema and inflammation reduce pulmonary compliance and increase airway resistance, air exchange occurs with more difficulty. The increase in resistance to airflow and decreased compliance require greater pressure to force gases into the airway, and an increase in FiO_2 is required

to provide the gradient of oxygen concentration necessary to overcome the barrier to gas exchange provided by the proteinaceous debris in the alveolus. This increase in ventilator pressure and oxygen concentration results in further injury to the lung in the form of barotrauma and oxygen toxicity, respectively. In these patients the goal is to provide sufficient respiratory support to maintain vital functions while minimizing further injury to the lungs.

Conventional ventilatory support provides respirations that mimic normal tidal breathing, providing a physiologically appropriate number of breaths of appropriate size and duration for age. Modern ventilators are designed to synchronize respirations with the patient's own breathing efforts (synchronized intermittent mandatory ventilation) in an effort to minimize the discomfort that the patient experiences with assisted ventilation. The various modes of conventional ventilation can be distinguished according to the method by which individual breaths are limited. In pressure-cycled ventilation, the peak inspiratory pressure is preset, providing for inspiratory airflow up to a predetermined maximum, with the size of individual breaths determined by peak inspiratory pressure, the rate of airflow, inspiratory time, and airway resistance and chest compliance. The size of individual breaths varies with changes in resistance and compliance. In volume-cycled modes of ventilation, air fills the lungs to a preset tidal volume at a flow rate determined by the tidal volume and a preset total inspiratory time. The pressure required to provide any given breath depends on and varies with changes in airway resistance and chest compliance. In both forms of ventilation, the desired goal is the achievement of stable minute ventilation (the product of tidal volume and respiratory rate). As the severity of lung disease increases and as pulmonary compliance worsens, the peak inspiratory pressure required to provide a given tidal volume increases. Excessive ventilator pressures have been associated with the development of ventilator-associated lung injury or barotrauma. Maintaining peak inspiratory pressure at the minimum value necessary to provide adequate

ventilation and oxygenation is essential to successful ventilator management. As a rule of thumb, peak inspiratory pressure should be maintained below 35 cm H₂O whenever possible.

In patients with significant parenchymal lung disease, alveolar collapse and ventilation/perfusion mismatching result in failure of oxygenation of the blood, with resulting desaturation of arterial blood and tissue hypoxia. FiO₂ should be adjusted to maintain adequate PaO₂ and hemoglobin oxygen saturation. The use of high levels of supplemental oxygen (FiO₂ >0.5) is associated with the development of pulmonary oxygen toxicity. Maintenance of adequate lung volume, which minimizes ventilation/perfusion mismatching within the lung, minimizes the need for supplemental oxygen. Lung volume is maintained best by the addition of positive end-expiratory pressure in the ventilator circuit. The appropriate level of positive end-expiratory pressure is determined by the severity of lung disease and the degree to which ventilation/perfusion inequality exists within the lung. The optimal level of positive end-expiratory pressure must be individualized to the specific situation and it is the level of positive end-expiratory pressure that maintains alveolar patency without overdistention and that allows maintenance of FiO₂ at nontoxic levels (FiO₂ <0.6).

Ventilator-induced lung injury is recognized to be an important factor in the outcome of ARDS. Lung protective strategies that emphasize low pressure, low-tidal volume ventilation with tolerance of respiratory acidosis (pH >7.15), and hypoxia (oxygen saturations >88%) have been suggested in an effort to minimize iatrogenic lung injury [23]. This strategy is termed *permissive hypercapnia* [24, 25]. No randomized pediatric studies have been performed to assess the efficacy of these strategies in children with ARDS, although they are widely practiced.

For some patients with severe lung injury, despite lung protective strategies, the patient's requirement for ventilator support and supplemental oxygen may be great enough that conventional mechanical ventilation poses an unacceptable risk of ventilator-associated lung injury. For these patients, alternative strategies of

cardiorespiratory support must be considered. These strategies include high-frequency ventilation and ECMO. Published information regarding the use of alternatives to conventional ventilation in poisoned children is limited. The common pathophysiology of ARDS allows extrapolation of data from nontoxicologic causes of ARDS to the poisoned patient, however.

High-Frequency Ventilation

High-frequency ventilation is an alternative to conventional ventilation in which small volumes of air are injected into the airway at high frequencies. Two primary modes of high-frequency ventilation are currently in use. In high-frequency jet ventilation, jets of air are delivered into the airway via a high-velocity injector port at rates of 100–600 breaths/min. Inhalation in this mode of ventilation is active, whereas exhaled gases are expelled passively. Total lung inflation is controlled primarily by adjustment of tidal volume and inspiratory time. The precise mechanism of gas exchange in high-frequency jet ventilation is poorly understood. High-frequency oscillatory ventilation is a more commonly used form of high-frequency ventilation in children (3100A and 3100B high-frequency oscillatory ventilator, CareFusion, Yorba Linda, CA); a piston or diaphragm actively oscillates air into and out of the lung at high frequencies, generally ranging from 6 to 12 Hz. The mechanism of gas exchange in high-frequency oscillatory ventilation is similarly poorly understood. The purported advantage of high-frequency ventilation lies in the small tidal volumes (generally 1–3 mL/kg) used, which result in lower peak airway pressure and less ventilator-associated lung injury (Grade III evidence). In patients with significant alterations in compliance and in patients with significant air leak, high-frequency ventilation provides a theoretically less traumatic alternative to conventional ventilation. In patients with severe ARDS, early initiation of high-frequency ventilation has been shown to result in significant improvement in oxygenation with lower frequency of barotrauma [26].

Noninvasive Ventilation

Although the role of noninvasive ventilation in the pediatric poisoning patient is not established, there are a number of noninvasive modalities that are used in pediatrics to provide an alternative to endotracheal intubation and mechanical ventilation with its associated risks and complications.

A brief description of these devices and techniques will be provided here.

Heated, humidified high-flow nasal cannula (HHHFNC), providing heated and humidified gas at a high rate of flow (ranging from 3 to 50 l per minute), is utilized in patients ranging from premature neonates to adults. A blended oxygen/air mixture, humidified to 100% relative humidity and heated to body temperature, is blown into the airway through specially designed nasal cannulae at flow rates well in excess of the patient's minute ventilation. The mechanisms of action of HHHFNC remain incompletely defined. An evolving body of evidence suggests that the high-flow rates washout gases from the nasopharyngeal dead space, improve oxygen delivery and CO₂ clearance. Distention of pharyngeal tissues reduces resistance to airflow in the nasopharynx, thus decreasing work of breathing, and delivery of positive distending pressure to facilitate lung recruitment preventing atelectasis [27]. HHHFNC has been utilized in pediatric patients for prevention of apnea, facilitation of oxygen delivery for patients with hypoxia, reduced need for invasive mechanical ventilation, and transition from mechanical ventilation back to independent breathing. Few randomized trials of HHHFNC have been done in pediatric patients beyond the neonatal period, and no cases have documented its use in poisoned patients, but its increasing use for a broad range of indications in both children and adults makes its use in poisoned patients likely.

Continuous positive airway pressure, or CPAP, is a similar noninvasive mode of support in which a fixed distending pressure is applied to the pharyngeal airway. This modality is generally applied via nasal cannulae or nasal mask (nasal CPAP) or by full face mask (face mask CPAP). Positive

pressure is applied to the pharynx, with or without a device that retards expiratory flow. The positive pressure in the airway is transmitted to the lung, facilitating lung recruitment, decreasing atelectasis, and improving oxygenation. CPAP differs from HHHFNC in that a fixed pharyngeal pressure is targeted, with lower flow rates and less variability in airway pressure than HHHFNC. Both CPAP and HHHFNC reduce work of breathing and facilitate oxygenation by maintaining the airway in an open state. CPAP has been used after exposure to pulmonary irritants including hydrocarbon aspiration and chlorine inhalation.

Noninvasive ventilation, also known as bilevel positive airway pressure (BiPAP), is a form of respiratory support which provides mechanical ventilatory assistance via a nasal or full face mask. In this modality, the ventilator provides positive distending pressure between breaths (expiratory positive airway pressure or *ePAP*), along with a higher level of positive pressure with patient breaths (inspiratory positive airway pressure or *iPAP*), thereby augmenting the patient's respiratory work to facilitate tidal breathing. In addition to setting *ePAP* and *iPAP*, a minimum rate can be set to facilitate minute ventilation. This mode of ventilation is useful for patients requiring mechanical support of breathing in the treatment or prevention of respiratory muscle weakness or fatigue, for patients with parenchymal lung disease, and to facilitate transition to and from invasive mechanical ventilation. BiPAP provides mechanical support for patients with respiratory failure, without the attendant risks of endotracheal intubation (airway injury, infection, etc.) and with less discomfort, thereby requiring significantly less sedation. BiPAP does require that the patient have sufficient airway protective reflexes to avoid aspiration in the event of emesis and that the patient be sufficiently cooperative to keep a tight fitting mask in place. Noninvasive positive pressure ventilation can also be provided through a nonocclusive nasal cannula (RAM Cannula[®], Neotech) connected to a standard ventilator such as the Servo-i[®] (Maquet Medical Systems USA). Parameters specified are similar to BiPAP. The cannula provides 60–80%

occlusion of the nares. It is used in the PICU and neonatal intensive care unit to treat infants with respiratory distress from a number of causes and appears to be well tolerated.

The RTX ventilator (Hayek Medical) is a negative pressure ventilator that utilizes a cuirass on the thorax to provide biphasic ventilation. Cuirasses are available in sizes from infant to adult. Although there are no case reports of its use in intoxicated patients, it has been used in a number of different scenarios of respiratory failure [28, 29].

The role of noninvasive respiratory support in patients after poisoning is poorly defined. A number of case reports have documented the use of noninvasive respiratory support for patients with exposure to intoxicants. Noninvasive ventilation has been used in overdose situations involving opioids and other respiratory depressants [30], for support of lung-injured patients [31], and for treatment of pulmonary edema following amlodipine overdose [32].

Mechanical Circulatory Support/ECMO

For children with massive overdoses of drugs with cardiac depressant, proarrhythmic, or vasodilator effects who are unresponsive to the therapies described above, mechanical support of the circulation may be the only alternative to mortality.

The most commonly available, most invasive, and probably most effective mechanical supportive device is ECMO. In ECMO, the patient's blood is removed from the body; pumped through a membrane oxygenator, which adds oxygen and removes carbon dioxide from the blood; and then returned to the body. Extracorporeal membrane oxygenation is a treatment with substantial risk, because it requires systemic anticoagulation and is technically sophisticated, requiring the expertise of a center familiar with and prepared to perform ECMO regularly. Complications of ECMO, even in centers that perform ECMO regularly, include life-threatening hemorrhage, embolic complications including cerebrovascular accidents, development of multisystem organ

failure, and risk of systemic infection. ECMO is indicated only in situations in which the risk of mortality is great and only in centers with established experience (Grade III recommendation).

Extracorporeal membrane oxygenation is only indicated in cases of reversible cardiorespiratory failure. As such, poisoning represents an ideal indication provided it can be instituted in a timely fashion. Many tertiary pediatric centers offer rapid response ECMO teams and can have patients cannulated and on ECMO in about 30 min [33]. Two forms of ECMO are available. Venoarterial ECMO, in which cannulae are placed via a central vein (usually jugular vein) and central artery (usually carotid artery), provides complete cardiorespiratory replacement for the duration of time necessary for clearance of an intoxicant and recovery of cardiac and respiratory function. Blood is removed from the right atrium and returned to the arterial circulation into the aortic arch.

Venovenous ECMO, in which either two venous cannulae (usually femoral vein and jugular vein) or one double-lumen venous cannula is placed, primarily provides replacement of respiratory function and requires adequate native cardiac output for adequate tissue perfusion. Venoarterial ECMO is most useful if the primary problem is myocardial dysfunction and poor cardiac output or combined cardiorespiratory failure; venovenous ECMO may be considered if the primary problem is pulmonary, as in hydrocarbon aspiration or smoke inhalation associated with carbon monoxide poisoning. The advantage of venovenous ECMO in this circumstance is the avoidance of return flow into the arterial circulation, hence decreasing the risk of systemic thromboembolic complications, such as cerebrovascular accidents and peripheral arterial embolism. ECMO has been used in selected circumstances with ready availability of this specialized technology in a timely fashion during the acute deterioration of a patient after a lethal ingestion. The use of ECMO has been reported in patients with overdoses with a variety of intoxicants causing intractable cardiovascular or respiratory collapse [34]. In one review, the mean time on ECMO was 35 h, and the survival rate was 80% [35].

Circulatory Assist Devices

The intraaortic balloon pump (IABP) and ventricular assist device (VAD) are widely used as cardiovascular assistive devices in adults with intractable cardiac failure, in most cases after cardiac surgery, after myocardial infarction, or as a bridge to transplant in patients with congestive cardiomyopathy. The size of the patient may limit the use of an IABP in children. A VAD is more suited to the nonemergent setting of more chronic ventricular failure. A pediatric center that has access to these modalities is highly likely to have an ECMO program, and ECMO can be instituted in a timelier fashion although a VAD might still find use in drug-induced chronic ventricular dysfunction such as that caused by anthracyclines as a bridge to recovery or transplantation.

Renal Toxicity

The indications for hemodialysis in the poisoned child include both extracorporeal drug removal and renal replacement therapy for patients with drug or toxin-induced renal dysfunction. Indications for extracorporeal removal are further discussed elsewhere in the book and are similar to the criteria used in adults. Drugs and toxins that might be associated with acute renal dysfunction in the pediatric patient are listed in Table 6. Hemodialysis can be performed in patients under 3 kg, so patient size is rarely a barrier to its use although, depending on the size of the patient and hemodynamic status, it might be necessary to prime the circuit with blood instead of the usual solutions.

Organ Donation

Despite the best efforts of the care team, it is not possible to save every child with an intoxication. Particularly in cases where there was significant hypoxic-ischemic central nervous system injury, patients may progress to brain death. Although the criteria for the diagnosis of brain death in children

Table 6 Drugs and toxins associated with acute renal insufficiency in children

Drugs
Acyclovir
Aminoglycosides
Cyclosporine
Cytolytic agents
Nonsteroidal antiinflammatory drugs
Other toxins
Aristolochic acid
Diethylene glycol
Ethylene glycol
Hemoglobin/myoglobin
Mercuric salts

can vary by jurisdiction, national guidelines have been published and adopted widely [36]. The first brain death examination must be performed *at least* 24 h following the brain insult. Since severe drug-induced central nervous system depression can mimic brain death, it is important to allow adequate time, individualized to the pharmacology of the intoxicating substance, for the offending agent(s) to fall to levels that are not clinically important before proceeding. Two brain death examinations, each performed by two physicians independently, must occur before making the declaration of brain death. These two examinations should be separated by at least 24 h in infants under 1 month of age and by at least 12 h in older infants and children. Intoxication itself is not a contraindication to organ donation, although medicolegal considerations necessitate close communication and coordination between organ retrieval agencies, medical examiners, and law enforcement.

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Exposures to toxicants in the workplace can cause severe illness and death similar to intentional poisonings and overdoses. In some cases, without a careful occupational history, the relationship between the job and the illness may be missed. Prolonged exposure to an insoluble gas, such as nitrogen dioxide after arc welding in a confined space, can cause a delayed pulmonary injury and acute respiratory distress syndrome (ARDS) that occurs one day later, when the link may go unnoticed. Careful questioning about the particular sequence of events is important when an illness occurs after performance of a common task. Another example is exposure to phosgene gas after torch-cutting or welding metal that had been recently degreased with a chlorinated hydrocarbon solvent. Alternatively, a worker may experience a delayed illness such as metal fume fever (MFF) if he or she is welding on galvanized metal or had been working in close proximity to someone doing so. It is important to ask not only about the job of the ill worker but also about the nature of the workplace and the other processes being performed there.

The U.S. Department of Labor, Bureau of Labor Statistics, reported that there were 4,679 occupational fatalities in 2014, most caused by physical hazards, accidents, and falls. Of these

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fatalities, 390 (8.3%) were due to exposure to harmful substances or environments, and 137 (2.9%) were due to fires and explosions [1]. Of the 1,162,210 nonfatal occupational illnesses and injuries involving lost work days in 2013, 4.8% were due to exposures to harmful substances [2]. Globally, ILO and WHO data indicate that work-related diseases account for 2,022,000 deaths annually, 32% due to work-related cancer, 23% due to work-related cardiovascular diseases, and 17% due to communicable diseases [3]. The actual incidence may be higher because the connection between work and the illness may be missed unless a detailed occupational history is obtained.

It is imperative that every poisoned worker be considered an index case in order to prevent further cases from that workplace or from those working with that same chemical or process. The clinician must ascertain whether other workers from the index patient's work environment have been similarly exposed and therefore may also be at risk. Many countries have reporting requirements that mandate the clinician who becomes aware of workplace injuries notify relevant governmental agencies.

Commensurate with the orientation of this book, this chapter highlights the most important occupational exposures that may result in critical illness or death. A comprehensive review of all exposures is beyond the scope of this book. This chapter stresses the workplace-related issues regarding these exposures. Since accidental ingestion of a toxicant is exceedingly rare in the workplace, airborne exposures and subsequent inhalation by the worker is the predominant exposure pathway for nearly all occupational illnesses and injuries of consequence. Some chemicals also have a "skin designation," meaning systemic effects and/or toxicity can occur due to transcutaneous absorption. More comprehensive discussions of the particular toxicants discussed here may be found in their respective chapters. Minor illnesses, such as occupational dermatoses, and chronic diseases, such as asbestosis, beryllium disease, cancers, and the pneumoconioses, are not addressed in this chapter.

Occupational Pulmonary Toxicology

Occupational Asthma

Asthma is a common chronic condition, affecting about 7.7% of the working population, and occupational disease surveillance data indicate that occupational asthma is the most common occupational respiratory disease in industrialized nations [4]. Occupational asthma is second only to contact dermatitis as the most common work-related disease. The all-encompassing term work-related asthma (WRA), includes asthma that may be *caused by* the workplace exposure, which is termed Occupational Asthma or OA, or preexisting asthma that may be *aggravated by* workplace exposures (termed Work-Exacerbated Asthma or WEA). Using this extremely broad definition, it has been estimated that 3–33% of all asthma cases may be considered WRA [5–7]. The American Thoracic Society estimated in 2003 that 15% of new onset asthma in adults is due to work [8], and that 25% of adult asthmatics have either OA or WEA [4, 7].

WRA is diagnosed when there is a work-related variable airway obstruction or airway hyperresponsiveness resulting from exposures encountered in the workplace. Occupational asthma can be further subcategorized as sensitizer-induced asthma (SIA) and irritant-induced asthma (IIA-also known as *reactive airways dysfunction syndrome* or *RADS*). SIA is far more common and is the more classic form of occupational asthma which requires a variable amount of time between the first exposure and onset of illness, whereby the worker becomes sensitized to the offending agent. Once the worker is sensitized, exposure to even minute quantities of the agent may cause significant signs and symptoms. Most SIA is caused by exposure to high-molecular-weight organic compounds that are considered "complete allergens," such as animal dander and plant proteins. The asthma is a manifestation of type I or IgE-mediated immediate-type hypersensitivity reactions. Low-molecular-weight (LMW) compounds can cause SIA by acting as incomplete allergens or haptens (e.g.,

antibiotics, metals) or by other mechanisms that are poorly understood (toluene diisocyanates [TDI], trimellitic anhydride [TMA] are but two examples). The chemical structure of the LMW agent is an important factor: the presence of at least two reactive groups with the ability to form bonds with native human macromolecules, such as albumin, seems to be required for such an agent to cause SIA [5, 7]. More than 200 LMW compounds have been implicated in the cause of occupational asthma, the most well known being plicatic acid in western red cedar, TDI, and colophony (rosin) [5, 7].

Exposure to an overwhelming dose of an irritating gas, dust, mist, fume, or fire smoke can cause reactive airways dysfunction syndrome (RADS), a form of OA which develops without an intervening latent period. True RADS occurs only after an acute, intense, high level exposure, often in a confined space where the victim cannot escape the exposure. This irritant-induced asthma is a form of occupational asthma that is usually short-lived, since most RADS victims improve within a year; rarely, generalized airway hyperresponsiveness to temperatures, dusts, or irritants can persist in patients with RADS (see irritant gas exposure discussion below) [25, 27].

The physician evaluating a patient who presents with bronchoconstriction always must consider the possibility of work-related asthma, especially in a patient with no prior history of asthma, with asthma of recent onset, or with acute exacerbations of stable asthma. Careful questioning regarding the time of onset of symptoms as they relate to exposures at work can be helpful.

SIA can have a biphasic or dual response, in which exposure to the allergen may induce an immediate bronchoconstriction, known as the *early response*, and a delayed or *late response* approximately 4–8 h later. The early response often is self-limited, only to be followed later by the inflammation, airway hyperresponsiveness, and airway obstruction seen in the late response. Some workers may exhibit only the late response, becoming ill hours after leaving the workplace, when the causal relationship may not be apparent.

The presence of the dual response may hinge on factors such as the type of compound, dose, length of exposure time, and concomitant use of medication. LMW agents seem more likely to induce an isolated late response, whereas high-molecular-weight “complete” allergens more commonly cause a dual response [5, 7].

Treatment of occupational asthma acutely is no different than conventional asthma treatment and consists of inhaled β -agonists, supplemental oxygen, and systemic corticosteroids as the condition dictates. As mentioned above, a particularly sensitive individual with SIA may react after an exposure to even minute amounts of the offending allergen and could potentially be in status asthmaticus. Severe exacerbations associated with hypoxia or carbon dioxide retention or both require treatment in the intensive care unit. Long-term management hinges on identifying the sensitizer when possible and removing the patient from further exposure. Tables 1 and 2 list exposures and occupations known to be associated with sensitizer-induced occupational asthma. Patients presenting after an exposure to an irritant gas, while at risk for RADS, may also present initially with acute respiratory distress syndrome (ARDS- see below). Rarely, high dose exposures to irritant gases can cause permanent RADS, and victims may have significant long-term sequelae that do not improve with removal from the workplace.

Toxic Inhalant Injury

Many occupations have potential exposure to gases, and often these have significant potential for lung injury or systemic toxicity. Because oral ingestion of toxins in the workplace is uncommon, the primary routes of systemic entry are pulmonary, and, to a lesser extent, dermal. Gases of toxicologic importance can be divided into three major categories: (1) simple asphyxiants, (2) toxic or chemical asphyxiants, and (3) irritant gases. Simple asphyxiants have no inherent toxicity other than displacing oxygen in inspired air, thus inducing anoxia. This toxicity is especially important in

Table 1 High-molecular-weight sensitizing agents and jobs associated with occupational asthma

HMW sensitizing agents	Associated occupations/industries
Animal dander	Animal handlers, veterinary workers, farmers
Pigeons (e.g., excreta, feathers)	Pigeon breeders
Chickens, turkeys	Poultry processing workers
Mice	Laboratory technicians
Guinea pigs	Laboratory technicians
Insects (bees, beetles, weevils, mites, silkworms, flies, others)	Many outdoor workers, silkworm farmers, insect research workers, granary workers, others
Grains (wheat, rye, buckwheat)	Farmers, grain mill workers, silo workers
Raw tobacco	Tobacco industry workers
Flours (wheat, rye)	Bakers, food processing workers
Enzymes	
<i>Bacillus subtilis</i>	Detergent manufacturers
Papain	Meat processing workers
Trypsin, pepsin	Pharmaceuticals workers
Wool	Wool workers, sorters
Marine organisms (prawns, crabs, oysters)	Prawn workers, oyster processing workers, crab processing workers
Foods (spices, grains, flours)	Chefs, food industry workers, food preparers
Natural rubber latex	Health care workers, rubber industry workers
Gums (acacia, arabic, tragacanth, karaya)	Pharmaceuticals workers, printers
Coffee beans, tea leaves	Coffee production workers, tea workers
Castor beans	Castor oil production workers
Seeds (flaxseed, cottonseed, linseed, psyllium seed)	Bakers, oil extraction workers, seed workers
Woods (oak, mahogany, California redwood, others)	Sawmill workers, carpenters, woodworkers
Hops	Brewery workers, farmers
Fungi, molds	Farmers, bakers, various industrial workers

Data from Refs. [4, 5, 7–11]

HMW high molecular weight

confined spaces, where the lack of air movement and ventilation may allow these gases to replace oxygen in the ambient air. Some simple asphyxiant gases like carbon dioxide are heavier than air and tend to accumulate in low areas, so workers at lower levels are at increased risk. Similarly, a victim who collapses to the floor due to injury or asphyxiation is subjected to higher concentrations of these heavier gases. In the chemical production worker, confined spaces such as reactor vessels may contain no oxygen; entry for vessel cleaning requires self-contained breathing apparatus or other supplied air respirators, and specific lock-out, tag-out procedures and specific training to prevent worker exposures.

Simple Asphyxiants

The simple asphyxiants commonly encountered by chemical workers include nitrogen, methane, ethane, ethylene, propylene, carbon dioxide, butadiene, isobutylene, and hydrogen. When encountered in confined spaces, simple asphyxiants can cause anoxic central nervous system (CNS) injury due to oxygen deprivation. The degree of injury depends on the extent and duration of anoxia. Additionally, some simple asphyxiants such as the hydrocarbons mentioned above pose a significant fire or explosive hazard. These confined-space exposures usually occur in the situation with inexperienced workers, inadequate safety training,

Table 2 Selected low-molecular-weight sensitizing agents and jobs associated with occupational asthma

LMW sensitizing agents	Associated occupations/industries
Antibiotics (penicillins, cephalosporins, tetracyclines)	Pharmaceuticals workers
Drugs (α -methyldopa, cimetidine, hydralazine, opiates, penicillamine, others)	Pharmaceuticals workers
Inorganic chemicals	
Ammonium persulfate	Beauticians, chemical production workers
Fluoride	Aluminum pot-room workers
Metals	
Aluminum	Aluminum smelting workers
Chromium salts	Leather tanning workers, metal plating workers, hard metal workers
Cobalt	Tungsten carbide hard metal workers
Nickel	Metal plating workers
Palladium	Metal plating workers, jewelers
Platinum	Platinum refining workers, electroplating workers, fluorescent screen manufacturers, jewelers
Vanadium	Ferrovanadium workers (hard metal workers)
Zinc	Metal plating workers
Organic chemicals	
Abietic acid (colophony-pine resin)	Soldering workers, electronics manufacturers
Acrylates	Glue workers
Aldehydes (formaldehyde, glutaraldehyde)	Hospital workers, laboratory technicians
Amines (ethanolamine)	Soldering workers, paint application workers, machining metal workers
Anhydrides (trimellitic anhydride, phthalic anhydride)	Plastics workers, epoxy resins workers
Dyes	Dye industry workers, fabrics workers
Insecticides (pyrethrins, organophosphates)	Farmers, insecticide applicators
Isocyanates	
Toluene diisocyanate	Polyurethane foam manufacturers
Diphenylmethane	Foundry workers, paint application workers
Plicatic acid (western red cedar)	Lumber workers, loggers, carpenters, cabinet-makers
Paraphenylenediamine	Fur dyers, chemical workers
Phenol	Chemical workers, laboratory workers
Piperazine	Chemical processing workers
Styrene	Chemical production workers, polymer industry workers

Data from Refs. [4, 5, 7–11]

or lack of proper supervision. Treatment of simple asphyxiant exposure involves removing the victim from the source, ensuring adequate ventilation, and providing supplemental oxygen.

Chemical Asphyxiants

The gases considered chemical asphyxiants act either by decreasing the oxygen-carrying capacity of the blood (carbon monoxide [CO]) or by interfering with cellular utilization of oxygen (cyanide,

hydrogen sulfide, and CO). These toxins are covered in detail in their respective chapters in this book.

Irritant Gases

Irritant gases cause injury patterns directly related to their water solubility (Table 3). Highly soluble gases, such as hydrogen chloride (HCl), ammonia, sulfur dioxide, formaldehyde, and acid vapors, cause immediate irritation of the mucous membranes of the upper respiratory tract because they dissolve easily in the moisture of these tissues. These soluble gases first are deposited in the upper airways, which acts as a “scrubber,” lowering the concentration in the lower respiratory

tract. After significant exposure to highly soluble gases, the symptoms of burning in the eyes, nose, mouth, throat, and trachea tend to limit the exposure duration because the victim will not tolerate the irritation and will rapidly exit the area, if possible. The lack of these upper respiratory signs or symptoms after a known exposure to a highly soluble gas virtually rules out any significant exposure to that soluble gas and obviates the need for prolonged observation. By contrast, workers with significant symptoms of upper respiratory tract burning and irritation associated with signs of mucosal and conjunctival inflammation, laryngeal symptoms, and cough indicate a significant dose of the water-soluble gas was inhaled

Table 3 Relative solubility of common irritant vapors and gases

Gas	Conversion factor	MW (d)	Relative vapor density (Air = 1)	Solubility in water	Relative solubility
Hydrofluoric acid (HF)	1 ppm = 0.82 mg/m ³	20.006	1.86	Freely soluble in water	Very high
Hydrochloric acid (HCl)	1 ppm = 1.49 mg/m ³	36.46	1.27	82.3 g/100 mL water	Very high
Chloramine (NH ₂ Cl): formed from bleach + NH ₃		51.48	NA (liquid)	Freely soluble in water	Very high
Formaldehyde (CH ₂ O)	1 ppm = 1.23 mg/m ³	30.03	1.04	55 g/100 mL water	High
Ammonia (NH ₃)	1 ppm = 0.70 mg/m ³	17.03	0.59	47 g/100 mL water	High
Fluorine (F ₂)	1 ppm = 1.55 mg/m ³	38	1.31	Reactive	Medium high
Acrolein (C = C = O)	1 ppm = 2.29 mg/m ³	56.1	1.9	21 g/100 mL water	Medium high
Sulfur dioxide (SO ₂)	1 ppm = 2.62 mg/m ³	64.065	2.263	17.7 g/100 mL water	Medium high
Methyl isocyanate (MIC) (CH ₃ NCO)	1 ppm = 2.34 mg/m ³	57.06	1.42	10 g/100 mL water	Medium high
Chlorine (Cl ₂)	1 ppm = 2.90 mg/m ³	70.9	2.47	1.46 g/100 mL water	Medium
Phosgene (carbonyl chloride [COCl ₂])	1 ppm = 4.05 mg/m ³	98.9	3.48	0.9 g/100 mL water	Low
Chlorine dioxide (ClO ₂)	1 ppm = 2.76 mg/m ³	67.46	2.33	0.3 g/100 mL water	Low
Nitrogen dioxide (NO ₂)	1 ppm = 1.88 mg/m ³	46	2.62	0.3 g/100 mL water	Low
Ozone (O ₃)	1 ppm = 1.96 mg/m ³	48	1.66	0.001 g/100 mL water	Very low

Data from Refs. [12–15]

MW molecular weight, NA not applicable

and raises the possibility of lower respiratory tract injury. Under these circumstances admission and observation is indicated (level III recommendation). Significant exposures to highly soluble gases can cause ARDS hours later. Immediate and long-term sequelae may include RADS (see full discussion below), or other obstructive defects including BOF, bronchiectasis, and bronchial stenosis [16, 17].

Phosgene, oxides of nitrogen, and ozone are poorly water-soluble gases. These are discussed in greater detail in ► Chap. 100, “Irritant and Toxic Pulmonary Injuries.” These insoluble gases cause little or no upper respiratory tract symptoms. Because there is no initial irritation, employees often are unaware of ongoing exposure, and much longer exposure durations are tolerated. The longer exposures allow a higher concentration to reach the lower airways, along with the lack of deposition in the moisture of the upper airway mucosa as happens with soluble gases. Delayed alveolar injury is possible after insoluble gas exposures, and the onset of lower respiratory tract injury and ARDS occurs later, often several hours or a day after a significant exposure. Phosgene is encountered in chemical synthesis as an intermediate for isocyanate and pesticides or as a byproduct when chlorinated hydrocarbons are burned or heated. Phosgene was a World War I warfare agent responsible for numerous deaths. Heavier than air, it accumulates in lower areas, making it an ideal agent for the trench warfare that was common during World War I. The only clue to phosgene exposure may be the reported odor of freshly mown hay.

Oxides of nitrogen (NO , NO_2) are commonly found in recently stored silage (silo filler’s disease), from combustion products (especially of nitrocellulose films [18]), from oxidation of ambient nitrogen during high-temperature arc welding, or from gas-powered Zamboni ice resurfacers in indoor ice rinks [19, 20].

Because of the lack of upper respiratory tract irritation from the low solubility gases, patients often go home and develop these symptoms remote from the worksite. The clinical picture may present as ARDS, and sepsis or CHF or

some other nonoccupational etiology may be suspected if an adequate occupational history is not obtained. Treatment consists of supplemental oxygen and ventilatory support as dictated by the clinical picture. A full discussion of potential therapeutic approaches can be found in ► Chap. 16, “Treatment of Acute Respiratory Distress Syndrome in the Poisoned Patient.” Depending on the severity of injury, mortality rates from severe ARDS may be significant, and rarely patients who recover may be left with permanent pulmonary impairment. Based on very old evidence, corticosteroids maybe useful to prevent the late sequelae of bronchiolitis obliterans fibrosa that is seen after nitrogen dioxide exposures [21, 22] (Level III recommendation). Their value in other toxic inhalational injuries is suggested by animal studies but is not verified in humans [16].

Medium-solubility gases, such as chlorine (Cl_2), have dissolution rates in the upper airway moisture that are midway between highly soluble and poorly soluble irritant gases. Significant medium-solubility gas exposures can cause upper airway symptoms of burning and irritation, but these may be milder than the highly soluble gases and may progress to lower airway injury and delayed pulmonary edema. Clinical suspicion and careful evaluation are necessary when making disposition decisions after exposures to medium-solubility gases. Chlorine behaves more like a highly water soluble gas, even though its rank in water solubility chart would suggest otherwise, since the chlorine dissolution equation: $\text{Cl}_2 + \text{H}_2\text{O} \Rightarrow \text{HOCl} + \text{HCl}$ is preferentially driven to the right due to the high water solubility of the hypochlorite (HOCl) and HCl produced, and may explain some of the prolonged signs and symptoms, as new HCl is continually formed as more Cl_2 dissolves [23, 24].

Reactive Airways Dysfunction Syndrome

RADS is an acute pulmonary injury that can occur after high-level exposure to an irritant gas. RADS is defined as a sudden onset of “acute irritant-induced asthma” that follows a single high-level, overwhelming exposure to an

irritant gas, vapor, or a similar overwhelming exposure to products of combustion in a fire (e.g., severe smoke inhalation injury) [25]. It has not been described after low-level, non-irritating exposures, or to brief exposures to soluble irritant gases or smoke.

The original criteria described by Brooks [25] were:

1. A documented absence of preceding respiratory complaints.
2. The onset of symptoms occurred after a single specific exposure incident or accident.
3. The exposure was to a gas, smoke, fume, or vapor which was present in very high concentrations and had irritant qualities to its nature.
4. The onset of symptoms occurred within 24 h after the exposure and persisted for at least 3 months.
5. Victims required immediate medical assistance and ICU admission.
6. Symptoms simulated asthma with cough, wheezing, and dyspnea predominating.
7. Pulmonary function tests (PFTs) may show airflow obstruction.
8. Methacholine challenge testing was positive.
9. Other types of pulmonary diseases were ruled out.

The development of RADS after an irritant exposure is actually a very rare event. RADS cases originally described by Brooks and subsequent reports in the medical literature are characterized by intense high-level exposures to a pulmonary irritant which results in acute respiratory symptoms of a severity requiring immediate medical attention and hospitalization, usually in an intensive care unit. Often, the exposure occurs in a confined space, an environment with limited ventilation, or in circumstances in which the individual was not able to immediately escape the exposure due to an injury.

It is very likely that RADS is frequently misdiagnosed. Shakeri et al. (2008) conducted a systematic review to identify those agents reported as being associated with reactive airways dysfunction syndrome (RADS) from 1985 to

2005. They used the Brooks criteria above to evaluate how many of these reported RADS cases actually met the criteria for that diagnosis. The authors found that in >40% of cases, the physical exam and diagnostic findings and exposure scenario did not support a diagnosis of RADS, despite being reported as such. In many cases, data was missing; the purported causative agents weren't even identified in some cases. The most commonly reported agent was chlorine, followed by TDI and oxides of nitrogen. The authors did note that a reporting bias occurs, such that once an agent has been reported to cause RADS in the appropriate setting, submitting a new RADS case report of that agent would have a small chance of being published. This would tend to show a bias for only unusual or new agents being accepted for publication [26].

The massive irritant exposures that cause RADS produce damage to bronchoepithelial cells lining the airways, and this can lead to persistent airway inflammation by way of release of inflammatory mediators and subsequent sensitization causing nonspecific heightened airway responsiveness. These effects do not occur after trivial exposures. True RADS victims always have need for immediate intensive care admission because of the severity of the airway injury.

It is not possible to exactly quantify the magnitude of the irritant exposure that will cause RADS, but almost all cases of RADS are associated with an unanticipated massive accidental release of irritant gasses, either due to an explosion or from a sudden release under pressure. This also usually occurs in an enclosed environment or from smoke inhalation in victims caught in structural fires. Patients so affected by RADS report asthma-like complaints acutely (immediately after soluble irritant gas exposures, and within 24 h in the case of insoluble irritant gasses) after a huge exposure. This irritant-induced asthma does not require any latency or immunologic sensitization that is so characteristic of the more common sensitizer-induced occupational asthma (see SIA above) [25, 27, 28].

The exact incidence of RADS is not known, but due to the extreme exposure levels that are

required to cause it (i.e., an overwhelming gas exposure that induces respiratory distress requiring hospitalization), the syndrome is very uncommon, and in this author's experience, often misdiagnosed. It has been reported that RADS accounts for only a small fraction (<20%) of workers with "occupational asthma." There is no "chronic irritant-induced RADS," since people alleging this condition are, in reality, suffering from an exacerbation of a pre-existing asthmatic condition (and therefore have WEA), a mild or relatively asymptomatic asthma patient who had not previously required medications, or persons with pre-existing baseline airway hyperresponsiveness (which has quite a significant prevalence in the normal population). This can also be true for a previously undiagnosed COPD patient whose disease progressed to become symptomatic. When tested, true RADS patients respond with a "positive" methacholine challenge test with a PC20 of 8 mg/mL (the concentration which causes a 20% or more reduction in FEV1), and there are typically no radiographic abnormalities after the acute inciting incident has resolved [27]. It also must be understood that there are a certain number of asymptomatic individuals who do not have RADS but have a positive methacholine challenge test, since there is a baseline positive reactive airway incidence in the normal population- 10–40% in nonasthmatic normal population, depending on the study – to as high as 50% or more in other nonasthmatic medical conditions [29, 30].

By definition, then, true RADS cases present critically ill, with dyspnea, hypoxia, and acute lung injury. They may also have stridor as a manifestation of concomitant upper airway injury. Chest radiographs often can progress fairly rapidly to reflect ARDS. Treatment consists of securing the airway and providing oxygenation and ventilatory support, with PEEP as needed, along with intensive supportive care. Systemic corticosteroids have been used, especially when significant reactive airway symptoms are present, and presumably to prevent sequelae. However, no controlled human clinical trials have proven the efficacy of corticosteroids in this situation, although there is evidence for efficacy in animal

models [31] (level of evidence II-3). Antibiotics are probably contraindicated due to selecting out resistant organisms, unless radiographic, microbiologic, and clinical confirmation of infection/pneumonia is present. In the case of chlorine gas and other acid vapor exposures, nebulized standard sodium bicarbonate (NaHCO_3) for injection (diluted with 1:1 with normal saline) is advocated and has been anecdotally reported several times to provide symptomatic relief of upper airway burning symptoms [32–34]. In Turkey, where bleach-acid cleaning mixtures are used frequently and have been reported as having caused RADS, a randomized, placebo-controlled clinical trial showed benefits of NaHCO_3 nebulizers in improving FEV1 measurements and subjective improved symptoms in the immediate postexposure period (patients in both arms also received nebulized albuterol and intravenous corticosteroids). No long-term follow-up was performed [35] (Level of evidence I). In hydrogen fluoride (HF) exposure, dilute calcium gluconate solution (3:1 NS to calcium gluconate injection solution) nebulizer treatments are commonly used in a similar manner at petroleum refineries, where HF is commonly used as an alkylation catalyst [36–38]. No controlled clinical trials prove better outcomes, but is standard practice in the petroleum industry and is recommended in the U.S. Agency for Toxic Substances and Disease Registry Medical Management of HF inhalation exposures [39] (Level III recommendation). The relatively benign nature of this treatment and the reported symptomatic relief after exposure to such a corrosive substance justifies its use.

Several authorities advocate systemic corticosteroids in acute RADS management [40] based on limited evidence in animal models [41]. Human case reports generally report use of inhaled steroids and some treatment guidelines advocate for inhaled steroids [42, 43]. Historically, intravenous steroids have been recommended after significant exposures to low solubility irritant gasses like phosgene [44] and oxides of nitrogen [45], since onset of severe lung injury and pulmonary edema are often delayed, even after significant exposures; it is theorized their use may prevent the late onset of pulmonary injury.

The author of the original case series on RADS recommends against systemic corticosteroids, but feels nebulized steroids are beneficial [27] (Level III recommendation).

Further information on this topic can be found in ► [Chap. 100, “Irritant and Toxic Pulmonary Injuries.”](#)

Inhalational Fevers and Hypersensitivity Syndromes

Inhaling a wide variety of organic and inorganic materials can cause a self-limited, flulike illness consisting of fever, chills, generalized body aches, and malaise. The prototypical occupational fever syndrome of this type is metal fume fever (MFF), but other exposures present similarly (see below). Patients frequently complain of headache, sore throat, chest pain, and cough and may have some dyspnea. There often is an elevated white blood cell count but generally no hypoxemia, radiographic abnormalities, or pulmonary infiltrates. The syndrome usually arises within a few hours after exposure and resolves within 1 day, with no residual effects. The mechanism may be an immunologic reaction in the alveolus, causing release of cytokines and immune mediators. Repeated exposures cause a “desensitization” or tachyphylaxis, whereby symptoms are worse at the beginning of the work week (“Monday morning fever”), and repeated exposures may elicit no symptoms at all.

Diagnosis is made based on the above-mentioned criteria, after ruling out influenza or other infectious causes. Treatment for inhalational fevers is supportive because this clinical entity is entirely self-limited. Proper education of the worker regarding the exposures that lead to this syndrome can prevent further episodes.

Many of the occupational settings where inhalational fevers occur also harbor risks of other acute lung injuries. Welding of stainless steel produces zinc oxide fumes responsible for MFF, but welding metal with cadmium can produce ARDS, and high-temperature arc welding in a confined space can cause significant NO₂ exposure leading to ARDS and subsequent risk of RADS. Farmers who unload silos may be exposed to silage that is contaminated with bacteria, grain, mold, cellular

debris, peptidoglycans, and glucans that can cause inhalational fever (“silo unloader’s disease” and *organic dust toxic syndrome* [ODTS]), but exposure to freshly stored silage can cause silo filler’s disease owing to liberation of NO₂ and causing ARDS. Farmers with moldy hay exposure may induce extrinsic allergic alveolitis (EAA, also known as hypersensitivity pneumonitis) as a result of exposure to the thermophilic bacteria that grow in wet hay.

In contradistinction to inhalational fevers, the ARDS due to EAA/HP often is accompanied by cough, dyspnea, hypoxemia, and pulmonary infiltrates on chest radiographs. Although fever is required for the diagnosis of inhalational fevers, fever may also be present in EAA/HP or in ARDS. The key distinguishing feature is that inhalational fevers have no chest x-ray abnormalities and usually no hypoxia, whereas chest x-ray abnormalities (typically ground glass opacities) and hypoxia are prominent features of ARDS and of EAA/HP. While repeated exposures to the causative agents of inhalational fevers cause a tolerance or significantly diminished response, repeated insults of EAA/HP may cause restrictive defects on pulmonary function testing due to interstitial edema and can lead to fibrosis and permanent restrictive lung disease. Attack rates after typical exposures for inhalational fevers are often greater than 80%, whereas EAA/HP occurs only in a small percentage of exposed individuals. Sensitization is required for the development of hypersensitivity pneumonitis, but this is not true for inhalational fevers. Repeated bouts of inhalational fevers due to certain materials (humidifier fever) may predispose individuals to the development of EAA/HP due to sensitization (see full discussion of EAA/HP below).

Metal Fume Fever. Heating metals above their melting point, such as while welding or torch cutting, causes formation of solid aerosols (fumes), often with accompanying oxidation. The resultant particle size of 0.1–1.0 μm easily reaches the alveoli, where an acute inflammatory cell response causes release of cytokines, producing the constellation of symptoms. The classic syndrome involves a metallic taste in the mouth, fever, rigors, headache, chest pain, and dyspnea with an abrupt onset 4–12 h after exposure.

Clinical tolerance to these effects occurs after regular exposure [46]. Zinc oxide fumes are the classic cause of MFF, and in the eighteenth century this was predominantly seen in brass foundries – hence the common name of *Brasser's Flu* or *Brass Founder's Ague*. More recently, MFF has been seen after welding galvanized steel, from the heating of zinc in the galvanized coatings [47, 48]. Limited epidemiologic evidence suggests that other metal fumes, such as the fumes produced when magnesium and copper are heated, can produce MFF [49, 50].

Polymer Fume Fever. Heating of polytetrafluoroethylene (PTFE, Teflon®) causes the formation of pyrolysis degradation products, the inhalation of which can lead to polymer fume fever. This fever occurs commonly when PTFE-coated metals are welded or flame cut. It also may occur after smoking cigarettes that are contaminated with PTFE resins from the hands of workers. This usually self-limited, flulike illness presents similarly to MFF, and diagnosis is based on the history of appropriate exposure. With prolonged exposures or when higher temperatures are involved, pulmonary involvement with accompanying chest x-ray findings of consolidation is possible [7]. There has even been a case of PFF reportedly due to exposure from burning of the PTFE coating of a nonstick frying pan [51].

Humidifier Fever. Humidifier fever is an inhalational fever syndrome of uncertain etiology associated with exposure to air contaminated by humidifier water that has excessive growth of microorganisms, most notably *Pseudomonas* and other gram-negative bacteria. It has similarities with HP (see below), but its high attack rates among exposed persons and benign course lend credence to the theory of an immunologic mechanism similar to MFF. Diagnosis is usually made only after numerous workers from the same building present with the appropriate signs and symptoms, and is one of exclusion. It occurs more often during winter months in cold climates, when these humidification systems are commonly in use, and nonsmokers are more susceptible than smokers. Humidifier fever is not to be confused with humidifier lung, which is a type of EAA/HP that occurs after long-term exposure to humidifier

contaminants. There may be considerable overlap of these entities [10, 52, 53].

Pontiac Fever. Pontiac fever can be thought of as a type of humidifier fever that is caused by exposure to water contaminated by *Legionella pneumophila*. In contrast to legionnaires' disease caused by the same organism, Pontiac fever is a self-limited, flu-like illness that has occurred after common source exposure to buildings with contaminated air-conditioning systems (County Health Department Building in Pontiac, Michigan, in 1968, hence the name). It also has been seen after *Legionella* contamination of indoor fountains, whirlpools, and spas [54, 55]. In contrast with Legionaire's disease, Pontiac fever has a high attack rate (<90%) among exposed persons, no associated pneumonia or infection, onset usually within 24–48 h after exposure, and is a benign self-limited fever syndrome; whereas Legionaire's disease is a pulmonary infection often associated with pneumonia and respiratory failure, has a low incidence among exposed persons (<5%, usually those with underlying respiratory illnesses), a longer incubation period, commonly requires hospitalization, and has a case-fatality rate of 5–30% [56].

Organic Dust Toxic Syndrome (ODTS) [57–59]. Organic dust toxic syndrome (previously called *pulmonary mycotoxicosis*, *grain fever*, and *silo unloader's disease*) is a catch-all term applied to a variety of inhalational fevers that occur after exposure to many different organic dust mixtures. Many of these dusts are associated with agricultural industries and include bacteria, fungi, grains, silage, hay, animal danders, pollen, and other complex mixtures. Responsible agents probably include bacterial endotoxins, fungal mycotoxins, cell wall debris, and peptidoglycans. Symptoms include fever, malaise, chest tightness, headache, cough, dyspnea, and generalized aches – usually beginning within hours of exposure. Hypoxia and chest x-ray abnormalities are typically absent, and the syndrome usually resolves without sequelae. There is a strong overlap, however, with the causative agents of EAA/HP, and in these exposure settings, ODTS is a diagnosis of exclusion after hypersensitivity pneumonitis is ruled out (see below).

Extrinsic Allergic Alveolitis. EAA (also known as hypersensitivity pneumonitis [HP]) is an interstitial lung disease probably caused by a combination of type III (humoral or IgG-mediated) and type IV (cell-mediated) delayed hypersensitivity reactions that occur after repeated exposure to a wide variety of antigens and some chemicals. It is felt that an exaggerated immune response occurs in genetically predisposed susceptible persons. Hypersensitivity pneumonitis most commonly has been associated with occupations with exposures to moldy organic materials, such as moldy hay (responsible antigen is actually a thermophilic bacteria) in Farmer's Lung and moldy grain in grain handler's lung. It has been estimated that between 1% and 19% of farmers exposed to moldy hay develop farmer's lung [60]. Many other EAA/HP syndromes are described and are named after the job or antigen exposures (see Table 4). It can even be seen in musicians due to heavy mold growth associated with salivary moisture in their horns and woodwind instruments. Animal handlers can develop EAA/HP secondary to exposure to animal proteins and excreta (such as pigeon breeder's lung), and between 6% and 20% of individuals exposed to bird droppings develop bird fancier's lung [66]. Exposures to various chemicals that cause occupational asthma (e.g., TDI, TMA) have also been implicated in causing EAA/HP [61, 67].

Outbreaks of EAA/HP have been reported in office buildings, the etiology of which was traced to air conditioning and humidification systems contaminated with bacteria and molds [53]. EAA/HP may occur in the home setting due to contaminated humidifiers or by pigeon or pet bird antigens. Due to its immune pathogenesis, there is a period of sensitization prior to developing the first reaction, which can be as long as months or even years. Acute symptoms, which occur 4–6 h postexposure and recur on challenge with the offending agent, include cough, dyspnea, chills, myalgia, fatigue, and high fever.

The pathophysiology of EAA/HP involves immune complex deposition in the lungs of sensitized individuals, with the resultant release of immune mediators and cytokines and inflammatory cell infiltration. Acutely, neutrophils are

involved, but later (or after repeated episodes) lymphocytes predominate, along with fibroblast recruitment. The typical presentation occurs 4–6 h after an intense inhalational exposure to the responsible antigen, and patients commonly have fever, chills, malaise, cough, and dyspnea. Chest x-rays are abnormal in about 80% of cases [68] and often have a reticulonodular pattern or reveal patchy infiltrates; patients are often misdiagnosed as having bacterial pneumonia due to inadequate history and failure to consider occupational or environmental exposures. There is usually hypoxia, and patients have crepitant rales on auscultation of the chest. The white blood cell count is elevated, as is specific IgG to the offending antigen, which can aid in the diagnosis (serum precipitins to specific antigens). The findings of reactive IgG antibodies to the specific antigen in itself is not diagnostic, however, since many asymptomatic similarly-exposed workers will have positive precipitins (40% of farmers; even higher in pigeon breeders), but only a small percentage develop disease. Smokers have less incidence than their similarly-exposed peers. Pulmonary function testing can be normal or may show a restrictive defect and a decreased diffusion capacity due to interstitial inflammation and edema. The acute episode usually resolves within 1–3 days. Initial treatment with corticosteroids is recommended along with removal from exposure and avoidance of further antigen contact to prevent future episodes. Repeated exposures often cause a worsening of the presentation, and tolerance, such as that seen in inhalational fevers, does not occur. Repeated low-level exposures cause a progressive, often irreversible, interstitial pulmonary fibrosis from interstitial collagen formation, along with occasional granuloma formation in about 30% of cases [67]. These patients may present from a typical occupational setting with the insidious onset of a constellation of signs and symptoms, including dyspnea, cough, weight loss, and fatigue. Chest x-rays may reveal increased interstitial markings and fibrosis, and pulmonary function testing usually shows restrictive disease and decreased diffusion capacity. Chronic EAA/HP may be clinically and radiographically indistinguishable from Idiopathic

Table 4 Serious illnesses, selected causative agents, and associated occupations/workers^a

Illness	Causative agent	Associated occupations/workers
ARDS (also possible late sequelae of RADS, BOF)	Irritant gases	
	Soluble gases	
	HCl, HF, H ₂ SO ₄ , HNO ₃ , NH ₃ , and other alkali and acid mists	Acid and alkali production workers; manure pit workers (NH ₃)
	SO ₂	Sulfuric acid production workers; air pollutant workers
	Tear gas	Law enforcement workers
	Isocyanates	Polyurethane industry workers, firefighters
	Insoluble gases	
	Phosgene	Polymer industry workers, welders, burning chlorinated metal degreasers
	NO ₂	Silo fillers, high-temperature arc welders
	Medium-solubility gases	
	Chlorine	Water purification workers, paper pulp workers, swimming pool workers
	Acrolein	Polymer industry workers, firefighters (component of smoke)
	Smoke inhalation	Firefighters
	Pesticides	
	Organophosphates, carbamates, type II pyrethroids, dinitrophenol, pentachlorophenol (wood preservative), paraquat	Farmers, exterminators, crop dusters, pest control workers, lumber industry workers
Acute toxic encephalopathy	Metals and metal compounds	
	Cadmium, mercury, manganese, Ni(CO) ₄	Smelters
	Lead	Lead-acid battery workers, HAZMAT site clean-up workers, lead reclamation workers, bridge painters, automobile radiator repair workers
	Mercury	Chlor-alkali workers (electrolytic production of chlorine and caustic soda), mercury-containing instrument manufacturers, fungicide users, topical antiseptics workers ^a
	Toluene, xylene, other hydrocarbon solvents	Painters, chemical production workers, solvent users (confined space)
	Simple asphyxiant gases (CO ₂ , CCH ₄ , propane)	Gas production workers, various workers with confined space issues
	Cyanide	Metal plating workers, jewelers, firefighters (smoke inhalation)
	Hydrogen sulfide	Farmers (manure pits), sewer workers, petroleum refinery workers
Acute hemolysis	Carbon disulfide	Viscose rayon workers ^a , rubber manufacturers ^a
	Carbon monoxide	Garage workers, firefighters, paint strippers (methylene chloride) (any exposure to incomplete burning, improper ventilation, or exhaust)
	Chlorates	Match and explosive production workers, dye manufacturers, paper pulp bleach manufacturers (ClO ₂)
	Arsine (AsH ₃), stibine (SbH ₃)	Workers with dopant gas for n-type semiconductors in the microelectronics industry
	Organic nitro and amino compounds	Synthetic dyes workers, leather and shoe industry workers, fabric dyers ^a

(continued)

Table 4 (continued)

Illness	Causative agent	Associated occupations/workers
Cyanosis	Methemoglobin-forming agents: organic amino and nitro compounds ^a	Synthetic dyes workers, leather and shoe industry workers, fabric dyers ^a
	CNS depressants causing hypoventilation and hypoxia	Various workers (see acute toxic encephalopathy above)
Hyperthermia/fever	Pentachlorophenol – wood preservative	Lumber production workers
	Nitrophenol pesticides, chlorophenoxyacetic acid herbicides	Exterminators, pest control workers, agricultural workers, farmers, forestry workers, landscapers
	Inhalational fever syndromes	See fume fever syndromes below
Seizures	Metals	
	Arsenic	Copper smelters, leather tanning workers, pesticides workers
	Copper	Copper smelters, miners
	Lead	Lead-acid battery workers, Hazmat site clean-up workers, automobile radiator repair workers, lead reclamation workers
	Manganese	Manganese miners, welders, chemical industry workers, metal refining workers
	Nickel	Workers in metal plating, coins, batteries, electronics, metal alloying industries
	Pesticides	
	Organochlorines ^a (lindane, cyclodienes, DDT), organophosphates, paraquat ^a , diquat (herbicides), pentachlorophenol, dinitrophenol, chlorophenoxyacetic acid herbicides	Farmers, agricultural workers, forestry workers, landscapers, pest control workers
	Rodenticides ^a (thallium, SMFA, strychnine, zinc phosphide, arsenic, methyl bromide)	Rodenticide users: granary workers, longshoremen, exterminators
	Phosphine, methyl bromide (fumigants)	Grain workers, pest control workers
	Any general CNS depressant producing hypoxia: toxic inhalants (CN, H ₂ S, carbon monoxide), simple asphyxiants (hydrocarbons, CO ₂ , He, N ₂), chlorinated hydrocarbons	See acute toxic encephalopathy above
Rhabdomyolysis	Any agent causing seizures (see above)	See above
	Any agent causing hyperthermia associated with hypermetabolic state (pentachlorophenol, dinitrophenol, chlorophenoxy herbicides)	Farmers, lumber industry workers, pest control workers, exterminators
	Carbon monoxide (direct cellular toxicity)	Workers who have any exposure to incomplete burning, improper ventilation, or exhaust: garage workers, firefighters; paint strippers (methylene chloride)
	Any CNS depressants causing coma and inducing rhabdomyolysis from pressure	See acute toxic encephalopathy above

(continued)

Table 4 (continued)

Illness	Causative agent	Associated occupations/workers
Fume fever syndromes	Metal fume fever	Welders (galvanized metal), foundry workers, smelting workers, metal refining workers
	Polymer fume fever	Welders (cutting through polytetrafluoroethylene coatings or polymer pipes), polymer workers
ODTS and other inhalational fevers	ODTS: Bioaerosols of fungi, bacteria, exotoxins	
	Moldy hay, moldy silage, compost	Farmers (“silo unloader’s disease”)
	Sewage sludge	Sewer workers, plumbers
	Grain dust	Grain mill workers (grain fever)
	Cotton dust	Cotton mill workers (mill fever)
	Animal confinement buildings	Veterinary workers, laboratory workers
	Other inhalational fevers	
	Contaminated humidifiers	Workers in any building with contaminated humidifiers (humidifier fever)
	Contaminated water cooling systems, spas, fountains	Workers in any building with contaminated cooling system or fountain (Pontiac fever)
	Contaminated wood dusts/chips/bark (moldy wood chip exposure)	Sawmill workers, pulp and paper mill workers, landscapers (“wood-trimmer’s disease”)
Hypersensitivity pneumonitis and Extrinsic Allergic Alveolitis	Organic antigen exposures	
	Moldy hay	Farmers (farmer’s lung)
	Moldy compost	Mushroom workers (mushroom worker’s lung)
	Contaminated humidifiers, dehumidifiers, HVAC	Office workers in any contaminated building (humidifier lung)
	Bagasse (moldy pressed sugarcane)	Sugarcane workers (bagassosis)
	Animal products (excreta, serum, feathers, dander)	Animal handlers (pigeon breeder’s disease, duck fever)
	Chemicals	
	Trimellitic anhydride, phthalic anhydride	Painters, epoxy resin users
	Diisocyanates	Polyurethane foam industry workers
	Plicatic acid (red cedar)	Red cedar workers, lumber industry workers, carpenters
	Pyrethrum insecticides	Exterminators, pest control workers, insecticide manufacturers
	Sodium diazobenzene-sulfonate (Pauli’s reagent)	Chromatographers
	Many others	Workers in varied industries
Myocardial infarction/ischemia	Carbon monoxide	Workers with exposure to exhaust or poorly ventilated combustion: miners, forklift operators, mechanics, firefighters
	Carbon disulfide	Viscose rayon workers ^a , rubber industry workers
	Organic nitrates	Explosive industry (TNT) workers
Cardiac arrhythmias		
Tachydysrhythmias	Chlorinated hydrocarbon	Mechanics, degreasers, dry cleaners
	Hydrocarbon solvents	Printers, painters, mechanics, degreasers, dry cleaners
	Carbon monoxide	Paint strippers (CH ₃ Cl), workers with exposure to exhaust or poorly ventilated combustion: miners, forklift operators, mechanics, firefighters

(continued)

Table 4 (continued)

Illness	Causative agent	Associated occupations/workers
Bradydysrhythmias	Organophosphates, carbamates	Farmers, pest control applicators
Acute renal failure	Arsine, stibine (due to hemolysis)	Semiconductor industry workers
	Halogenated hydrocarbon solvents (many)	Dry cleaners, degreasers, plastics industry workers
	Toluene (ATN)	Painters
	Any agent associated with rhabdomyolysis	See rhabdomyolysis above
	Cadmium	Welders
Acute hepatic failure	CCl ₄ , CBr ₄ , CHCl ₃ , other halogenated hydrocarbons	Mechanics, degreasers, dry cleaners, plastics industry workers
	Solvents: 2-nitropropane, DMF	Painters
	Dimethylacetamide	Textile workers

Data from Refs. [11, 61–65]

ARDS adult respiratory distress syndrome, *ATN* acute tubular necrosis, *BOF* bronchiolitis obliterans fibrosa, *CN* cyanide, *CNS* central nervous system, *DDT* dichlorodiphenyltrichloroethane, *HVAC* heating, ventilating, and air conditioning, *RADS* reactive airways dysfunction syndrome, *SMFA* sodium monofluoro acetate

^aMany of the chemicals/toxins no longer may be used or manufactured in the USA but are still in common use in other parts of the world. US industries with modern industrial hygiene practices have limited or eliminated many exposures to industrial toxins, but workers in other nations may remain at substantial risk

Pulmonary Fibrosis; a careful, detailed occupational history, serum precipitins to a specific antigen to which the patient is exposed, bronchoalveolar lavage, and histologic examination of lung tissue would likely all be needed to make the diagnosis.

Several authors have proposed specific diagnostic criteria for EAA/HP. These involve the presence of major and minor findings, including antigen exposure, specific antibodies, physical exam findings, presence of dyspnea, radiographic findings, pulmonary function testing including DLco, lymphocytic alveolitis on bronchoalveolar lavage, and lung biopsy findings, among others. None of these have been systematically evaluated. LaCasse (2006) has shown data that suggest the presence of several variables increases the odds ratio for predicting EAA/HP. Ranking from highest OR to lowest are: Exposure to a known offending antigen 38.8 (CI: 11.6–129.6); positive precipitating antibodies 5.3 (CI: 2.7–10.4); recurrent episodes of symptoms 3.3 (CI: 1.5–7.5); presence of inspiratory crackles 4.5 (CI: 1.8–11.7); onset of symptoms 4–8 h after exposure 7.2 (CI: 1.8–28.6); and weight loss 2.0 (CI: 1.0–3.9) [69].

Treatment of acute episodes of EAA/HP consists of administering oxygen and admission to the hospital when necessary. Corticosteroids are the only medications of any utility in the treatment of acute EAA/HP, but only have benefit in acute attacks. A single randomized, placebo-controlled trial [70] confirmed findings from other controlled but nonrandomized trials [62, 71] and from previous case series: the administration of corticosteroids can hasten the recovery from the acute stage of EAA/HP, but have no demonstrated effect on long-term prognosis and have no value in treatment of chronic EAA/HP, which is largely supportive. The decision to administer systemic corticosteroids should be guided by the severity of symptoms and physiologic abnormalities. Although the study above used 40 mg/day tapered over 8 weeks, higher doses such as prednisolone 1 mg/kg/day with a more rapid taper have been advocated more recently. The mainstay of treatment is withdrawal from exposures and strict prevention of any further contact with the inciting antigen or chemical [62, 69, 72] (Level 1 recommendation).

Miscellaneous Causes of ARDS. Exposures to metal fumes such as cadmium, manganese, and mercury can induce an MFF-like illness, which

then progresses hours later to acute chemical pneumonitis and pulmonary edema. This illness also can occur after exposure to gaseous metal compounds, such as nickel carbonyl, vanadium pentoxide, and zinc chloride [49].

Toxicants other than the above-described irritant gases can cause ARDS by altering pulmonary capillary membrane permeability. Fluid can leak into the alveolar air spaces with subsequent pulmonary edema. Examples are the pesticides dinitrophenol and pentachlorophenol. These toxicants act similarly to salicylates in that they uncouple oxidative phosphorylation, leading to a hypermetabolic state with fever, tachypnea, sweating, and pulmonary edema [73]. The acetylcholinesterase-inhibiting pesticides (organophosphates, carbamates) and nerve agents cause acetylcholine excess and can lead to cholinergic stimulation and muscarinic effects with copious pulmonary secretions and pulmonary edema, as well as acetylcholine-stimulated bronchial smooth muscle constriction. Neuromuscular blockade from the nicotinic effects of these insecticides can contribute to the respiratory failure and deaths associated with large exposures. Massive poisoning by a type II pyrethroid insecticide can cause pulmonary edema that has been mistaken for a reaction to an organophosphate. Subsequent atropine treatment was ineffective, and some deaths have occurred owing to atropine toxicity [74]. Aspiration of hydrocarbon solvents also can lead to pneumonitis and ARDS

Occupational Cardiac Toxicology

A variety of toxins encountered in the workplace can have deleterious effects on the heart (Table 4).

Myocardial Infarction

Carbon disulfide is the industrial toxin classically associated with accelerated atherosclerotic disease in workers. This property has been recognized since the 1800s and was well described in the occupational literature in workers with high

exposures in the rubber industry [20]. The mechanism by which carbon disulfide causes accelerated atherosclerosis is poorly understood but may be mediated by its propensity to inhibit various enzyme systems, and workers exposed to high levels have elevated total and LDL cholesterol. Workers exposed to high levels of carbon disulfide may have five times the incidence of coronary disease compared with nonexposed workers. However, at current recommended occupational levels, such as the threshold limit value (TLV) promulgated by the American Conference of Governmental Industrial Hygienists there appears to be no significant CV effects [75–77]. Carbon disulfide is also reported to cause peripheral neuropathies and neurobehavioral abnormalities at the very high exposure levels seen in the past [20].

Carbon monoxide is the leading cause of toxic deaths in workers worldwide. Chronic exposure is believed to accelerate atherogenesis, and acute exposures to high levels can induce myocardial infarction, vasospasm, and sudden death. Mechanisms and treatment of carbon monoxide poisoning are described in detail in ► Chap. 96, “Carbon Monoxide.”

Organic nitrates, such as nitroglycerin and ethylene glycol dinitrate, are used in the manufacture of explosives. Because they are well absorbed by inhalation and through the skin, workers can have significant systemic effects from simply handling or packing explosives. After a few years of exposure, the coronary vasodilatory effects of the nitrates are opposed by vasoconstriction. When organic nitrate exposure is withdrawn abruptly, the vasoconstriction is unopposed, and coronary vasospasm ensues with subsequent angina, myocardial infarction, or sudden death (“Monday morning angina”). Treatment is directed at reversing coronary vasospasm with calcium channel blockers and nitrates and prevention of further exposures [78].

Cardiac Dysrhythmia

Cardiac tachydysrhythmias can be caused by a variety of solvents, most notably chlorinated

hydrocarbon solvents, such as trichloroethylene (TCE), but they also can occur with aromatics (xylene, toluene), aliphatic hydrocarbons (naphthalene, gasoline), and chlorofluorocarbon refrigerants. These compounds sensitize the myocardium to the arrhythmogenic properties of catecholamines and in significant exposures can predispose the worker to tachydysrhythmias, syncope, and sudden death. Additionally, any toxin causing cellular hypoxia causes a subsequent tachycardia. This can include all the asphyxiants (carbon monoxide, hydrogen sulfide, cyanide, and simple asphyxiants) and any CNS depressant that causes hypoventilation and resultant hypoxia.

Cholinesterase-inhibiting pesticides, such as organophosphates, carbamates, and nerve agents, can cause effects secondary to an excess of acetylcholine and subsequent dysrhythmias. Depending on whether muscarinic or nicotinic effects predominate, tachycardia or bradycardia can be seen. There usually are other concomitant systemic signs of acetylcholine excess, such as *SLUDGE* (salivation, lacrimation, urination, defecation, gastrointestinal cramping, and emesis). There have been reports of QT prolongation and polymorphous ventricular tachycardia associated with these insecticides. These agents are described in detail in the Organophosphorous and Carbamate Insecticides and the Nerve Agents chapters. The metals arsenic and thallium have been reported to cause QT prolongation and torsades de pointes as well (see ► Chaps. 80, “Arsenic” and ► 85, “Thallium”).

Occupational Hepatic Toxicology

Many toxins encountered in the workplace have effects on the liver (see Table 4) because these xenobiotics are metabolized by the same hepatic enzyme systems that metabolize pharmaceuticals. In many cases, such as with methanol, ethylene glycol, benzene, and *n*-hexane, the parent molecules are not toxic but are metabolized into toxic compounds or highly reactive intermediates. These metabolites exert the toxic effects in humans. In many cases, chronic ethanol intake is

associated with an increased susceptibility to the hepatotoxic effects of these compounds, owing to P-450 enzyme induction. Many of the reported acute hepatotoxicities occur only after massive exposures. A wide variety of liver injury can be seen, however, after industrial exposures, including steatosis, cholestasis, hepatocellular necrosis, and vascular lesions [79, 80].

Halogenated Hydrocarbons

Halogenated hydrocarbons, primarily chlorinated hydrocarbons, are used mainly as solvents and degreasers. Many were used in the dry cleaning industry. The classic hepatotoxic chlorinated hydrocarbon is carbon tetrachloride (CCl₄). This compound is of historical interest because it was used widely as a solvent, degreaser, and fire extinguisher in the early twentieth century. After large exposures, such as inhalation in a confined space or intentional suicidal ingestions, carbon tetrachloride caused a centrilobular necrosis pattern similar to that seen with acetaminophen overdose. *N*-Acetylcysteine, the antidote for acetaminophen toxicity, and hyperbaric oxygen have both shown efficacy in animal models of CCl₄ poisoning, and favorable outcomes reported in case series. (Level III recommendation) CCl₄ is not used as widely today, having been replaced by other, less toxic products [81]. The main use of carbon tetrachloride today is as a chemical precursor for the manufacture of chlorofluorocarbons. Chloroform and carbon tetrabromide poisonings produce a similar pattern of hepatotoxicity. Other halogenated compounds, such as polychlorinated biphenyls and polybrominated biphenyls, have been associated with elevated liver enzymes and chloracne [82].

The primary degreaser and dry cleaning agent in the USA today is tetrachloroethylene (perchloroethylene). In large exposures, it may be associated with acute hepatic injury [83]. Related compounds, TCE, trichloroethane, and tetrachloroethane, also are hepatotoxic in large doses [84]. All these volatile compounds can cause CNS depression via a general anesthetic-type mechanism and can cause cardiac

dysrhythmias (see earlier). Their thermal breakdown products include phosgene and hydrogen chloride (see earlier section on irritant gases).

Solvents

The solvent 2-nitropropane has been associated with acute hepatic failure after confined space exposures in painters [85]. *N,N*-Dimethylformamide can cause hepatic injury and a disulfiram-like reaction with ethanol ingestion [87]. Dimethylacetamide is a hepatotoxin used in acrylic fiber production [87, 88]. Other petrochemicals have been implicated in liver injury [89].

Miscellaneous Compounds

Trinitrotoluene (TNT), an explosive, and elemental white phosphorus have also been reported to cause acute hepatic injury. Compounds associated with chronic liver disease and hepatic angiosarcomas (vinyl chloride monomer, arsenic) occur in the workplace but are not of concern to the intensivist. Copper causes chronic hepatic injury, but only in individuals who are genetically predisposed [65].

Occupational Renal Toxicology

Acute Renal Failure

Many of the industrial hepatotoxic compounds also are injurious to the kidney, the most notable being carbon tetrachloride. Renal failure is usually a consequence of acute tubular necrosis due to volume depletion from the hepatotoxic effects. Because P-450 enzymatic metabolism of xenobiotics also occurs in the kidneys, there can be direct nephrotoxicity as well [90]. Toluene is metabolized to hippuric acid which can induce an elevated anion gap metabolic acidosis after significant intoxication, but this is seen primarily with intentional abuse and not workplace

exposures. Renal failure has occurred secondary to acute tubular necrosis after toluene poisoning [91]. Other halogenated compounds associated with acute renal failure are chloroform, ethylene dichloride (solvent, fumigant), trichloroethylene (TCE), tetrachloroethane, vinylidene chloride (plastic intermediate), diesel fuel, and ethylene chlorohydrin (chemical intermediate) [92]. TCE can induce acute kidney injury, but only at very high long-term exposure levels [93], and chronic exposures at the levels associated with kidney injury are necessary before a risk of kidney CA is seen in workers [94]. Any compound that induces rhabdomyolysis can cause myoglobinuric renal failure (see Table 4). Treatment classically has involved ensuring adequate urine volume (with the use of mannitol) and alkalinization of the urine to prevent pigment deposition in the renal tubular cells. While there is theoretical rationale for the use of these agents, the clinical evidence is poor, and based on small studies with small sample sizes. A retrospective review studied over 2,000 patients in an ICU setting and found no efficacy for the use of either agent in preventing myoglobinuric renal failure. (Level II-2 recommendation) [95] Analogously, arsine and stibine gases cause acute renal failure because of hemoglobinuria induced by massive hemolysis. Exchange transfusions often are needed in addition to dialysis. Cadmium is associated with acute renal failure. Exposures in the industrial setting occur via torch-cutting or welding metals with cadmium coatings. Although chromium has been associated with acute tubular necrosis after massive oral exposures, these are not encountered in the workplace setting [96]. Arsenic, cadmium, and lead are known to induce chronic renal disease, and the effects of concomitant exposure to combinations needs further study [97]. By measuring LMW proteins (β -microglobulin, free retinol binding protein) in the urine of exposed workers, biomonitoring for early nephrotoxic effects is possible, but usually only as an epidemiologic tool [98]. In the USA, the Occupational Safety and Health Administration requires whole blood Cd, urine Cd, and urine β_2 -microglobulin monitoring of exposed workers [99].

Occupational Neurotoxicology

Central Nervous System

CNS depression caused by volatile solvents can occur in the workplace and is usually due to inadequate ventilation or confined space issues. The CNS depression is due to the general anesthetic properties of these compounds, since they act just like general anesthetic (GA) agents. Historically, many of these solvents, like TCE, were used as GA agents. Any hydrocarbon or halogenated hydrocarbon can produce these effects, even chlorofluorocarbon refrigerants and Freon (C). Many workers are at risk for this type of exposure, including painters; mechanics; heating, ventilation, and air conditioning (HVAC) personnel; and workers in a varied assortment of occupations in which these solvents are used (Table 5). A purported chronic toxic encephalopathy due to long-term exposure to solvents, known as painter's syndrome and initially reported in Scandinavian workers in the 1970s and 1980s, has been shown to be related to other factors, such as depression, low educational level, or chronic alcohol abuse, and not due to workplace exposures [100]. Many of these compounds, especially toluene and xylene, are inhaled intentionally for recreational use for their CNS depressant effects; and heavy users can develop a leukoencephalopathy (see below). Deaths have occurred in some cases owing to cardiac rhythm disturbances due to sensitized myocardium, as well as respiratory arrest due to over-sedation. The arrhythmias are seen especially with halogenated hydrocarbon abuse, and known as "sudden sniffing death." The malignant arrhythmia in these cases is felt to be due to endogenous catecholamine surge, such as from sudden startle/excitation response or heavy exertion/exercise while abusing. This catecholamine surge in the face of "sensitized myocardium" can initiate an "R-on-T phenomenon," and subsequent re-entrant arrhythmias, since these agents can delay repolarization. In addition, a chronic leukoencephalopathy can develop in chronic toluene abusers; recovery may occur after cessation of abuse. Toluene is also associated with a nonanion gap metabolic acidosis [101].

Methylene chloride (MeCl) is a unique chlorinated solvent that is metabolized to CO and can cause injury or death via GA effects, cardiac arrhythmias, or CO poisoning manifested as elevated carboxyhemoglobin concentrations. It is the only instance where carboxyhemoglobin levels can continue to rise after removal from the source of exposure. While well-known to cause life-threatening exposures to furniture strippers and factory workers, a relatively new source is from its use in bathtub refinishing. The products used are aircraft grade paint stripping products and usually contain high concentrations of MeCl (60–100%). In virtually all reported cases, deaths have occurred in small residential bathrooms, acting as confined spaces, and workers had inadequate ventilation and did not use proper air-supplied respirators. Since MeCl is heavier than air, concentrations in the tub can be orders of magnitude higher than the rest of the bathroom, right in the worker's breathing zone [102]. Treatment of cardiac arrest in these cases would necessitate deviation from standard acute cardiac life support protocols of using of epinephrine, since further arrhythmias can be precipitated by this agent in the sensitized myocardium; the use of beta blockers is suggested to reduce the possibility of R on T and further arrhythmias [103] (Level III recommendation).

Ethanol ingestion after TCE and trichloroethane exposure (and possibly other hydrocarbon solvents) induces a disulfiram-like reaction known as degreaser's flush, which may induce hypotension and subsequent syncope when alcohol is ingested after exposure. Any asphyxiant gas can cause CNS depression secondary to oxygen deprivation, including the simple asphyxiants, such as carbon dioxide, methane, and nitrogen, and the toxic asphyxiants, such as carbon monoxide, cyanide, and hydrogen sulfide (see earlier section on pulmonary toxicology).

Some occupational toxicants have been shown to cause CNS stimulation and occasionally seizures; these include the organochlorine insecticides DDT, cyclodienes, chlordecone, lindane, and related compounds [35–37]. Although most no longer are registered with the US Environmental Protection Agency and have been banned in

Table 5 Selected occupations and representative possible toxic exposures^a

Occupations	Possible toxic exposures
Agriculturalist, farmer	Pesticides, H ₂ S, CH ₄ , NH ₃ , CO ₂ , NO ₂ ; moldy hay (hypersensitivity pneumonitis), ODS agents
Artist	Cadmium, toluene, other HC solvents, lead glazes as in ceramics
Battery manufacturer/reclamation	Lead, cadmium, mercury
Beautician/cosmetologist	Persulfates, phenylenediamine, thioglycolates
Carpenter/lumberjack	Plicatic acid (western red cedar), multiple wood dusts, wood preservatives (PCP, chromium-copper arsenate)
Chromatographer	Sodium diazobenzene-sulfonate (Pauli's reagent)
Construction worker	Asphalt, PAH, solvents, paints, glues, wood dusts, lead
Dentist/hygienist	Amalgams (silver, mercury), nitrous oxide
Electrician	PCBs, lead (cable splicing)
Electroplater	Chromium, copper, lead, Ni, cadmium, solvents
Firefighter	CO, CN, acrolein, phosgene, HCl, HF, NH ₃ , NO ₂ , SO ₂ , isocyanates, hydrocarbons, PAH, smoke
Forester/landscaper	Wood dusts, wood preservatives (PCP, copper arsenate), pesticides, herbicides
Foundry worker/smelter/metal refining	Zinc, copper, lead, mercury (gold and silver refining), cadmium (zinc smelting), acrolein, arsenic, selenium (copper refining by-product)
Health care worker	Ethylene oxide, mercury, natural rubber latex, formaldehyde, glutaraldehyde, radioisotopes, x-rays, chemotherapeutics, blood-borne pathogens, anesthetic gases
Heating, ventilation, and air conditioning personnel	Lead (solder), contaminated water coolant systems (Pontiac fever), contaminated humidifiers (humidifier fever), natural gas, PAH
Highway worker	PAH (coal tar fumes), HC solvents, CO (exhaust)
Jeweler	CN, zinc, lead, solvents
Law enforcement personnel	Lead (firing ranges), CO (traffic exhaust), tear gas
Machinist	Cutting oils, solvents
Mason	CaOH (lime)
Mechanic/gas station attendant	CO, trichloroethylene, gasoline (HCs, benzene, MTBE, ethanol), lead
Mortician	Embalming fluids: formaldehyde, methanol, glutaraldehyde, isopropanol
Painter	TDI, solvents: toluene, xylene, turpentine, VOCs, CH ₃ Cl, lead
Paper pulp industry worker	Chlorine dioxide, chlorine, H ₂ S, SO ₂ , methyl mercaptan
Pest control/exterminator	Pesticides: organophosphates, carbamates, pyrethroids; HC solvents, herbicides, wood preservatives (PCP, chromium-copper arsenate)
Petroleum refinery worker	Gasoline, benzene, MTBE, PAH, ethanol
Plumber	Sewage, lead (solder)
Printer	Solvents: naphthas, toluene, xylene
Semiconductor industry worker	Dopant gases: arsine (AsH ₃), stibine (SbH ₃); gallium arsenide, diborane, phosphine, solvents, HF
Shipbuilder	Styrene
Shoemaker/repairer	Hexacarbons: n-hexane, methyl n-butyl ketone; solvents: benzene, toluene, cyclohexane
Textile worker	DMF, PTFE, dimethylacetamide, dyes; CS ₂ (viscose rayon)
Trucker	CO, diesel exhaust, lead
Veterinarians/animal handlers	Pesticides, animal dander
Welders	NO ₂ , phosgene, zinc oxide fumes (metal fume fever), polymer (polymer fume fever), lead, mercury, cadmium, chromium

CN cyanide, CO carbon monoxide, DMF N,N-dimethylformamide, HC hydrocarbon, HF hydrofluoric acid, MTBE methyl-tert-butyl ether, ODS organic dust toxic syndrome, PAH polycyclic aromatic hydrocarbons, PCB polychlorinated biphenyls, PCP pentachlorophenol, PTFE polytetrafluoroethylene, TDI toluene 2,4-diisocyanate, VOCs volatile organic compounds

^aMany of the chemicals/toxins no longer may be used or manufactured in the USA but are still in common use in other parts of the world. US industries with modern industrial hygiene practices have limited or eliminated many exposures to industrial toxins, but workers in developing nations may remain at substantial risk

Canada and Europe, developing nations still use these products extensively for pest control. Additionally, any agent that causes hypoxia or CNS depression to the point of hypoventilation can cause seizures by that mechanism (see Table 4).

Severe, acute poisoning by a few neurotoxins can induce a parkinsonian-like neurologic disorder. The most common such neurotoxin is carbon monoxide, which causes ischemic injury to the basal ganglia after severe poisoning episodes. Similarly manganese [104], carbon disulfide, and methanol have been reported to cause a parkinsonian-like syndrome. Lead poisoning can cause an acute encephalopathy with coma or seizures or both, primarily seen in the pediatric population. The same blood levels associated with lead encephalopathy in children from more chronic exposure due to pica are well tolerated in adult workers after short-term exposures; even levels exceeding 100 ug/dL (4.8 umol/L) can be seen in asymptomatic workers.

Mercury is well known to exert most of its toxicity on the CNS [105]. The most toxic form, methylmercury, was the cause of severe permanent CNS impairment in children in Japan, termed *Minamata disease*. Mothers ate fish contaminated with methylmercury from industrial wastes dumped in Minamata Bay [106]. The potency of other organic mercurials cannot be discounted. A chemistry professor in New England was reported to have suffered a fatal neurodegenerative disease from a seemingly trivial exposure to a few drops of a related compound, dimethylmercury, on her gloved-hand; the compound was being used as a nuclear magnetic resonance internal standard for mercury compounds. Aggressive chelation was ineffective and she died a few months after the incident [107]. Ethylene oxide is used as a gas sterilant for surgical equipment. It can cause CNS depression and peripheral neuropathy.

Peripheral Neuropathy

A wide assortment of toxicants have been associated with peripheral neuropathy, including the hexacarbons (hexane, methyl n-butyl ketone), carbon disulfide, acrylamide monomer, lead, arsenic,

thallium, mercury, and ethylene oxide. Certain organophosphates that inhibit the enzyme neuropathy target esterase induce a delayed myeloneuropathy called *organophosphate-induced delayed neuropathy*. This was seen during prohibition when alcoholics drank Jamaican ginger extracts contaminated with triorthocresyl phosphate (TOCP). More recently, there have been reports of occupationally-acquired organophosphate-induced delayed neuropathy [41]. Many older pesticides can cause chronic effects on the peripheral nervous system, owing to their heavy metal components, such as arsenic, lead, mercury, and thallium [108].

Occupational Hematopoietic Toxicology

Methemoglobinemia and Hemolysis

Many aromatic amino and nitro compounds are strong oxidizing agents. They are used as chemical intermediates, in the production of aniline dyes, and as accelerators and antioxidants in rubber production. These compounds can oxidize the ferrous iron in hemoglobin, causing methemoglobinemia (see ► Chap. 30, “Toxicant-Induced Hematologic Syndromes”). Nitrates from fertilizers, TNT, and naphthalene are other compounds that have been shown to cause methemoglobinemia. Chlorates, used in match and explosive manufacturing, can cause oxidation of the hemoglobin and denaturing of the protein molecule. The end result is methemoglobinemia unresponsive to the antidote methylene blue and, frequently, hemolysis. Arsine and stibine are semiconductor dopant gases that add a controlled amount of impurities to the silicon wafer to alter its electrical conductivity. Even brief exposures to these toxins can cause severe hemolysis, with subsequent acute renal failure and death in some cases [49].

Aplastic Anemia

Benzene is a well-known bone marrow toxin, exerting these effects through its electrophilic

reactive metabolite benzene epoxide. Exposures can cause depression of all blood cell lines, and it has been shown to be a cause of aplastic anemia and acute myeloblastic leukemia (AML). Other marrow toxins shown to cause aplastic anemia are ionizing radiation and chemotherapeutic agents (alkylating agents and antimetabolites).

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Complications of Chronic Alcoholism That Affect Critical Illness

11

Alison L. Jones

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The worldwide consumption of alcohol and alcoholism, or alcohol use disorder (defined as a “problematic pattern of alcohol use leading to clinically significant impairment or distress” by DSM-5) [1], are increasing [2]. This is particularly so among women as the social stigma surrounding drinking declines and alcohol is more readily accessible. Women are less likely to be diagnosed early and more likely to relapse after treatment.

Alcoholism is estimated to cause approximately 2.5 million global deaths annually (4 % of all-cause mortality) which mostly ensue from liver disease [2]. Approximately 90 % of alcoholics develop fatty liver, 25 % develop alcoholic hepatitis, 15 % develop cirrhosis and 10 % develop hepatocellular carcinoma [3, 4]. Alcoholic liver disease (ALD), especially cirrhosis, also accounts for increasing numbers of hospital admissions across the world, including ICU admissions [5, 6]. Each year about 26,000 patients with cirrhosis require ICU admission and support in the UK alone, which has a population of 60 million [7].

The risk of developing liver disease from alcohol relates to the daily dose and duration in years of exposure, together with other factors. The consumption of alcohol often is expressed in terms of *units* of ethanol ingested (Table 1). Drinking ≥ 30 g/day of ethanol increases the risk of ALD in both men and women [8]. Women have a greater risk of ALD than men, presumed due to differences in ethanol metabolism and distributional factors [9]. A retrospective study in men

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Table 1 Calculation of units for alcohol^a

Type of drink	% Alcohol by volume	Volume	Alcohol content (Units)
Beer/lager/cider			
Alcohol-free	<0.05	440 mL	0
Low alcohol	0.5–1.0	440 mL	0.4
		1 pint	0.6
Standard strength	3.0–4.0	1 pint	1.7–2.3
Premium strength	5.0–6.0	1 pint	2.8–3.4
“Alcopops”	5.0–6.0	330 mL	1.7–2.0
Wine	8.0–13.0	750 mL	6.0–10.0
Fortified wines (e.g., sherry, vermouth)	14.0–20.0	750 mL	10.5–15.0
Spirits (e.g., gin, vodka, rum)	37.5–40.0	700 mL	26.3–28.0

^a1 Unit = volume % ethanol × 0.78

showed that 50 % of men with an average intake of alcohol of greater than 160 g per day for 20 years developed cirrhosis [10]. Later studies showed risk levels with alcohol consumption of 40 g per day for men [11]. Neither alcoholic hepatitis nor cirrhosis was seen in patients who consumed 160 g of ethanol per day for fewer than 5 years [10]. Abstinence from alcohol is critical in the ongoing management of patients and can reverse fatty liver, but not advanced ALD. Cofactors that worsen the risk of developing ALD include metabolic syndrome/obesity, type 2 diabetes mellitus, malnutrition, smoking, hemochromatosis, and chronic viral hepatitis B or C [9, 12].

The clinical diagnosis of ALD is made by a history of excessive alcohol consumption, together with active exclusion of other causes of liver disease. Important scoring systems for severity of liver disease include the Child–Turcotte–Pugh [13] (a semiquantitative score used to roughly characterize severity), MELD [14, 15] (a quantitative prognostic score based on serum bilirubin, creatinine, and INR – and a recent addition of serum Na⁺ [16] used to prioritize liver transplantation), and Maddrey discriminant function [17] using serum bilirubin and prothrombin time (to guide use of corticosteroids in alcoholic

hepatitis). Unfortunately the only definitive treatment of cirrhosis is hepatic transplantation.

Pathophysiology and Clinical Features of Liver Injury

Alcoholic liver injury seems to progress from fatty change through alcoholic hepatitis to cirrhosis, the full progression occurring in about 20 % of individuals [18, 19]. Alcoholic hepatitis develops in only a proportion of drinkers, even after several decades of alcohol abuse, and is assumed to be pre-cirrhotic, although not a required stage for progression [20].

Fatty liver is characterized histologically by microvesicles and macrovesicles of fat within the hepatocyte [18]. Most individuals with fatty liver are asymptomatic, although some have right upper quadrant pain or epigastric discomfort, nausea, or bowel disturbances [18]. Hepatomegaly is the most common clinical finding. The γ -glutamyl transferase and aspartate aminotransferase are usually high and the serum bilirubin modestly elevated in 20–30 % of cases. Alkaline phosphatase is elevated in about half of cases. Macrocytosis is commonly observed. Most lab results show marked improvement, if not complete reversal, with alcohol abstinence in a few weeks. The abdominal ultrasound shows an echogenic liver. Liver biopsy shows accumulation of triglycerides that may be mild, moderate, or severe in extent but is not routinely required for management purposes.

Alcoholic hepatitis is characterized by the presence of neutrophils in the lobules of the liver together with necrosis of hepatocytes [18]. The clinical presentation varies from hepatomegaly to jaundice, ascites, bleeding, and coma. Most patients with mild-to-moderate hepatitis on liver biopsy have anorexia, fatigue, lethargy, or epigastric pain [18]. Patients with severe hepatitis tend to present with jaundice, ascites, hemorrhage, or encephalopathy. On examination, patients may have ascites (60 %), bruising, and splenomegaly (15 %). Fever is a feature in 50 % of patients. Serum γ -glutamyl transferase and aspartate aminotransferase are increased and

higher than in other forms of alcoholic liver disease; 66 % of patients have increased serum bilirubin and alkaline phosphatase. More than half of patients are anemic, and macrocytosis is prominent. Patients with hepatitis often show a marked deterioration in their condition when admitted to the hospital.

Cirrhosis is defined as widespread fibrosis and nodule formation within the liver [18, 19]. It follows hepatocellular necrosis due to a variety of insults [18, 19]. The fibrosis disrupts hepatic architecture, impeding exchange of oxygen and nutrients through the basement membranes between liver cells and the blood and causing portal hypertension [21]. Cirrhosis usually is believed to be irreversible, but fibrosis has been shown to regress in hemochromatosis and Wilson's disease. The clinical spectrum of cirrhosis varies widely from asymptomatic hepatomegaly to hepatocellular failure to portal hypertension with ascites or variceal hemorrhage [18, 19]. Patients with alcoholic cirrhosis who are actively abusing alcohol are more likely to present with features of decompensation, owing to the superimposed hepatitis. The most common clinical sign is irregular hepatomegaly. Visible features of portal hypertension, such as collateral veins, are present in at least 60 % of patients. Clinical evidence of encephalopathy is seen in about one third of patients. Patients who are abstinent may show few laboratory abnormalities [21]. Plasma albumin concentrations are low in approximately half of patients, and macrocytosis is common [21].

While the diagnosis of the histological category above depends on liver biopsy, there are many noninvasive ways to diagnose alcoholic liver disease such as acoustic radiation force impulse imaging, shear wave elastography, MRI elastographic techniques (Fibroscan), and use of serum markers, all of which are covered in review [22, 23].

Low Platelet Count and Coagulopathy

Very low platelet counts often accompany portal hypertension (due to hypersplenism), despite relatively normal liver function tests [24]. There also are direct toxic effects of alcohol on both platelet

production and functionality [24]. The risk of bleeding is higher in patients with infection or coexistent abnormalities of coagulation.

The liver plays a major part in the control of hemostasis by producing vitamin K-dependent clotting proteins; factors II, VII, IX, and X; and proteins C and S. It also has a role in fibrinolysis by protein generation and clearance of active enzymes from the blood. Increased prothrombin time (PTT) is not usually seen in fatty liver or hepatitis. An increased prothrombin time is seen in alcoholic cirrhosis, as a result of decreased synthesis of clotting factors and increased fibrinolysis [25]. Interestingly, a relative decrease in liver production of anticoagulant factors offsets the increase in procoagulant factors in cirrhotics *with compensated disease*; thus, spontaneous bleeding is rare [7]. Thromboelastography (TEG) is a new approach to assessing such balance and importantly can be used to guide blood product replacement [7]. Even cirrhotic patients with a high PTT or INR can develop deep vein thrombosis [26] and in the absence of contraindications should have mechanical (but *not* pharmacological) prophylaxis [7]. Stable patients who are not bleeding and are not undergoing invasive procedures generally do not require therapy for coagulopathy. Patients who are actively bleeding need blood component therapy (red blood cells and platelets), fresh frozen plasma, and cryoprecipitate therapy, together with measures to control the bleeding. Fibrinolysis is common, assessed by TEG and treated with tranexamic acid when bleeding persists despite the measures above [Level V evidence]. When the PTT is very prolonged, protamine may assist in counteracting endogenous heparin-like compounds [Level V evidence] [7]. If patients present with GI bleeding, correction of coagulation abnormalities must also be accompanied by antibiotic therapy (IV ceftriaxone or oral norfloxacin) for up to 5 days [Level V evidence] [27].

Bleeding can complicate invasive procedures such as liver biopsy or invasive hemodynamic monitoring in patients with alcoholic cirrhosis. Risk of bleeding can be diminished by use of sites for insertion of catheters where pressure can be applied to the insertion site to control the bleeding (e.g., external jugular insertion of central

venous line rather than a supraclavicular or subclavian approach). Transthoracic liver biopsies should not be done when the prothrombin time ratio (PTR) or international normalized ratio (INR) is greater than 1.2. Safer alternatives include direct-vision laparoscopic liver biopsy with subsequent coagulation and transjugular liver biopsy, which can be carried out even with an PTR or INR greater than 3 [28]. Particular care must be taken with arterial blood gas sampling, and often insertion of an arterial catheter saves several attempts and reduces the risk of bleeding in patients in the ICU. Intramuscular injections should be avoided because of bleeding risk into muscle.

In the presence of coagulopathy or thrombocytopenia, the insertion of invasive catheters or intracranial pressure monitors should follow prophylactic administration of concentrated clotting factors or fresh frozen plasma, together with platelets if the platelet count is less than $50,000/\text{mm}^3$ [Level V evidence] [25]. Fresh frozen plasma which contains coagulation factors and inhibitors to fibrinolysis is effective for protection against bleeding and correcting the bleeding associated with alcoholic liver disease: it should be given until the measured INR or prothrombin time ratio is less than 1.2 [Level IIB] [29]. It does not contain activated clotting factors and does not precipitate or worsen the disseminated intravascular coagulation that can be seen in these patients [30]. Recombinant factor VII is a therapeutic advance that can fully correct coagulation and platelet function defects in cirrhosis and allow invasive procedures to be performed safely [Level IV] [31].

Infection is a precipitant for the coagulopathy of cirrhosis due to production of low molecular weight heparin-like substances [32]. Infection also increases portal pressure which adds to bleeding risks: thus, early administration of antibiotics reduces early bled rates of esophageal varices [Level IA] [33].

Hemodynamic Effects

Hepatic cirrhosis causes portal hypertension, which is thought to result from an increased resistance to portal venous blood flow through the liver

(backward resistance hypothesis) or from increased portal venous blood flow through the liver (forward flow hypothesis). When the portal circulation is obstructed by cirrhosis, a collateral circulation develops that returns portal blood into the systemic veins. The connection between portal and systemic circulations at the gastroesophageal junction is complex. Turbulent flow in perforating veins between the varices and the periesophageal veins at the lower end of the stomach may explain why esophageal variceal rupture is particularly frequent in this region [34].

In portal hypertension, submucosal arteriovenous communications develop between the muscularis mucosae and dilated precapillaries and veins [35]. This congestive gastropathy causes significant risk of bleeding, especially damage from aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) [35]. Paradoxically, this gastropathy may be increased after successful esophageal sclerotherapy [35]. Decreasing the portal pressure is the main intervention that stops bleeding in portal hypertension [Level I].

Patients with cirrhosis characteristically demonstrate systemic vasodilation and increased cardiac output [36] and are especially vulnerable to small decreases in arterial tone which precipitate hypotension. The greater the degree of hepatic decompensation, the greater the hyperdynamic changes. Several substances including bile acids, endothelins, glucagon, 5-hydroxytryptamine, nitric oxide, and prostaglandins have all been postulated to be vasoactive agents in such patients. What remains unclear, however, is how the vasodilation leads to the state of permanent high cardiac output and increased regional blood flow. The increased cardiac output is often associated with normal filling pressures, but cirrhotic patients have decreased myocardial contractility, which really becomes apparent when afterload is increased and the myocardium is stressed, i.e., "cirrhotic cardiomyopathy" [37, 38]. Alcohol is considered directly cardiotoxic [37, 38]. If surgery is contemplated in a patient with chronic liver disease, it is therefore important to formally assess the cardiac function by echocardiography first. This allows assessment of cardiac function, volume status, estimated right ventricular systolic pressure, and any right to left shunts (e.g.,

hepatopulmonary syndrome – see below) [7]. In patients with liver disease in the ICU, pulse contour systems provide measurement of cardiac output, stroke volume, and volume. Supra-arterial notch Dopplers can monitor changing volume status and cardiac flows. An invasive right heart catheter (e.g., Swan–Ganz catheter) assesses right heart function, pulmonary artery pressures, cardiac output, and pulmonary capillary wedge pressure.

The inotropic and chronotropic responses of the heart to β -adrenergic agonists are impaired in patients with cirrhosis. In one study, cirrhotics showed a nonsignificant increase in stroke volume with infusion of dobutamine [39]. The dose of isoproterenol required to increase the heart rate by 25 beats/min was three times higher in cirrhotics than in controls [40]. β -Adrenergic receptor density is reduced in cirrhotics, and importantly they may not manifest an appropriate tachycardia even when hemorrhaging [41].

Insertion of a transjugular intrahepatic portosystemic shunt (TIPS) (see later) may impair cardiac function and worsen the systemic hemodynamics in patients with cirrhosis [42]. Such patients have increased pulmonary capillary wedge pressure, diastolic dysfunction of the hyperdynamic left ventricle, and decreased systemic vascular resistance. TIPS reduces systemic vascular resistance further by diversion of blood through the splanchnic circulation, and a pronounced increase in central blood volume is seen [43]. TIPS insertion may therefore unmask a coexisting preclinical cardiomyopathy in patients with alcoholic cirrhosis [42].

Infection

A high index of clinical suspicion is needed to diagnose infection as it may be overt in patients with alcoholic liver disease. In patients suspected of infection, early use of broad-spectrum antibiotics (piperacillin/tazobactam) is recommended [Level IB] [44]. Infection may cause acute deterioration in liver function and is associated with poor clinical outcome [7]. The cytokines TNF α and interleukin-6 are key to the endothelial genesis of hepatocellular microcirculatory dysfunction

(characterized by higher portal pressures and reduced hepatic blood flow) that occurs in sepsis [7]. Bacterial infection is also a major risk factor in the development of renal dysfunction in cirrhosis, especially hepatorenal syndrome (see below). Regular surveillance for hospital-acquired infections is required and active measures are needed to prevent them.

A recent case series reports three patients with decompensated cirrhosis and invasive pulmonary aspergillosis (suspected because of worsening respiratory function and development of alveolar opacities) which proved fatal despite therapy with voriconazole [45]. Antigen and serology for aspergillus can be tested in blood and the organism in bronchoalveolar fluid samples.

Adrenal insufficiency is reported in 51–68 % of patients with cirrhosis (high Child–Pugh–Turcotte (CTP) score or MELD scores) and severe sepsis yielding hemodynamic instability and unsurprisingly is a poor prognostic factor [46]. Hydrocortisone treatment may improve survival in such patients, but should not be used unselectively in every ICU patient with cirrhosis [47].

Gastrointestinal Bleeding

Hematemesis from esophageal varices is the most common bleeding presentation of portal hypertension due to cirrhosis, although melena, without hematemesis, may occur from bleeding varices and portal hypertensive gastropathy (see earlier). Big, red varices bleed [48]. Esophageal bleeding is localized to the 5 cm above the cardia of the stomach [48]. This is the area in which sclerotherapy and band ligation, the treatments of choice for acutely bleeding varices, are directed [Level III] [48]. Variceal bleeding is a life-threatening complication of cirrhosis, and initial therapy is aimed at correcting hypovolemic shock and achieving hemostasis at the bleeding site and prevention of complications associated with bleeding (such as airway aspiration, encephalopathy, infections by enteric organisms, hypoxia, renal dysfunction). Excessive transfusion may occur with a consequent risk of continued bleeding or rebleeding [49].

Full discussion of the pharmacologic and endoscopic treatment modalities for acute variceal hemorrhage is beyond the scope of this chapter [50]. Octreotide reduces portal pressure and collateral blood flow and is effective in reducing blood loss and transfusion requirements as initial intervention which can be started quickly and as adjunct to endoscopic measures [Level IV] [51]. It does not have significant adverse effects [Level IV] [51]. Esophageal balloon tamponade is aimed at achieving temporary hemostasis by direct compression of bleeding varices. It is effective in controlling bleeding temporarily, but fatal complications occur in 6–20 % of treated patients, including aspiration pneumonia and airway obstruction [52].

Mortality from esophageal rebleeding is approximately 50 % within 6 weeks of the initial bleed [53]. The risk of rebleeding depends on the severity of the underlying liver disease and degree of portal hypertension. TIPS placement (see later) leads to lower recurrent variceal bleeding rates compared with controls [54]. In a recent meta-analysis comparing TIPS with endoscopic sclerotherapy for acute variceal bleeding, rebleeding in the TIPS group was lower than the sclerotherapy group [55]. However, the risk of developing hepatic encephalopathy was increased in the TIPS over the sclerotherapy group. There was no difference in survival time between the two groups [55].

Ascites

Portal hypertension due to cirrhosis is an important cause of ascites, i.e., detectable free fluid in the peritoneal space. Patients retain salt and water because homeostatic mechanisms become unbalanced, and the dysfunctional liver does not catabolize aldosterone efficiently, i.e., secondary hyperaldosteronism [56]. In the later stages of cirrhosis, there may be reductions in renal blood flow and glomerular filtration rate, as a result of vasoconstriction of the renal arteries. The kidney is less able to excrete free water because of reduced delivery of filtrate to the ascending loop of Henle and hypersecretion of antidiuretic hormone.

Ascitic fluid should be sent for analysis of cell count, total protein, and the serum-ascites albumin gradient (SAAG). A SAAG ≥ 1.1 g/dL supports the diagnosis of ascites due to portal hypertension [57].

The management of ascites is based on the combination of cessation of alcohol, a low-sodium diet (≤ 2 g/day), and the administration of oral diuretics, such as spironolactone (typically 100 mg/day). Resistant ascites often requires paracentesis, with intravascular albumin repletion (6–8 g of salt-poor albumin per liter of ascites removed) [58]. Resistant ascites (and acute esophageal variceal bleeding) has also been treated by insertion of a TIPS [59]. The flow across the shunt can be monitored by Doppler ultrasound and revised should occlusion occur. TIPS seems to be superior to large-volume paracentesis, improves renal function, and can improve the chance of survival without liver transplantation in patients with resistant ascites [Level III] [59]. Milodrine, an α -agonist, causes arterial vasoconstriction and improves the hemodynamics causing ascites [Level V] [60]. β -Blockers, ACE inhibitors, and $\alpha 2$ receptor blockers are no longer recommended in those with ascites as they cause systemic hypotension [58].

Renal Failure and Hepatorenal Syndrome

Most renal failure in cirrhosis is not due to hepatorenal syndrome and survival from all causes currently sits at 71 %. It is therefore important to actively seek sepsis and/or hypervolemia (secondary to GI bleeding, excessive diuretics, or GI fluid losses, e.g., diarrhea) as a cause of renal failure requiring active management [61]. Acute tubular necrosis is often due to a combination of nephrotoxic drugs, such as aminoglycosides, and intravascular depletion [61, 62].

Hepatorenal syndrome (HRS) is common in advanced cirrhosis and is characterized by renal failure due to marked renal hypoperfusion as the result of renal vasoconstriction as a result of arterial vasodilation in the splanchnic circulation [63, 64]. It is characterized by a progressive

increase in the serum creatinine >1.5 mg/dL, oliguria, and low urinary sodium (usually <20 mmol/L) in the presence of normal-sized kidneys and no other identifiable cause of renal failure (European Association for the Study of Liver Diseases). There are limitations to the value of creatinine as a marker of renal function in cirrhosis, and clearance of iohexol has been suggested as a suitable alternative. Pathological confirmation of renal disease such as transvenous renal biopsy is usually reserved for candidates for transplantation [65].

Historically the prognosis in HRS was 50 % alive at 1 month [66]. Management now includes rehydration, then albumin and terlipressin (a vasopressin analogue that improves the splanchnic circulation) [64, 67, 68], or albumin and octreotide plus midodrine [60] with better survival figures. Dialysis and subsequent joint hepatic and renal transplantation have resulted in survival of some patients. The development of HRS after spontaneous bacterial peritonitis (SBP) is best prevented by effective administration of albumin to patients who are hypoalbuminemic together with antibiotics (see the section on SBP for precise guidelines) [62, 69, 70].

Detailed management of hyponatremia is beyond the scope of this chapter but is the subject of a good review [71].

Pulmonary Abnormalities

Before anesthesia and surgery are contemplated, a complete assessment of the respiratory system of any patient with cirrhosis must be made. Many alcoholic cirrhotics are heavy cigarette smokers and develop emphysema, and as a result tidal volume, vital capacity, and functional residual capacity are reduced, and compensatory tachypnea may result in a respiratory alkalosis. Cirrhotic patients are also at higher risk of pneumonia [7]. Aspiration of blood or gastric secretions is particularly frequent in patients with impaired consciousness due to alcohol or hepatic encephalopathy. Prevention of aspiration is based on positioning patients safely, intubation in

comatose patients, and aspiration of gastric contents using nasogastric tubes. High risk includes during hematemesis, emergency endoscopy, and placement of balloon tamponade tubes. Aspiration pneumonia should be actively treated with antibiotics.

The incidence of pleural effusions is 5–6 % in cirrhotics with ascites [72]; 67 % are right sided, and 17 % are left sided. Small holes have been detected in the diaphragm by several methods [72, 73]. They usually respond to diuretics and salt and water restriction [72], but when large, thoracentesis should be performed. Rarely, pleurodesis or TIPS placement is necessary [72]. In any patient who abuses alcohol, but particularly in chronic alcoholics, pulmonary tuberculosis infection is common and must be excluded by chest X-ray and tuberculin testing.

In addition to the usual causes in the critically ill alcoholic, adult respiratory distress syndrome has been associated with sodium morrhuate sclerotherapy [74]. This sclerosant contains several toxic fatty acids and may affect pulmonary hemodynamics [74].

Chronic liver disease may also be complicated by hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN). HPS is characterized by arterial hypoxemia caused by intrapulmonary vascular dilation in cirrhosis [75]. Symptoms are dyspnea and platypnea (shortness of breath on rising to an upright position). Screening is by blood gas analysis ($A-a$ gradient ≥ 15 mmHg), with diagnostic confirmation by transthoracic echocardiography with contrast enhancement by microbubbles seen in the left atrium. The only definitive treatment is hepatic transplantation, but patients can be managed on long-term oxygen therapy. Extracorporeal membrane oxygenation has been used as a bridge to transplantation in a single case report [76]. PPHTN is pulmonary hypertension in the context of portal hypertension. It is said to result from vasoactive substances reaching the pulmonary circulation via portosystemic shunts [77]. Symptoms are dyspnea, chest pain, and syncope. Screening is by transthoracic Doppler echocardiogram ($RVSP > 40$ mmHg), with

diagnostic confirmation by right heart catheterization (MPAP >25 mmHg), MPAOP <15 mmHg, and pulmonary vascular resistance >240 dynes cm^{-2} [75]. Management includes pulmonary vasodilation (IV and inhaled prostacyclin) and long-term oxygen therapy. Ultimately liver transplantation provides a cure.

Spontaneous Bacterial Peritonitis

SBP is a frequent complication in cirrhotic patients with ascites (incidence 7–23 % of hospitalized patients) and has a mortality of 30–50 % [78]. All hospitalized patients with ascites should have a diagnostic paracentesis performed, even if they are in the hospital for an unrelated reason. The diagnosis is made presumptively on the basis of abdominal pain or worsening ascites or a polymorphonuclear cell count in ascitic fluid greater than 250 cells/mm³. The organism responsible is isolated in 60–70 % of cases. This requires that samples be taken into blood culture bottles rather than sterile plastic universal tubes [79]. The current treatment of choice is cefotaxime 2 g every 8 h [Level V], but local antibiotic guidelines should be consulted. The remaining 30 % are considered culture negative but are still treated with antibiotics because of the risk of peritonitis and death if SBP is left untreated [79]. The SBP resolution rate ranges from 70 % to 90 %, and hospital survival is 50–70 %. Risk factors for persisting SBP include MELD score >25, SAAGb >1.5, and positive culture [80].

Despite the resolution of infection, SBP may trigger severe complications, such as renal failure, gastrointestinal bleeding, and hepatic insufficiency [81]. The development of hepatorenal syndrome after SBP can be prevented effectively by administration of albumin at a dose of 1.5 g/kg at the time of diagnosis, followed by 1 g/kg on day 3, together with antibiotics [Level IB] [69]. Prophylaxis against future SBP after the first episode should be undertaken with norfloxacin or trimethoprim/sulfamethoxazole [Mostly IA level evidence] [64]. Cirrhotic patients who present with bleeding should also receive SBP antibiotic

prophylaxis with either IV ceftriaxone or oral norfloxacin for 7 days [Mostly IA level evidence] [64].

Encephalopathy

Chronic hepatic encephalopathy is a potentially reversible complex neuropsychiatric disorder usually precipitated by dietary indiscretions or accumulation of toxic substances not cleared by the failing liver, GI bleeding, infections, hyponatremia, or use of sedative medications [82]. There are also changes to permeability in the blood–brain barrier, to neurotransmitter concentrations, and cerebral metabolism in patients developing encephalopathy. Characteristically it includes a triad of asterixis, confusion, and hyperammonemia. Encephalopathic stages are defined by the West-Haven criteria as 0 = normal, 1 = mild, 2 = lethargy, 3 = somnolence-to-stupor, and 4 = coma [82].

In patients who develop encephalopathy, it is important to exclude bacterial infections or gastrointestinal bleeding as a precipitant [83]. Most bacterial infections in cirrhotic patients are hospital acquired: urinary tract infections, SBP, respiratory tract infections, and bacteremia [84]. Encephalopathy is treated with lactulose to increase GI transit time and/or rifaximin [82, 85] to reduce ammonia production. In the case of deep encephalopathy, in addition to the above measures, oral intake is withheld for 24–48 h, and intravenous glucose and thiamine are given until improvement occurs. Enteral nutrition can be started if the patient appears unable to eat after this period; this is started at 0.5 g/kg/day and increased up to 1.5 g/kg/day gradually.

Abnormal Glucose Metabolism

Most patients with cirrhosis show impaired glucose tolerance [86], and there is a higher prevalence of overt diabetes in patients with cirrhosis than in the general population. Most are resistant to the effects of insulin, particularly on skeletal muscle. These patients also tend to have

hyperinsulinemia [87] because of a combination of increased insulin secretion and reduced insulin clearance (due to hepatocellular dysfunction or portosystemic shunting). Glucose intolerance is also surprisingly common in fatty liver associated with alcohol use.

Patients with postprandial hyperglycemia and minor increases of fasting blood glucose should be treated with a low-sugar diet. Tight blood sugar control is not desirable because of the risk of hypoglycemia; hence, keeping the blood glucose in the 140–180 mg/dL (8–10 mmol/L) range is desirable. If persistent postprandial glucose elevations are above this range, then the patient should receive an oral hypoglycemic. Biguanides however (e.g., metformin) should be avoided in patients with liver disease because they are at risk for serious drug-induced lactic acidosis. Sulfonylureas (e.g., tolbutamide and glipizide) can be used cautiously in alcoholic patients, but glibenclamide is best avoided because it can cause prolonged hypoglycemia. Patients who require insulin are managed with injections of short-acting insulin 30–45 min before each meal. Patients with liver disease are more prone to fasting and nocturnal hypoglycemia, and longer-acting insulins should be avoided.

Recent evidence demonstrates that a subclinical impaired glucose tolerance (and independently Child–Pugh B score and high MELD scores) was associated with lower survival in liver disease [88].

Muscle Wasting and Nutritional Deficiencies

Alcoholic liver disease is characterized by muscle wasting and nutritional deficiencies (e.g., vitamins A, D, E, and K) which are associated with increased morbidity and mortality [89–91]. Nutritional therapy helps to reverse these. Previously a protein-restricted diet was used to prevent hepatic encephalopathy, but the American Association for the Study of Liver Diseases (AASLD) and the American College of Gastroenterology currently recommend supplementation for nutritional deficiencies, frequent

interval feeds especially night and morning snacks, and enteral feeding for severe ALD [92]. A recent systematic Cochrane review however questions whether there is sufficient well-designed clinical trial evidence to justify this widely adopted clinical approach [91]. Such a diet would include 1.2–1.5 g protein/kg per day and 35–40 kcal/Kg [92]. However, the standard needs to be altered depending on the patient's race, their daily activity, degree of protein–energy malnutrition, glucose intolerance, and obesity [93]. Interestingly high body mass index (BMI) is an independent predictor of decompensation of cirrhosis, together with the hepatic venous pressure gradient and serum albumin concentration [94].

In those with protein metabolism disorder, branched-chain amino acid granules are often prescribed in addition to a 1.2–1.5 protein/kg diet [93]. The role of probiotics remains to be fully evaluated [95]. Tight sugar control is not desirable because of the risk of hypoglycemia; hence, a 140–180 mg/dL (8–10 mmol/L) range of blood glucose is desirable. Zinc replacement is often given to patients with cirrhosis at a dose of 20–50 mg elemental zinc three times per day [96]. There is not current evidence to support giving selenium replacement routinely.

Alcoholic Ketoacidosis

In alcoholic patients, metabolic acidosis can be due to lactic acidosis associated with sepsis or thiamine deficiency, alcoholic ketoacidosis (AKA), diabetic ketoacidosis, or methanol or ethylene glycol poisoning [97]. AKA occurs in alcoholics who have had a heavy drinking bout with subsequent vomiting, dehydration, starvation, and β -hydroxybutyrate-dominated ketoacidosis [98]. Awareness of the syndrome, together with taking a proper history, clinical examination, and routine laboratory tests, leads to the diagnosis [98].

AKA and toxic alcohol ingestion can be difficult to distinguish on initial presentation. A high osmolar gap (e.g., >25 mmol/L) associated with increased anion gap acidosis is a strong indicator of methanol or ethylene glycol intoxication but is not

specific, and history or analytic confirmation (e.g., blood β -hydroxybutyrate-to-acetoacetate ratios) is crucial in determining the cause [98–100]. Ethylene glycol and methanol poisoning are discussed in detail in chapters on these substances.

In addition to a history of diabetes or alcoholism, patients with diabetic ketoacidosis are characterized by higher plasma glucose concentration (32 mmol/L [576 mg/dL] versus 6.6 mmol/L [119 mg/dL]) and lower β -hydroxybutyrate-to-acetoacetate and lactate-to-pyruvate ratios compared with patients with AKA [101]. If the serum glucose level (in mmol/L) is less than the anion gap, the diagnosis of AKA should be considered [102]. The initial hormone profile is characterized by decreased blood insulin concentrations in both conditions.

AKA is a cause of unexpected death in a chronic alcoholic with little or no alcohol in the blood, increased acetone concentration in the blood, and no specific features on autopsy or toxicology [103]. The diagnosis often is missed unless it is sought out specifically by analysis.

The treatment of AKA is replacement of fluid, glucose, electrolytes (especially potassium), and thiamine. Insulin or sodium bicarbonate should be avoided [98]. Some patients have serious coexisting acute illnesses, and treatment of these is also essential.

Altered Drug Metabolism

Many factors determine the elimination of a drug, including its rate of absorption, distribution, plasma protein binding, and metabolism and elimination, particularly by the liver and kidneys. The extraction ratio of a drug across an eliminating organ can be calculated by the clearance. Drugs are classified as highly cleared by the liver (>70 % cleared at each passage through the liver), poorly cleared (<30 %), or intermediate [104]. Hepatic clearance has an important effect on the extent to which drugs become available in the systemic circulation when given orally. Highly cleared drugs have high “first-pass” removal and low systemic availability. The main factor

responsible for the reduced clearance of drugs metabolized by the liver in patients with cirrhosis is impaired ability of the liver to remove the drug from the blood. Possible mechanisms are intrahepatic shunts, portosystemic shunts, reduced amounts of drug-metabolizing molecules, and reduced hepatic uptake of drugs. The metabolic capacity of the liver is not a homogeneous entity but depends on the metabolic pathways involved. Oxidation (phase I) takes place in the centrilobular location [105] and is more prone to hypoxia and more affected in liver disease than conjugation (phase II), which is periportal in location and well preserved in liver disease [105].

Other mechanisms that could be responsible for altered drug kinetics in chronic liver disease include altered protein binding and acid–base or electrolyte changes. Many drugs commonly used in critical care units have reduced clearance or increased half-life in cirrhosis, e.g., ampicillin (give the normal dose), chlorthalidone (reduce the dose by 50 % and prolong the interval to every other day or every third day), diazepam (prolong the dose interval), furosemide (efficacy may be reduced due to low albumin, increase the dose), lorazepam (normal dose), and *N*-acetylcysteine (give normal dose) [104, 106–108]. A significant increase in half-life calls for prolongation of the dosing interval, whereas a decrease in clearance calls for a reduction of dose. Whether a dose reduction is necessary also depends on the toxicity of a drug. For adequate antibiotic coverage in a patient with SBP, the dose of cephalosporin does not require reduction. In contrast however for aminoglycosides, the dose and dosing interval must be reduced.

Other drugs have high clearance in cirrhosis (e.g., lidocaine (dose reduction), morphine (can be used in mild-to-moderate liver disease), metoprolol (normal dose)) [105, 108]. Even moderate cirrhosis significantly reduces the clearance of alfentanil, which also must be used with care [109]. Atracurium is the muscle relaxant of choice in liver disease because its metabolism is independent of hepatic metabolism, occurring by Hoffman elimination and ester hydrolysis [110]. Vecuronium is well tolerated by cirrhotics in

small doses, but with doses of 0.2 mg/kg, recovery is prolonged [110]. An increased volume of distribution in cirrhotic patients means that a higher dose of most muscle relaxants may be needed.

Isoflurane is the inhalational anesthetic of choice in liver disease because it undergoes minimal biotransformation, is least hepatotoxic, and maintains hepatic oxygen supply and uptake better than halothane or enflurane, although there have been reports of postoperative elevation in liver function tests even with this agent [111]. Halothane is best avoided because of its known hepatotoxicity, which, although rare, is unpredictable [112]. A recent meta-analysis showed that propofol produces more rapid and effective sedation and recovery than midazolam for endoscopy [113].

Adverse drug reactions frequently occur in patients with liver disease, and it is important to carefully consider any use of medication in these patients. Prostaglandin inhibitors, such as NSAIDs, including selective COX-2 inhibitors, reduce renal perfusion, particularly in patients who are intravascularly depleted, and may precipitate renal failure. Aminoglycoside antibiotics are particularly nephrotoxic in patients with liver disease [114]. They should be used only when absolutely necessary, and their use must be stopped if nephrotoxicity due to acute tubular necrosis develops. The inadvertent use of sedatives, analgesics, or diuretics can precipitate encephalopathy, hepatorenal syndrome, and gastrointestinal hemorrhage in patients with liver disease.

Alcohol Withdrawal

Obtaining an alcohol consumption history is crucial in identifying individuals at risk from withdrawal. Anyone who drinks more than 2–3 units/day (see Table 1 for calculation of units) is at risk from withdrawal, but usually it is clinically obvious with ceasing alcohol abruptly after routine ingestion of the equivalent of a bottle of spirits per day, which is characterized by autonomic hyperactivity and agitation/delirium [115]. Approximately 40 % of individuals who drink excessive amounts of alcohol, if hospitalized, have the potential to experience symptoms of alcohol withdrawal, and a high index of clinical suspicion and vigilance is required [115]. The differential diagnosis of acute alcohol withdrawal from other conditions is given in Table 2 [115].

Most patients who drink heavily manifest a minor withdrawal symptom complex of hyperactivity, hypertension, nausea, and tachycardia. Symptoms peak between 10 and 30 h and subside by 40 h after the last alcoholic beverage is ingested. Minor withdrawal symptoms often do not require specific therapy.

The early administration of benzodiazepines may prevent progression of the alcohol withdrawal syndrome and it remains the gold standard treatment for withdrawal [115]. Seizures may occur in the first 12–48 h and typically occur in bursts of two and can be treated successfully with diazepam (10–20 mg intravenously) or lorazepam (2–4 mg intravenously). Delirium tremens is

Table 2 Differentiation of acute alcohol withdrawal from other events altering consciousness levels

Parameter	Alcohol withdrawal	Wernicke's syndrome	Subdural hematoma	Hypoglycemia	Hepatic encephalopathy
Consciousness level	Awake but agitated	Variable	Fluctuates	Variable	Reduced
Hallucinations	Yes	Yes	No	No	No
Anxiety	Yes	No	No	Yes	No
Speech	Rapid, incoherent	Slurred (cerebellar)	Normal	Slurred	Slurred
HR/BP	Raised	Tachycardia, BP normal	Slow pulse, hypertension	Tachycardia, hypotension	Normal
Sweating	Yes	No	No	Yes	No

Table adopted, with adaptation, from Ref. [116] (Data from Mayo-Smith MF [117])
BP blood pressure, HR heart rate

Table 3 Clinical Institute Withdrawal Assessment of Alcohol Scale Revised [119]

Components of the scale
Nine items scored on a scale of 0 (no symptoms) to 7 (most severe symptoms)
Nausea or vomiting, tremor, paroxysmal sweats, anxiety, tactile disturbances (itching, numbness, bugs under the skin), auditory disturbances (sensitive to sound, hallucinations), visual disturbances (sensitivity to brightness, hallucinations, headache, agitation)
One item scored on a scale ranging from 0 (no symptoms) to 4 (disorientated to place or person)

characterized by coarse tremors, agitation, fever, tachycardia, profound confusion, delusions, and hallucinations [118]. Delirium tremens occurs in <5 % of individuals withdrawing from alcohol and starts 60–80 h after the last alcoholic beverage, lasting from 1 to 8 days [117, 118]. Hyperpyrexia, ketoacidosis, and profound circulatory collapse may develop, and if untreated, the syndrome carries a mortality of 15 % versus 1 % in patients who are treated [116, 117].

Benzodiazepines (chlordiazepoxide, diazepam, or lorazepam) are good pharmacologic treatments for alcohol withdrawal, including delirium tremens. The duration of action, rapidity of onset, metabolism, and cost of the specific agent determine the choice of agent. Dosage should be individualized, based on withdrawal severity scores, comorbid illness, and history of seizures [115, 117]. As a guide, the daily doses employed in the early phase of management are chlordiazepoxide, 100 mg; diazepam, 40 mg; and lorazepam, 8 mg, with much higher dose needed for severe cases. Little or no modification of dose is needed in minimal liver disease, but if there is significant liver disease, the initial dose of longer-acting benzodiazepines should be reduced by about 25 %.

An alcohol withdrawal rating scale, e.g., Clinical Institute Withdrawal Assessment of Alcohol Scale [119], is used to monitor time course and severity of clinical symptoms (Table 3). On this scale scores below 8 rarely need withdrawal medications [118], 8–15 need modest benzodiazepines, and scores above 15 indicate close monitoring of alcohol withdrawal seizures and delirium tremens, especially if the systolic BP is

>150 mmHg or there is tachycardia [118]. There is good evidence that pharmacologic management of alcohol withdrawal is effective [116, 117]. Pharmacologic management of alcoholism, however, is only one component of the management of alcohol withdrawal. Provision of a calm, quiet environment, reassurance and attention to fluid and electrolyte disorders, and comorbidities are equally important.

The management of delirium tremens the management includes control of seizures etc with benzodiazepines in a safe environment [120]. Severe withdrawal may necessitate ICU admission and use of propofol or barbiturates [115]. Other drugs such as β -Blockers and α_2 agonists (clonidine and dexmedetomidine) can be used as adjunctive therapy to relieve some of the more distressing autonomic symptoms and delirium that accompany alcohol withdrawal [115, 117, 121]. Use of carbamazepine, sodium valproate, baclofen, gabapentin, and ketamine remains under investigation for AWS [115, 122, 123].

Patients receiving treatment for alcohol withdrawal also should receive group B vitamins (intravenously or orally). The administration of vitamin B₁ (thiamine) prevents Wernicke's encephalopathy (characterized by confusion, ataxia, nystagmus, and short-term memory defects). In patients where Wernicke's encephalopathy is suspected, the recommended doses of thiamine are 500 mg IV tds for 5 days, with multivitamins [124]. Thiamine is discussed in greater detail in the chapter on that agent in the "Antidote" section. Alcohol withdrawal is discussed further in another chapter (► Chap. 27, "Withdrawal Syndromes").

Prognostic and Ethical Considerations for Acute Deterioration of Patients with Alcoholic Liver Disease and the ICU

Acute deterioration of patients with chronic liver disease presents as multiple organ failure requiring admission to ICU. Alcoholic hepatitis and variceal hemorrhage are common precipitants [7]. Management focuses on preventing further deterioration in liver function, reversing

precipitants and supporting failing organs. Artificial and bioartificial liver support systems have not yielded significant improved survival in such patients, and for a select few hepatic transplantation provides better survival [7].

Historically patients in an ICU with chronic liver disease and critical illness had a mortality of >60 % [125, 126] or >89 % [127]. A more recent report including more than 16,000 ICU patients with cirrhosis in the UK found an overall mortality of 65 %, and this rose to 90 % with sepsis, if >1 day of renal and respiratory support were needed [128]. In contrast in a less highly selected group of patients with chronic liver disease (i.e., two nonliver transplant centers), the ICU mortality rates of 38 % were reported [6].

Prognosis is determined by the number of organs failing (SOFA score), the presence of infection, and the degree of liver dysfunction (Child–Turcotte–Pugh or MELD) [7]. EASL guidelines recommend organ support for patients with pre-morbid MELD <15, but not if the MELD is >30 and there are ≥ 3 organs failing [128]. The problem is that in acute illness, MELD can change significantly [6]. Thus, it appears that liver-specific scoring systems alone are less accurate in predicting outcome than the more generic scoring systems alone (e.g., simplified organ failure assessment (SOFA) or APACHEII) [129], and estimates of survival appear more predictive if used after 48 h of supportive care [130]. It is therefore vital to concurrently use the three predictors articulated by Olson et al. [7] together to determine the prognosis [130]. In essence, it is our ability to manage the underlying acute illness that is the critical prognostic factor [5] and hence determines the appropriateness or otherwise of ICU care.

If a patient deteriorates in ICU (e.g., their vasopressor requirement escalates, ventilatory support needs to be significantly increased, or they develop unresolvable acidosis), this normally indicates the need to discuss with the family a decision either not to increase therapy or withdraw it. EASL guidelines recommend that “the persistence of 3 or more organ failure after 3 days spent in ICU” should lead to withdrawal of treatment [128]. Ideally end-of-life wishes and

care are pre-planned and discussed with the patient with chronic liver disease and their family prior to acute deterioration and the possible need for ICU admission. Palliative care can be used early in terminal illness together with life-prolonging therapies [131].

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Along with active supportive care, judicious gastrointestinal decontamination, and antidotal therapy, elimination enhancement techniques should be considered in the comprehensive management of any poisoned patient. Elimination enhancement techniques are defined as any procedure that accelerates the endogenous clearance of poison already absorbed and located either in the blood or tissue compartment. Corporal techniques provide their effects inside the body and include multiple-dose activated charcoal (MDAC), resins, and urine pH manipulation, as discussed elsewhere. Extracorporeal treatments (ECTRs) occur in a circuit outside the body (with the exception of peritoneal dialysis) and include hemodialysis, hemoperfusion, hemofiltration, and plasma exchange [1]. As the prognosis of most toxic exposures remains excellent with supportive measures alone, only a small minority of poisonings benefit from active elimination enhancement; for example, MDAC, urine alkalization, and hemodialysis were only used in 0.06%, 0.5%, and 0.1%, respectively, of patients reported to the US poison control centers [2]. Although the large proportion of the literature reviewing the efficacy of elimination enhancement techniques is derived from human case reports, evidence-based and consensus-based recommendations are now available for extracorporeal treatments [3–16].

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Principles and Factors Influencing Poison Removal During Extracorporeal Treatments

The elimination of a poison by an ECTR depends on its physicochemical and pharmacological properties as well as the modality chosen for removal and the operational settings of the technique. Extracorporeal elimination of a poison is only possible if all of the following are present: (1) it can be extracted from the blood compartment, (2) a significant proportion of total body stores can be eliminated, and (3) extracorporeal clearance contributes to a significant extent to endogenous clearance. The first condition is dependent on the molecular size and protein binding of the poison, and it is correlated to the extraction ratio (ER) which can be calculated as $(A-V)/A$, where A represents the inflow (or prefilter) plasma concentration and V represents the outflow (or postfilter) plasma concentration. An extraction ratio of 1.0 implies complete elimination of a poison from the plasma through the extracorporeal circuit. The second condition relates to its volume of distribution (VD), and the third depends on the relative importance of ECTR versus endogenous clearance of poison.

Therapy-specific factors to consider include the process of poison removal (e.g., diffusion, adsorption, convection) as well as the parameters chosen for a specific technique such as the dialysis membrane (dialyzer surface area, membrane pore structure), characteristics of the filter/cartridge, rate of blood flow, and rate of effluent flow [17].

Poison-Related Factors

Molecular Size

Poisons with a molecular size below 1,000 Da will be removed by any of the three processes but best by diffusion. Poisons larger than 1,000 Da will be better removed by convection or adsorption [18], although present-day hemodialysis is usually capable of clearing poisons with a size up to 10,000 Da. Hemofiltration can remove poisons up to 50,000 Da. Poisons with very large molecular sizes (>100,000 Da) can only be removed by

adsorption (hemoperfusion) or by centrifugation/separation (Therapeutic plasma exchange).

Protein Binding

Poisons that are extensively bound to serum proteins cannot be removed significantly by hemofiltration and hemodialysis as the size of the poison-protein complex exceeds that of the pores of the hemofilter/dialyzer. During hemoperfusion, however, the adsorbent column (activated charcoal or resin) competes with plasma proteins for the poison and can therefore be an option for removal of protein-bound poisons. These principles are not universal; for example, in toxic concentrations, there may be saturation of the protein binding sites (e.g., valproic acid), increasing the fraction of unbound poison, which then can be more readily removed by hemodialysis. Further, if the binding constant of the poison to protein is low, the removal of the unbound poisons will result in rapid dissociation of the bound portion, resulting in a continuous pool of dialyzable substrate; phenytoin is one such example [19].

Volume of Distribution

A poison's volume of distribution is the apparent volume into which it is distributed at equilibrium assuming no clearance has occurred and assuming the body is a single compartment of homogenous water. The volume of distribution may be calculated by dividing the total poison content in the body by its concentration in the blood compartment.

Drug and poisons that distribute extensively in tissue (e.g., tricyclic antidepressants, digoxin) have a high VD. Conversely, those that distribute in total body water (e.g., methanol) have a $VD = 0.6\text{--}0.7$ L/Kg, while those exclusively confined to the blood compartment (e.g., rituximab) have a $VD = 0.06$ L/Kg. As ECTRs only remove poisons from the intravascular space, ECTR will not significantly enhance elimination of poisons with a high VD. For example, due to its low protein binding (25%) and relatively low molecular size (780 Da), digoxin easily crosses the dialyzer; however, because of its high VD (5–7 L/kg), less than 5% of total body burden of digoxin will be removed in a 6-h dialysis session. Many publications still erroneously conclude that a poison with

a high volume of distribution is amenable to extracorporeal clearance solely based on a high clearance or a rapid reduction of serum concentrations [20, 21]. Rarely, ECTR may be considered for poisons with a high VD: examples of these include situations where the poison has not yet fully distributed into tissues [5] and those where the toxic compartment is the blood [22].

Endogenous Clearance

Extracorporeal removal will not be useful if endogenous clearance of a poison (via metabolism and native elimination routes) far outweighs that which can be obtained via ECTR [23]. For example, because the hepatic clearance of lidocaine ($>1,000$ mL/min) greatly exceeds the clearance obtained with dialysis (150 mL/min), extracorporeal elimination of lidocaine is never indicated. This is also true of many street drugs. Any impairment in endogenous metabolic and elimination route will lower the decisional threshold to initiate dialysis, as the relative contribution of ECTR clearance versus endogenous clearance will become greater.

ECTR-Related Factors

Factors specific to the ECTR which affect poison elimination include the process of removal, characteristics of the dialysis membrane (i.e., material, surface area, porosity), the concentration gradient across the membrane, the blood flow rate through the dialyzer, and the dialysate/ultrafiltrate flow rates. Some hemoperfusion cartridges become saturated after a few hours and need to be replaced [24]. These characteristics are discussed later in this chapter where the different extracorporeal modalities will be further described.

Available Extracorporeal Treatments to Enhance Elimination of Poisons

Processes of Poison Removal

These can usually be classified by their process: diffusion (hemodialysis, peritoneal dialysis), convection (hemofiltration), adsorption

(hemoperfusion), centrifugation/separation (therapeutic plasma exchange) [17, 25].

Diffusion (Hemodialysis)

During diffusion, poisons transfer passively from one compartment (blood) to another (dialysate), separated by a semipermeable membrane down a concentration gradient (Fig. 1a). Dialysate flows countercurrent to the blood flow. Characteristics of a poison that is removable by diffusion are a low molecular size ($<10,000$ Da) and a low protein binding ($<80\%$). Specific components of the dialysis system will impact poison clearance; these include membrane type, its surface area, and blood and dialysate flow rates (Table 1). The development of synthetic high-flux and high-efficiency membranes now permit removal of larger poisons which were considered nondialyzable 20 years ago [18]. Increasing both the rates of dialysate and especially blood flow result in greater diffusion and elimination of the poison and should therefore always be maximized in poisoning situations [17].

Convection (Hemofiltration)

During convection, solute and solvent are removed by solvent drag and substituted by a physiological solution (Fig. 1b). Unlike diffusion, this process requires energy via a hydrostatic pressure gradient. Compared to diffusion, convective transport allows removal of poisons with larger molecular size (up to 50,000 Da) but performs slightly worse for smaller poisons [17]. Because most common poisons have a low molecular size ($<1,000$ Da), convection does not offer any advantage over diffusion for the majority of poisonings.

Adsorption (Hemoperfusion)

During adsorption, blood circulates through an extracorporeal circuit equipped with a charcoal or a resin cartridge onto which poison is trapped (Fig. 1c) [26]. Unlike diffusion, adsorption is not as limited by molecular size, lipid solubility, or protein binding of the poison. Alcohols and most metals, however, are poorly adsorbed to columns.

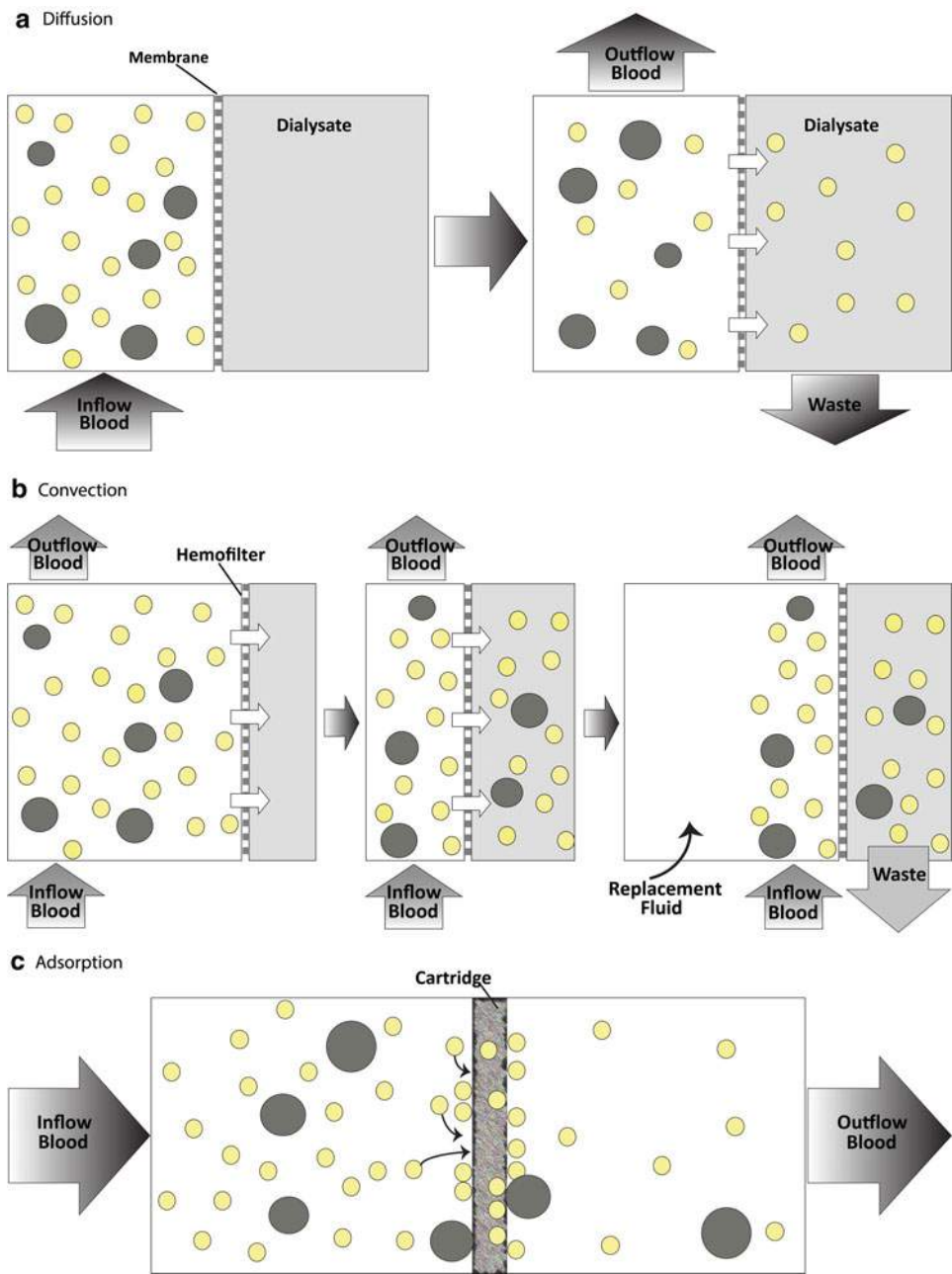


Fig. 1 Mechanisms of poison removal during ECTR (During diffusion, poison follows a concentration gradient. During convection, poison and solvent are eliminated

actively by a pressure gradient. During adsorption, poison is trapped within the cartridge. Notice that larger poisons do not get cleared as well during diffusion)

Table 1 Summary of extracorporeal treatments

ECTR	Process	Molecular size cutoff (Da)	Protein binding cutoff	Relative cost	Complications	Comments
Hemodialysis	Diffusion	<10,000	<80%	+	+	Corrects uremia and acid–base/E+ disorders
Hemoperfusion	Adsorption	<50,000	<95%	++	+++	Saturation of cartridge
Hemofiltration	Convection	<50,000	<80%	++	+	Corrects uremia and acid–base/E+ disorders
Therapeutic plasma exchange	Centrifugation/ Separation, Filtration	<1,000,000	None	+++	+++	
Albumin dialysis	Diffusion, Adsorption	<300,000	None	++++	++	Liver replacement support
Exchange transfusion	Centrifugation/ Separation, Filtration	None	None	++	++	Easier in neonates, corrects hemolysis
Peritoneal dialysis	Diffusion	<10,000	<80%	++	++	

All extracorporeal treatments above are less likely to be useful for poisons that have a high VD or a high endogenous clearance

Specific Extracorporeal Treatments

Hemodialysis, Hemoperfusion, and Hemofiltration

Worldwide, extracorporeal treatments are mainly used for the treatment of kidney failure. Hemodialysis and peritoneal dialysis are the preferred modalities for end-stage renal disease, while hemodialysis and continuous renal replacement therapies are usually preferred for acute kidney injury. In poisonings, intermittent hemodialysis has several distinct advantages over other extracorporeal modalities [27]: poison removal occurs rapidly, it corrects many complications associated with severe poisonings – acute kidney injury (AKI), volume overload, acid–base abnormalities, electrolyte disturbances, and even hypothermia. Hemofiltration provides all of these advantages but is less available as an intermittent therapy.

In contrast, hemoperfusion does not correct uremia or electrolyte disorders, requires more systemic anticoagulation than dialysis, and is limited to blood flows <350 mL/min because of the risk of hemolysis [28]. Furthermore, cartridges cost

severalfold more than dialyzers and need to be replaced every 2–4 h, as they become saturated. Finally, new dialysis membranes provide poison clearances comparable to that achieved by the best adsorbent columns. For example, clearances for both theophylline and phenobarbital, poisons for which hemoperfusion was historically considered superior to dialysis, can easily reach > 150 mL/min with dialysis [26, 29, 30]. For these reasons, hemodialysis is generally preferred in almost all settings where hemoperfusion is indicated [26]. These considerations are reflected by historical trends in ECTR choice for poisonings (Fig. 2) [31–34].

Adverse events and risks associated to ECTRs are relatively uncommon; systemic hypotension is often reported although this is usually encountered in patients with renal failure who require fluid removal. As poisoned patients rarely require fluid removal, the likelihood of hypotension is probably most related to the effect of the poison rather than the ECTR itself. The incidence of complications for hemoperfusion is higher, although these are usually reversible [30]: the nonselective adsorption of certain cells and

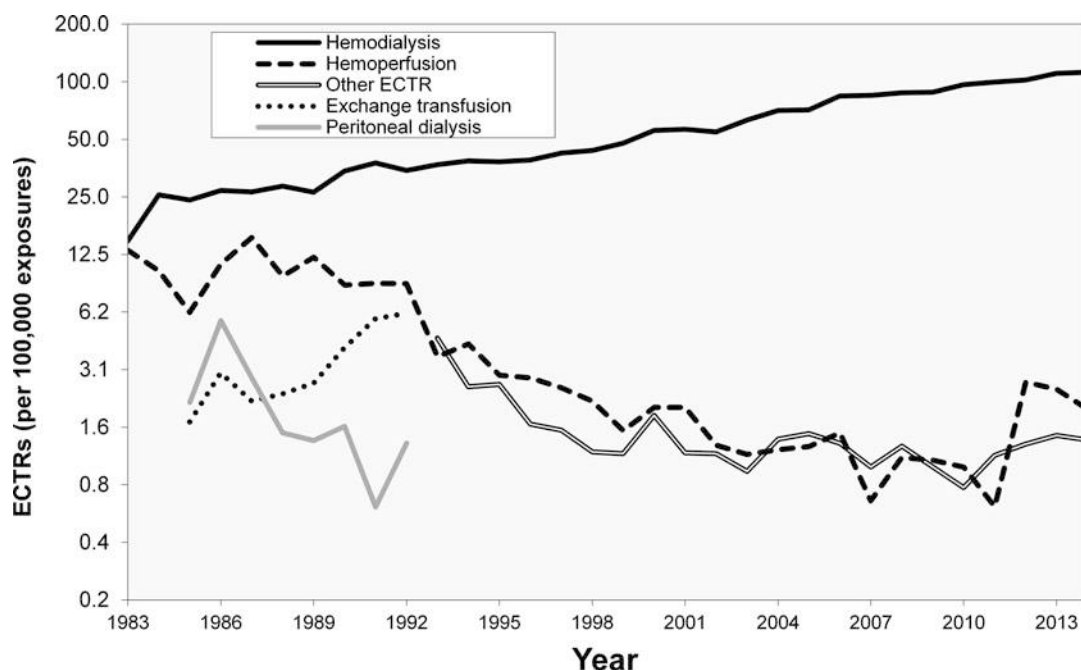


Fig. 2 ECTR trends in the USA from 1983 to 2014 (The Y-axis is a logarithmic scale)

molecules result in a fall in the concentration of platelets ($\cong 30$ – 50%), white blood cells ($\cong 10\%$), serum fibrinogen, fibronectin, calcium, or glucose [35, 36].

Continuous Renal Replacement Therapy

Continuous renal replacement therapies are popular modalities for the management of AKI. Continuous renal replacement therapies are a heterogeneous classification of ECTRs that share common characteristics: they are most often dispensed in the ICU setting, their blood and effluent flow are usually lower than those provided by intermittent therapies, and they are prescribed continuously until the patient recuperates or expires. Continuous renal replacement therapies include continuous arteriovenous hemodialysis, continuous venovenous hemodialysis, continuous arteriovenous hemofiltration, continuous venovenous hemofiltration, continuous arteriovenous hemodiafiltration, and continuous venovenous hemodiafiltration. Venovenous therapies have for the most part replaced arteriovenous therapies as they only require 1 dual-lumen catheter (instead of 2 single lumen catheters for

arteriovenous therapies), are not as dependent in systemic blood pressure, and have a lower incidence of thrombosis and embolization.

The role of CRRTs in the management of acute poisonings remains uncertain [37]. The solute clearance with continuous modalities is usually two to three times lower than that attained by intermittent therapies. Further, the hemodynamic benefits of CRRTs in poisoned patients are limited as net fluid removal is rarely required, unless AKI or pulmonary edema also develops. Although it has been suggested that CRRT may be preferred to avoid the sudden increase in poison concentration seen after discontinuation of intermittent therapies (“rebound”), the benefit of this remains uncertain, unless rebound is caused by ongoing absorption of poison from the gut.

Peritoneal Dialysis

There is little role for peritoneal dialysis in acute poisoning. It is an inefficient method of toxin elimination, achieving a maximum clearance of 10–15 mL/min (less than one tenth of that achievable by hemodialysis) [25]. Peritoneal dialysis has no advantages over the other extracorporeal

treatments in poisoning situations, although it may still be considered in the case of infants in whom hemodialysis may be too cumbersome to perform.

Therapeutic Plasma Exchange and Plasmapheresis

Plasmapheresis is a process in which plasma is separated either by filtration or centrifugation from withdrawn blood, and formed elements are retransfused back to the patient. In therapeutic plasma exchange (TPE), the removed plasma is discarded and replaced by 5% albumin, fresh-frozen plasma, cryoprecipitate-poor plasma, or stored plasma. Clearance during TPE is limited to 50 mL/min [25, 38]. The role of TPE in the treatment of acute poisoning is not well defined, but this method should only be considered for poisons which are very highly protein-bound (>95%) or in poisons that are larger than the accepted cut-offs for hemofiltration or hemoperfusion (>50, 000 Da) [39–41]. Adverse outcomes from TPE involve complications associated with placement of the vascular access, bleeding, hypocalcemia, and hypersensitivity reactions to the replacement plasma proteins [42, 43].

Exchange Transfusion

Exchange transfusion is a treatment in which apheresis is used to remove the patient's red blood cells and replaced with transfused blood products. Its role in poisoning is unclear but may be considered in poisons that cause massive hemolysis (e.g., sodium chlorate), in resource-poor settings where no dialysis machinery exists, or in infants, as it is technically less cumbersome to use than hemodialysis in this population.

Extracorporeal Liver Assist Devices (Albumin Dialysis)

Extracorporeal liver assist devices are ECTRs designed to replace failing liver function in the context of acute hepatitis and cirrhosis, especially as a bridge to liver transplantation or remission. There are several variations of these devices, but they all share a common principle in that an albumin-containing effluent competitively

competes with serum proteins for binding of poison. Theoretically, these devices are more performant at removing albumin-bound poisons than classical diffusive and convective techniques. However, preliminary clearance data does not show any superiority of these techniques in poisonings to theophylline, valproic acid, or phenytoin [44–46]. Because these procedures are expensive (>\$8000 per treatment in the USA) and seldom available, their application for poisoning situations remains unknown. Table 1 summarizes the various extracorporeal treatments available for poison removal.

General Indications for Extracorporeal Removal of Poisons

The EXTRIP (EXtracorporeal Treatment In Poisoning, <http://www.extrip-workgroup.org/>) workgroup [3, 4] have published guidelines for the use of blood purification for 16 key poisons [5–10, 12, 15, 47, 48]. For poisons not covered by these clinical recommendations, a comprehensive risk assessment that includes weighing the cost-benefit ratio for ECTR is required, which can be summarized in Fig. 3.

Absolute indications for ECTR include the following (all must be present) [27]:

1. *The poisoning exposure must be severe.* The exposure to a specific poison must be significant enough to warrant the cost and complications associated with ECTR. Obviously, a patient with life-threatening clinical signs (status epilepticus, respiratory depression, ventricular dysrhythmias), especially if prolonged, will classify as severe. In rare cases, a poison may produce delayed effects (methanol, paraquat); monitoring of levels might therefore predict future clinical compromise and would prompt *prophylactic* ECTR, i.e., before the appearance of toxic effects.
2. *There must be an absence of life-saving alternatives.* Rarely, an antidote may either amend or prevent the apparition of toxic effects related to a poison. Extracorporeal purification then becomes less crucial or indicated. This is the

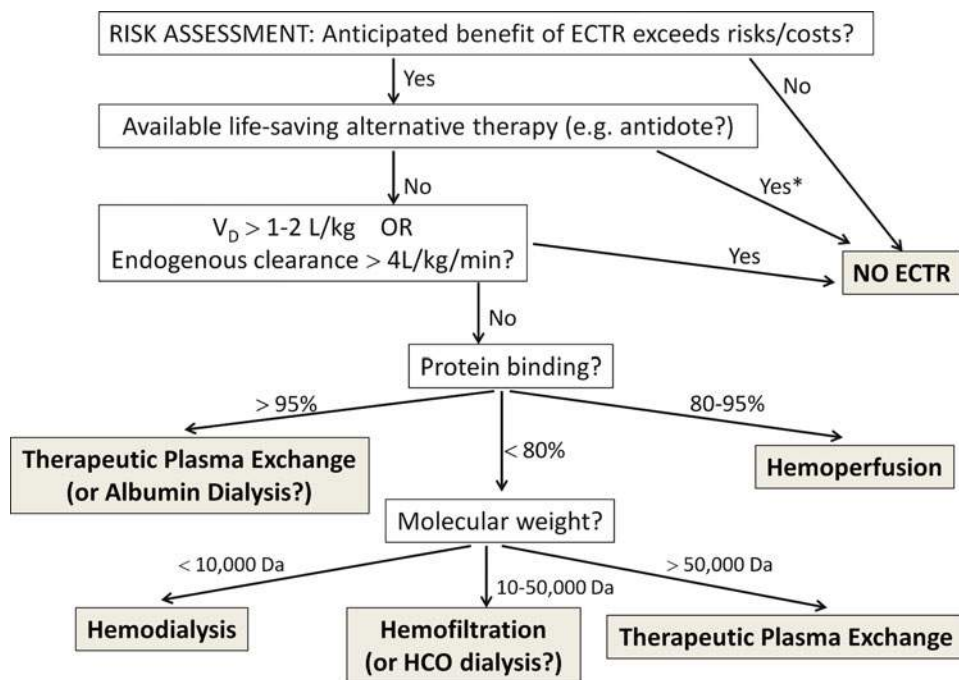


Fig. 3 Decisional process to the use of an ECTR in a poisoned patient (Reproduced with permission from Seminars in Dialysis: Ghannoum, M., et al. (2014). "A stepwise

approach for the management of poisoning with extracorporeal treatments." *Semin Dial* 27(4): 362–370)

case for acetaminophen poisoning, when N-acetylcysteine is available. Because ECTR is somewhat invasive and may require transfer to a specialized center, its cost and benefit should be weighed against those of the antidote.

3. *The ECTR must be capable of removing the poison from the blood compartment.* The poison to be removed should permeate readily through the dialysis membrane or the column. This relates to a high extraction ratio and a high extracorporeal clearance (see above).
4. *The ECTR must be expected to significantly contribute to total body clearance.* As shown previously, if a poison is mostly confined outside of the intravascular space (high V_D), or if it is extensively and rapidly metabolized by endogenous routes, ECTR will likely not be removing poison from the body to a proportion that justifies its initiation.

A proper risk assessment requires weighing potential benefits of the ECTR to its complications. Some exposures are associated with a high risk of short-term mortality (e.g., salicylates $> 500 \text{ mg/kg}$, paraquat), while others may cause irreversible tissue damage (e.g., blindness for methanol). In other situations, ECTR will expectantly reduce the length of mechanical ventilation and immobilization (e.g., barbiturates, carbamazepine). Finally, there may be situations where ECTR will likely not affect outcome but may reduce hospitalization and associated costs (e.g., dialysis versus fomepizole in a methanol poisoned patient without metabolic acidosis) [49, 50]. Any of these benefits should be weighed to potential adverse events associated to ECTR; in general, these are minimal and limited to the traumatic insertion of a vascular access (which can be minimized with ultrasonographic guidance) [51]; more rarely, ECTR can potentiate elimination of

certain antidotes [52] and/or precipitate withdrawal symptoms if drug levels fall below the therapeutic range [53]. Costs of a single dialysis, including equipment and nursing/physician fees, are minor compared to the cost of a day in the ICU. In the absence of any clinical outcome data, studies should demonstrate significant drug removal, or, at a minimum, molecular characteristics that may predict extracorporeal removal.

Practical Considerations

A double-lumen central catheter is required for administering most forms of extracorporeal treatments. A temporary femoral catheter is often preferred, using ultrasound guidance to limit complications and ensure patency [54]. To maximize efficacy, the largest surface area dialyzer should be used. Heparinization of the circuit is favored to prevent clotting of the extracorporeal circuit unless there is a significant risk of bleeding. The blood flow and dialysate/effluent flow should be maximized for optimal clearance [17].

Poisoned patients may not share the same metabolic profile as those with renal failure; it is therefore important to tailor the composition of the dialysate to the requirement of the poisoned patient to avoid dangerous imbalances. This may include adjustment of the concentration of calcium, phosphate, magnesium, potassium, and/or bicarbonate.

A single 6-h extracorporeal treatment will usually suffice to substantially lower blood levels of most xenobiotics. When significant toxicity is present or suspected to be prolonged, there is little risk to extend this for several more hours (hemoperfusion cartridges may need to be replaced because of saturation).

Patient disposition

Many poisoned patients die prior to initiation of dialysis [55]. If the risk assessment suggests that a

patient may require dialysis, prompt communication with a center that can dispense acute dialysis and even prophylactic transfer to one may be required, even if the patient does not yet meet criteria for blood purification. Because significant delay may occur between the time a decision is taken to perform ECTR and the time when it is initiated, the dialysis personnel should be rapidly contacted and a temporary dialysis catheter installed as early as possible. If an admission to the ICU is required, the patient should be placed in a bed that has the required water canalization for dialysis. In special circumstances (e.g., nursing, logistics), a clinician may prefer the lesser efficient CRRT over intermittent dialysis if the former can be initiated sooner.

Following ECTR, serial poison concentrations and clinical status should be monitored for a period long enough to account for redistribution or ongoing absorption ($\cong 12\text{--}24$ h). The catheter should remain in place until the physician is convinced that additional sessions are unnecessary. Factors to consider when deciding if the catheter can be removed are the position of the catheter, the likelihood of the need for further ECTR, the risks of infection, and the complications of replacement of the catheter if needed.

Poisons Amenable to Extracorporeal Elimination

In the large majority of poisoning cases, ECTRs are not required. In fact, the drugs or poisons that are most commonly responsible for poisoning-related fatalities (e.g., opiates, stimulants, tricyclic antidepressants, and “street drugs”) are not effectively amenable to extracorporeal removal. Poisonings that are most likely to benefit from extracorporeal removal include those by: salicylates, lithium, methanol, ethylene glycol, valproic acid, biguanides, and theophylline. In special circumstances, poisoning to carbamazepine, acetaminophen, isopropanol, methotrexate, barbiturates, or paraquat may necessitate

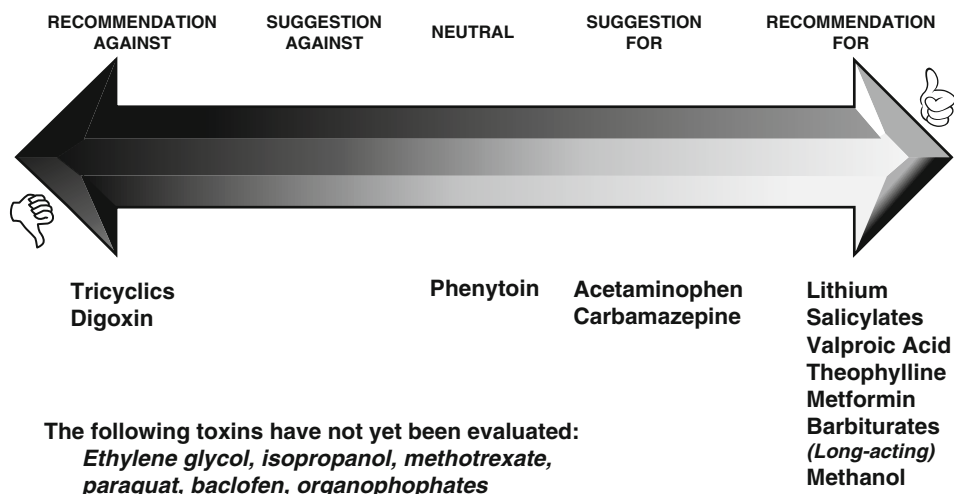


Fig. 4 Pictorial summary of EXTRIP recommendations

treatment with an ECTR. The EXTRIP workgroup has provided recommendations for several poisons, the summary of which are presented in Fig. 4. Specific indications will be covered in detail in the following chapters.

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Epidemiology of Toxic Deaths

The understanding of the epidemiology of poisoning deaths remains difficult for several reasons. Many comorbid factors contribute to the outcome, including the patient's age, underlying medical condition, and the delay between exposure and treatment. The literature on poisoning deaths does not reflect the true prevalence. A major discrepancy exists between hospital and nonhospital deaths, and there is a wide variation according to the sources of reporting. The main sources of information in the United States are the data collected by the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers and by the National Center for Health Statistics (NCHS) [1, 2]. There are marked differences between these two data sets [2]. Fatalities are underreported to poison control centers, and the NCHS data set gives a larger profile of poisoning deaths by reporting more out-of-hospital deaths.

In 2013, 43,982 poisoning deaths were recorded by the NCHS, and only 1552 deaths were recorded by the TESS [1, 2]. In these data sets, the relative distribution of death circumstances differed for unintentional drug poisonings, unintentional nondrug poisonings, and intentional poisonings. The death rate associated with drug poisoning has increased in the USA by roughly 300% over the past three decades and is now the leading cause of injury death exceeding the number of motor vehicle traffic deaths. The

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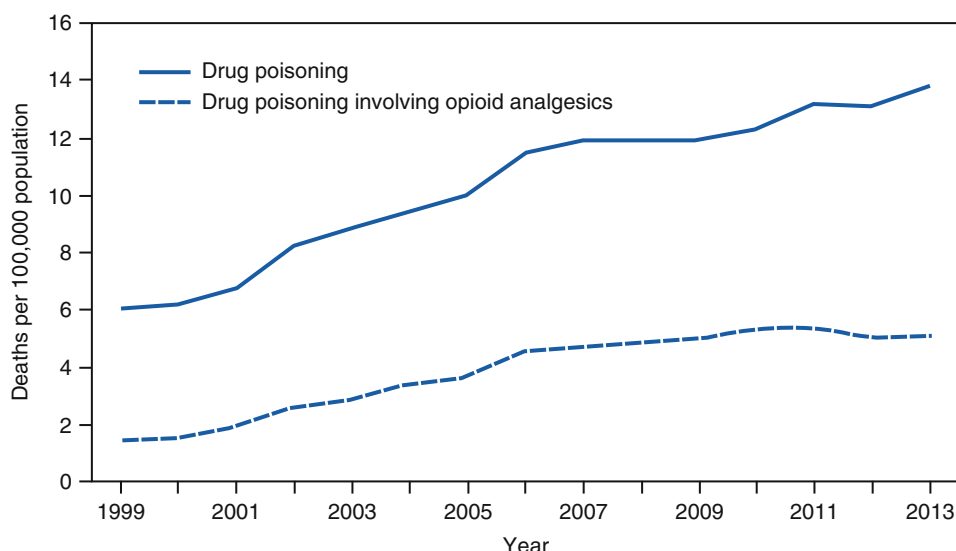


Fig. 1 Rates of deaths from drug poisoning and drug poisoning involving opioid analgesics – United States, 1999–2013 <http://www.cdc.gov/nchs/data/databriefs/db166.htm>

data from the National Vital Statistics System reveal that from 2000 through 2013, the age-adjusted rate for drug-poisoning deaths involving heroin nearly quadrupled from 0.7 deaths per 100,000 in 2000 to 2.7 deaths per 100,000 in 2013 [3]. During the same period of time (1999–2013), the drug poisoning death rate more than doubled from 6.1 to 13.8 per 100,000 population, and the rate of drug poisoning deaths involving opioid analgesics nearly quadrupled from 1.4 to 5.1 per 100,000 [4] (Fig. 1). Benzodiazepines were also present in a significant number of opioid-analgesic poisoning deaths.

Most cases reported to poison control centers are not managed in a health care facility [3]. In 2013, of 2,188,013 human poison exposure cases, 99,117 (4.5%) were admitted to critical care units. On the same number of exposures, only 1552 fatalities (0.07%) were reported [2]. Human exposures with more serious outcomes have increased by 4.7% per year since 2000. The top five substance categories associated with reported fatalities were: sedative/hypnotics/antipsychotics, cardiovascular drugs, opioids, stimulants and street drugs, and alcohols.

There are limited statistical reports specifically addressing intensive care unit (ICU) mortality rates.

The ICU and in-hospital mortality of poisoned patients is generally described as low. There is a variability according to the type of poisons and the sample of the population that is analyzed. A small American retrospective study found an ICU mortality rate of 2.7%, while a larger German study showed a mortality of only 0.2% in patients younger than 65 years, whereas patients older than 65 years had a mortality of 2.2% [5, 6]. The in-hospital and long-term mortality of ICU patients admitted with an acute intoxication was recently analyzed in Dutch hospitals on a large population sample [7]. The ICU mortality was 1.2% and the in-hospital mortality was 2.1%. The mortality 12 and 24 months after ICU admission was 6.5% and 9.3%, respectively, and was relatively low compared with other ICU admissions. The adjusted observed mortality showed that intoxications with street drugs have a significantly higher mortality 1 month after ICU admission [7].

Mechanisms of Death

Death may be the consequence of the direct or indirect action of a toxic substance on an isolated organ (target organ) or on the whole organism. For

example, the lung is the target organ in paraquat poisoning; progressive respiratory failure develops within a few days or weeks after exposure, with evident pathologic lesions. Mortality also exists, however, with toxins that do not have lesional effects. Outside the hospital, death due to acute poisoning is mainly the result of central nervous system (CNS) depression with subsequent cardiorespiratory failure. CNS depression is the mechanism of toxicity for opiates and most psychotropic drugs. Under these circumstances, death usually is related to the lack of early supportive treatment. Early cardiocirculatory failure, before hospital admission or a few hours after, is another common cause of toxic death. It is observed not only with cardiotropic drugs, such as calcium-channel blockers and digoxin, but also with other substances, including cocaine, colchicine, and chloroquine. Delayed complications, such as infection, renal failure, hepatic failure, and respiratory failure, may account for late mortality in the ICU.

Brain death is encountered less commonly after acute poisoning. The early recognition of this condition by critical care physicians leads to major decisions, such as care withdrawal and organ donation. A first question to be answered is the possible mechanism of brain death in this setting. Brain death cannot be the sole consequence of anoxia due to unsuccessful resuscitation because pure anoxia seldom gives rise to brain death except when associated with brain edema leading to acute intracranial hypertension. In our experience, brain edema consistently preceded brain death in poisoned patients in whom a cerebral computed tomography scan was performed. Brain edema classically is said to be from a vasogenic or cytotoxic origin. The first mechanism is illustrated by hepatic encephalopathy in the case of acetaminophen poisoning (Fig. 2) [8]. Cytotoxic brain edema may be caused by numerous metabolic disorders. It has been documented after intoxications by some anoxic agents (CO) or following profound hypoglycemia in the case of insulin overdose [9]. Extremely severe metabolic acidosis is likely responsible for irreversible brain damage (with associated brain edema) in the case of methanol or ethylene glycol poisoning [10–12]. Ionic disorders and

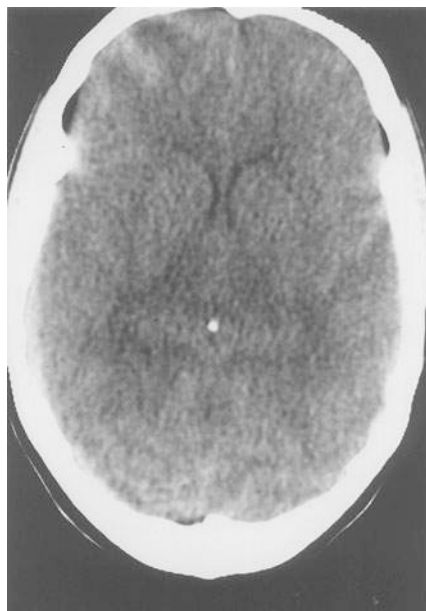


Fig. 2 Major brain swelling in a 30-year-old woman who presented with fulminant hepatic failure after acetaminophen overdose

hyperthermia have been reported to contribute to cerebral edema associated with the use of 3,4-methylenedioxymethamphetamine (Ecstasy) or other substances leading to the serotonin syndrome. Ionic disorders may be related to the inappropriate secretion of antidiuretic hormone [13]. The clinical picture usually is complicated by other disorders, such as autonomic instability or disseminated intravascular coagulation. Finally, epileptogenic substances may provoke irreversible brain injury after status epilepticus.

Intracranial hypertension also may be the result of focal anatomic lesions. Extensive neuronal destruction with hemorrhages was found at post-mortem examination in an autopsy study of 28 patients who died from methanol poisoning [14]. In a personal observation of fatal methanol poisoning, extensive hemorrhagic necrosis originating from the basal ganglia was observed (Fig. 3). In methanol-poisoned patients investigated by magnetic resonance imaging, the putamen preferentially is involved [10]. The lesions can be edematous and fully reversible at the early stage or, in some instances, can become hemorrhagic and necrotic. These lesions are probably

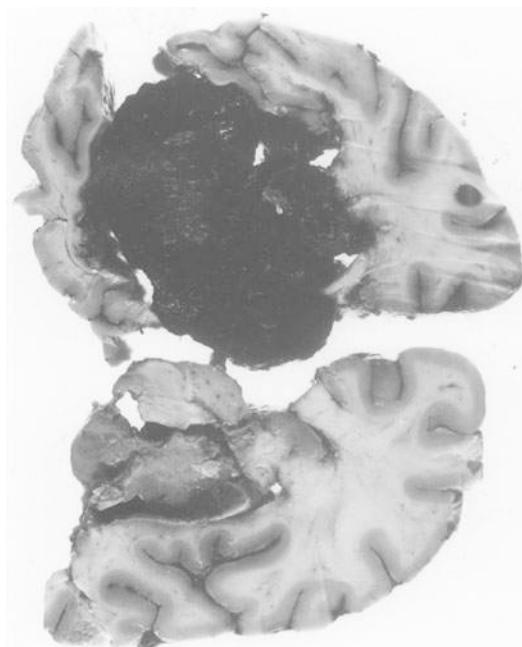


Fig. 3 Extensive hemorrhagic necrosis originated from the basal ganglia in a 32-year-old man who died as a result of acute methanol poisoning

due to the combination effects of tissue acidosis and hypoxia-ischemia status. Cerebrovascular accidents, including subarachnoid hemorrhage, intracerebral hemorrhage, and cerebral infarction, have been reported with increasing frequency in association with cocaine use. Although most patients have evidence of underlying cerebrovascular disease, reports have failed to show underlying disease in some patients [15–18]. These observations illustrate the need to obtain brain imaging when irreversible brain damage is suspected after acute poisoning, because functional disturbances are considerably more frequent than anatomic lesions.

Diagnosis of Brain Death in Poisoned Patients

The accuracy of the brain death diagnosis is crucial in cases of poisoning [19–22]. With concurrent misleading conditions (hypothermia, drugs, metabolic disturbances), the brain death diagnosis

should be verified by using a reliable, accurate, and safe confirmatory test. Even if brain death is primarily a clinical diagnosis, confirmatory tests are required. In the case of brain death, the confirmatory tests show the absence of cerebral blood flow (four-vessel arteriography, radioisotopic technique, and transcranial Doppler) or the absence of electrocerebral activity (electroencephalogram [EEG], multimodality evoked potentials [MEPs]).

Cerebral four-vessel angiography remains for most authors the confirmatory test of choice to determine brain death. Cerebral angiography has a high accuracy because cerebral blood flow cannot be abolished completely by any toxic substance and gives clear-cut results in misleading conditions. Angiography cannot be performed at the bedside, however, and cannot be repeated easily. It can cause deleterious effects, which may be found ethically unacceptable if one considers that the prognosis of a patient presenting with barbiturate overdose with transient isoelectric EEG can be excellent. Depending on the mechanism of acute brain injury, there may be some discrepancy between EEG findings and cerebral angiography when diffuse cerebral anoxia is not followed by major brain edema formation [23].

Brain scintigraphy with ^{99m}Tc -HMPAO technique has been used in brain death diagnosis. Clinical conditions such as hypothermia or metabolic coma exhibit no, or little, effect on brain ^{99m}Tc -HMPAO uptake. Few data are available concerning the use of cerebral angioscintigraphy for the diagnosis of brain death in poisoning [24–26]. Facco and colleagues [27] investigated 50 deeply comatose and brain-dead patients by single-photon emission computed tomography (SPECT). In this series, a cerebral circulation test was mandatory by law. In the 21 patients in whom brain death could not be diagnosed properly by EEG and clinical examination owing to the presence of associated factors (e.g., sedation, drug intoxication), SPECT showed brain perfusion arrest in 15 patients on the first test and in six patients on retesting. These six last patients had residual weak perfusion of the basal ganglia, thalamus, and/or brainstem that totally disappeared within 3 days. This illustrates that SPECT

findings were closely related to the dying process by rostrocaudal deterioration.

Positron emission tomography has not been used to a significant extent in brain death diagnosis owing to practical difficulties. Only two reports have been found in the literature from 1988 to the present [28, 29]. The reports showed the absence of significant intracerebral fludeoxyglucose uptake or retention in three cases and one obvious case of clinical brain death. In the second report, a slow rise of tracer was noted over time within the sagittal sinus, providing a false-negative scintigraphic evaluation for brain death diagnosis.

Transcranial Doppler is also a helpful method of estimating cerebral blood flow. This modality is more dependent on examiner skill and the patient's anatomic features, however. The results are not influenced by the action of sedative drugs.

EEG is by far the most often used confirmatory test for brain death diagnosis. Nevertheless, EEG is sensitive to hypothermia, drugs, and metabolic disorders and is of little help in the case of poisoning or other misleading conditions. The possible occurrence of reversible isoelectric EEG has been documented in hypothermia and with several drugs, including barbiturates, methaqualone, diazepam, meprobamate, and trichloroethylene [30–38].

Evoked potentials may offer significant advantages over EEG. Evoked potentials are a minimally invasive technique largely used for many years in the operating room and in the ICU. Numerous conditions that may influence electrophysiologic testing have been studied extensively [39]. In all cases of suspected brain death, the general policy of our institution is to use the combination of EEG and MEPs (flash visual evoked potentials [VEPs], somatosensory evoked potentials [SEPs], and brainstem auditory evoked potentials [BAEPs]) to confirm brain death [39–43]. MEPs are recorded easily and rapidly at the patient's bedside and evaluate the brainstem and the cerebral cortex. The three-modality evoked potential pattern of brain death is highly specific and associates the disappearance of all cortical and brainstem activities to the persistence of retinal, peripheral, and spinal activities (Fig. 4). It is unequivocal in most situations mimicking

brain death. Only the association of a bilateral optic nerve section, a spinal cord interruption at the cervical level, and a bilateral auditory nerve section could mimic the MEP pattern of brain death. MEPs can differentiate brain death from misleading factors, such as hypothermia, drugs, and metabolic disturbances, by the persistence of brainstem activities (waves from II to V in BAEPs and lemniscal P14 in median nerve SEPs).

Brain death diagnosis can be considered more difficult in infants than in children and adults, taking into account the immaturity of brainstem reactivity and EEG. The high proportion of anoxic encephalopathies in infants and the persistence of open fontanelles, which prevents transtentorial herniation, decrease the likelihood of a brain death occurrence in such comatose patients. BAEPs and VEPs are present in all premature infants older than 30 weeks. BAEPs are sensitive to pathologic conditions frequently encountered in infancy, such as anoxia (cochlea sensitivity) and hyperbilirubinemia (cochlea and brainstem sensitivity), that can give rise to null BAEPs. VEP alterations in anoxic infants are poorly documented. Cortical SEP components are inconstant, and their absence in normal term newborns is not pathological. After 6 months of age, the absence of cortical SEP components indicates a poor prognosis (death or severe neurologic sequelae). Consequently, MEPs should not be taken as a reliable brain death confirmatory test in these misleading conditions (anoxia, hyperbilirubinemia, and probably poisoning) in infants younger than 6 months old [42].

The interpretation of MEPs in poisoning cases should take into account some specifics. Concerning VEPs, it is important to keep in mind that the same factors that provoke electrocerebral silence (CNS depressant intoxications, hypothermia) can abolish the VEPs. A completely abolished VEP has the same meaning as electrocerebral silence. The lower sensitivity to environmental artifacts due to the averaging process is a significant advantage over EEG and makes the interpretation easier [42]. Owing to the high toxicity to retina and optic nerve of formic acid, the main toxic metabolite after biotransformation of methanol, VEP interpretation in

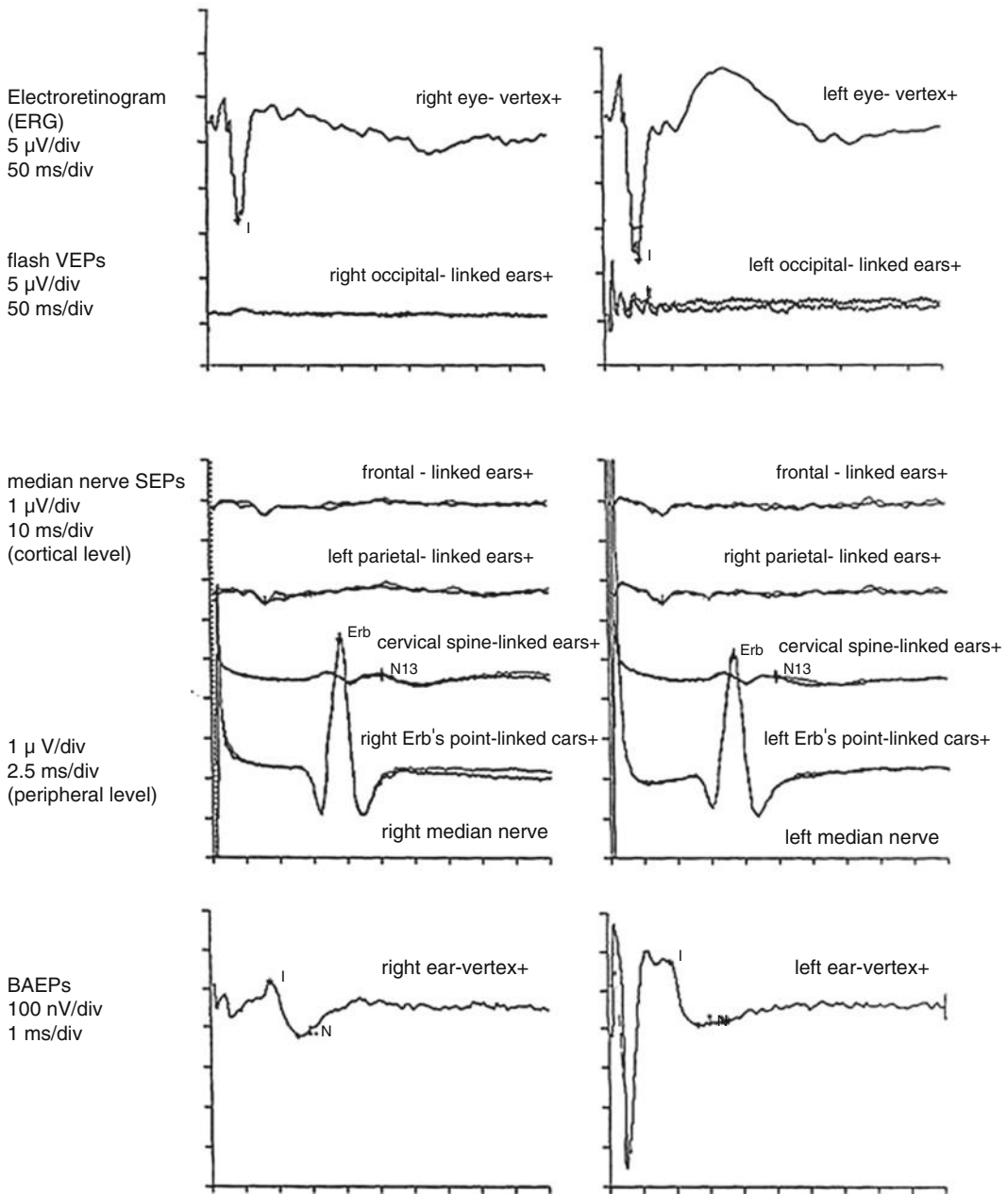


Fig. 4 Multimodality evoked potential pattern in a brain death patient. Multimodality evoked potentials were recorded from a 33-year-old man. At the time of recording, clinical examination was consistent with brain death diagnosis. Flash visual evoked potentials (VEPs) show only a retinal component (wave I) on the cortical channel and the

periocular recording. Median nerve somatosensory responses are represented only by peripheral (Erb) and spinal (N13) components, whereas brainstem and cortical components are bilaterally absent. Brainstem auditory evoked potentials (BAEPs) are limited to a cochlear nerve component (wave I) (From Ref. [21])

the case of methanol poisoning may not be reliable [44]. Early retinal dysfunction can be documented; it may or may not be followed by the development of optic neuropathy. In the case of disappearance of VEP activities in methanol poisoning, the preservation of BAEP and SEP components precludes the brain death diagnosis.

Hypothermia often is experienced in comatose patients secondary to poisoning or other causes. It has been shown that BAEPs also are less influenced by hypothermia and may help to rule out brain death diagnosis as long as the body temperature exceeds 20–22 °C [45]. From our experience in recording SEPs during profound hypothermia for surgical aorta repair, the lemniscal P14 of median nerve SEPs also is resistant to hypothermia and disappears only at temperatures less than 18 °C, whereas cortical SEP activities can be recorded at temperatures around 22 °C [46]. In most clinical situations, the hypothermia level is less marked and does not interfere with MEP interpretation.

There is a consensus among authors that SEPs and BAEPs can be considered relatively insensitive to CNS depressant drugs, and these evoked potentials are a good tool for examining brainstem function when these drugs are present [47–49]. Increased SEP latencies with increased central conduction time (as measured between cervical N13 and parietal N20) have been observed in amitriptyline, meprobamate, and nitrazepam overdose [50]. In the presence of CNS depressant drugs, BAEPs either are unchanged at therapeutic levels or are delayed at therapeutic or toxic levels. Amplitude or morphologic changes can occur with enflurane, cholinergic and serotonergic agents, phentolamine, and propranolol [51]. Mauguière and colleagues [52] showed deep reversible BAEP alterations consecutive to the association of barbiturates and lidocaine in one case. In our experience, barbiturate intoxication sufficient to provoke a clinical and EEG pattern of brain death is associated with well-preserved BAEPs and persistent lemniscal P14 in median nerve SEPs (Fig. 5). The MEP

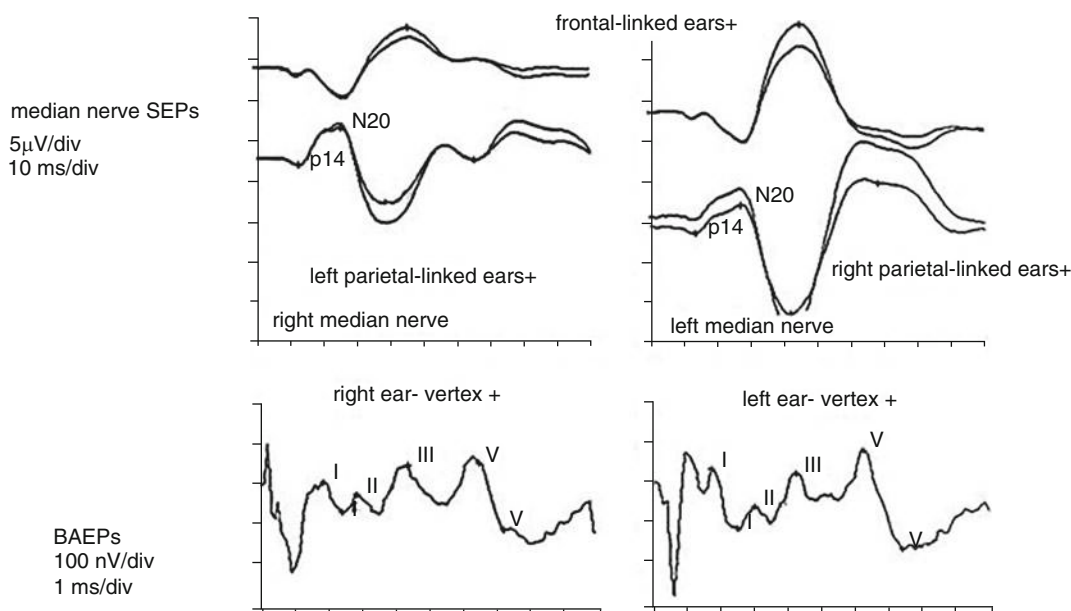


Fig. 5 Electrophysiologic study in a 5-year-old epileptic girl under barbiturate. At the time of recording, blood level of thiopental was 53 $\mu\text{g/mL}$, and all cephalic reflexes were absent. The electroencephalogram was isoelectric during long periods. Median nerve somatosensory evoked

potentials (*SEPs*) show delayed but recognizable lemniscal (P14) and cortical (N20) activities. Brainstem auditory evoked potentials (*BAEPs*) are well preserved but slightly delayed (From Ref. [21])

pattern in brain death is clearly distinct from that observed in CNS depressant intoxication and allows clinicians to differentiate both states clearly. For most authors, evoked potentials might be included in brain death criteria even in clinically difficult conditions [47, 51, 53]. Drug intoxication cannot account for a complete MEP pattern of brain death if brain death is not really present. Subcortical (and even cortical) activities persist in high doses of CNS depressant drugs sufficient to give rise to a clinical and EEG pattern of brain death. The MEP pattern of brain death is encountered in other drug intoxications only when irreversible damage occurs at the brainstem and the cerebral cortex [54].

Organ Donation from Poisoned Donors

Organ donation after acute poisoning with evidence of brain death is a poorly documented topic [55–57]. The current shortage of grafts for organ transplantation should lead to consideration, in selected cases, of poisoned subjects as organ donors. Over the last 10 years, it seems that the use of drug-intoxicated patients in the USA as organ donors progressed significantly. In 2013, poisoned donors represented 6.8% of all organ donors (6.8% for kidney, 5.1% for pancreas, 7.1% for liver, 7.1% for heart, 5.7% for lungs) [58]. There was also a significant difference across all US states, with a peak of donation from poisoned patients at 10.4% in the regions of New York and Vermont.

The knowledge of both the target organ and mechanism of action of each toxin is important. To increase the donor pool, a close cooperation between ICU directors, clinical toxicologists, and transplantation surgeons is essential. A postal survey performed in 2002 in the UK revealed that most transplantation physicians and surgeons and ICU directors would consider those who die following acute drug intoxication and poisoning as potential organ donors [59]. With some specific toxins (methanol, carbon monoxide, cocaine), there was some concern regarding poison-induced organ damage. This concern is also present among

medical toxicologists, particularly for heart donation after cocaine or carbon monoxide exposure [60]. There is, however, an increasing evidence of good outcome when using poisoned patients as potential organ donors, with a large variety of toxins (tricyclic antidepressants, benzodiazepines, barbiturates, insulin, CO, methanol, cocaine, pesticides, snakebites, and other toxins) [61–74]. Published experience indicates that in selected cases, the organs from such donors function as well in recipients as organs from more conventional sources. Some centers report a favorable experience in this setting [63, 75].

A first step is to exclude the risk of toxin transmission to the recipient by careful analysis of the toxicologic data (undetectable or nontoxic blood toxin levels). A second step is to check that the systemic consequences of acute poisoning are fully controlled. The routine biologic data are extremely helpful in excluding organ dysfunction (nonelevation of cardiac, hepatic, and pancreatic enzymes and normal serum creatinine). Morphologic analysis also is essential but is often possible only at organ harvest when biopsy also can exclude gross organ injury.

Heart Donation

Heart donation from poisoned donors is poorly studied [75]. Similar to the brain, the heart is extremely sensitive to hypoxic or ischemic injury. Some toxins may preclude donation, such as tricyclic antidepressants, dextropropoxyphene, cocaine, and ethylene glycol. Tricyclic antidepressants may accumulate in heart tissue [76]. Ultrastructural changes have been noted in the myocardium of patients who died from acute ethylene glycol and cocaine overdose [77, 78]. Cocaine interferes with cardiac biochemical functions, leading to oxidative stress, and with cellular calcium flux regulation [79]. Clear evidence of recovery from these toxicities must be shown. The impact of current or previous use of cocaine in cardiac donors on the overall recipient survival and development of coronary artery disease in the recipient was studied retrospectively. On a total cohort of 7937 heart recipients, 11.7%

of individuals received a heart from a donor with a history of cocaine use [80]. The overall mortality at 5 years and the development of coronary artery disease at 5 years were not significantly different according to the nonuse, previous use, or recent use of cocaine. Heart donation after CO intoxication is still a matter of debate because fatal outcomes have been published [65, 81–87]. Reversible cardiac dysfunction may be observed after CO exposure, prompting the hypothesis of myocardial stunning [88]. Ultrastructural myocardial changes, after acute CO exposure, also have been debated. Different factors may be involved in CO cardiotoxicity, such as individual susceptibility, duration of exposure, and type of exposure (e.g., smoke inhalation). In a systematic review of the published literature on heart donation after fatal carbon monoxide poisoning, 42 carbon monoxide-related donor deaths were identified, with a follow-up extending up to 7 years for individual organs. There was no difference in the mean peak carboxyhemoglobin concentration in donors between organs that survived and those that did not. The survival was obviously lower for heart and lungs in comparison with kidney, pancreas, and liver. However, the outcome of heart (and lung) transplants from carbon monoxide-poisoned donors was comparable to that expected from organs donated from donors with other causes of death [82]. The influence of specific therapy (hyperbaric oxygen) has to be clarified. Experience with heart donation after methanol poisoning is still limited [71, 89–91]. Severe metabolic acidosis may contribute to myocardial dysfunction at the acute phase, but this has been poorly investigated in acute methanol poisoning. After the complete elimination of the toxin, heart donation should be possible provided that metabolic acidosis has been corrected and that inotropic drugs or vasopressors are not required.

Insulin and cyanide are good examples of functional toxins. Cyanide induces cellular hypoxia by inhibiting cytochrome oxidase. After cyanide exposure, successful cardiopulmonary resuscitation can be achieved by supportive therapy and antidote administration. Heart donation is possible after cyanide poisoning [92]. The main

problem is to prevent cyanide intoxication of the recipient. It seems safe to wait until the donor's serum cyanide concentration is less than 100 ug/dl (23 μ mol/L) and lactic metabolic acidosis has been corrected.

Fatal acetaminophen poisoning is particularly frequent in some countries. Heart donation seldom has been considered, however. According to the data in the literature, it is unlikely that acetaminophen is directly cardiotoxic [66].

What criteria could be applied to minimize risk in heart donation after fatal poisoning? A normal electrocardiogram, intact left ventricular function (estimated by echocardiography), good hemodynamics with minimal inotropic support, and normal or near-normal cardiac enzymes would seem essential [82]. With CO poisoning, additional requirements might include relatively short ischemia time, favorable donor-to-recipient weight ratio, and avoidance of recipients with high pulmonary vascular resistance. It also is wise to avoid donors with prolonged CO exposure or sustained cardiocirculatory arrest. [82, 87] The severity of organ damage cannot be predicted from the carboxyhemoglobin levels.

Finally, heart donation after poisoning with cardiotoxicants was exceptionally reported in a donor who received extracorporeal life support because of refractory cardiac arrest caused by a flecainide and betaxolol overdose [93]. This case illustrates the possible reversibility of some toxin-induced cardiac dysfunction, while the patient may suffer from irreversible brain damage.

Lung Donation

Lung transplantation from a poisoned donor has been described rarely [69, 94–96]. A few toxins directly affect the lung (e.g., paraquat or bleomycin) contraindicating organ donation. Cardiogenic or noncardiogenic pulmonary edema may complicate some toxic deaths, however. CO poisoning illustrates the different mechanisms of lung injury, but is not a contraindication for lung donation [82]. Caution should be exercised when lung donation is considered after smoke inhalation following fire hazard (associated chemical

injury) [95]. Concerning cocaine, there is a retrospective analysis on a thoracic transplant database showing no difference in the propensity of recipient survival based on donor cocaine status [94]. In other cases, standard lung donation criteria can be applied.

Liver Donation

The liver is a target organ for some toxins (e.g., acetaminophen and some mushrooms) to the extent that liver transplantation is a successful therapy in the most severe cases.

Liver donation is possible in selected cases, and successful liver allografts have been reported after poisoning with benzodiazepines, methaqualone, barbiturates, cyclic antidepressants, insulin, CO, cyanide, methanol, cocaine, pesticides, and lead [61, 63, 72–74, 82, 90, 91]. Detectable alcohol concentrations are common in the blood of potential organ donors after motor vehicle accidents, intracranial hemorrhage, head injury, aspiration, and drug overdose; they are not a contraindication per se to liver harvesting. Many toxins might be expected to accumulate in the liver (e.g., tricyclic antidepressants); in practice, this has rarely proved the case. Risk can be minimized by a careful toxicokinetic analysis. The decision to harvest the liver should be guided mainly by donor history (chronic ethanol or drug abuse), liver function tests, serology, and liver morphology and biopsy at harvest.

Kidney Donation

The kidneys are relatively resistant to many hypoxic, ischemic, or toxic insults. Acute tubular necrosis, usually secondary to nontraumatic rhabdomyolysis, may occur in this setting but is generally reversible. The kidney is a target organ of acute ethylene glycol poisoning. Nevertheless, kidney transplantation has been performed with success after exposure to this substance, but this cannot be recommended routinely. There is experimental evidence that oxalate crystal deposition may lead to an inflammatory response with

permanent epithelial cell injury, and some patients who survived acute ethylene glycol poisoning have developed chronic renal failure [97, 98]. Clear evidence of recovery from the injury must be shown. In other instances, there is extensive experience with kidney grafts from poisoned donors, and the results are similar to those in the nonpoisoned donor population. There is, for example, an important published experience of successful kidney transplantation from methanol-poisoned donors [70, 71, 90, 91, 99]. The kidneys can be transplanted safely after fatal acetaminophen poisoning, even in the presence of acute tubular necrosis, a possible but rare complication of acetaminophen poisoning that probably could not be prevented by *N*-acetylcysteine administration [100]. Kidney donation may be considered safely after acute poisoning by most toxins that are not directly nephrotoxic. Renal function laboratory tests and pretransplant biopsy are mandatory.

Pancreas Donation

Pancreas transplantation from poisoned donors has been described rarely. Alcohol abuse is associated with acute and chronic pancreatitis. Several studies of the acute effects of ethanol administration have shown that the liver is affected significantly more often than the pancreas; no correlation is found between blood ethanol and serum amylase or lipase levels. Similar to ethanol, methanol is a possible cause of pancreatitis [101]. Pancreas injury may be exacerbated further by the ethanol therapy used as an antidote to methanol intoxication. The decision to harvest the pancreas should be based on laboratory indicators and organ morphology at surgery.

Organ Donation from Non-Heart-Beating Poisoned Donors

Donation after circulatory death (DCD) describes the retrieval of organs for the purposes of transplantation that follows death confirmed using

circulatory criteria [102]. The practice of DCD is not accepted in all parts of the world due to ethical concerns around the interface of end-of-life care and organ donation. Donors dying from acute poisoning may belong to category II (unsuccessful resuscitation) or category III (anticipated cardiac arrest, treatment withdrawal) of Maas-tricht. The published experience on DCD reveals that most of the donors suffered from irreversible brain damage, either after intracranial hemorrhage or after severe brain anoxia. Currently, there is no direct description of donation from poisoned patients after circulatory death, with the exception of two cases of kidney donation from paracetamol-poisoned donors who died after a decision of treatment withdrawal [103]. It is, however, conceivable that patients with severe and irreversible brain anoxia due to poison-induced cardiac arrest or to oxygen deprivation (e.g., following carbon monoxide exposure) could increase the pool of donors after circulatory death.

Conclusion

In-hospital death, particularly brain death, is a rare complication of acute poisoning compared with out-of-hospital deaths from a toxic origin. The diagnosis of brain death relies not only on the clinical examination but also on confirmatory tests, especially in poisoning cases. Among them, transcranial Doppler, brain scintigraphy, cerebral angiography, and overall MEPs are less susceptible to the influence of drugs or metabolic disorders than is the EEG. Analysis of the more recent literature shows successful organ transplantations with grafts obtained from donors poisoned by various substances. Experience indicates that in selected cases, the organs from poisoned donors function in recipients as well as organs from more conventional sources. Physicians should be guided by the accurate knowledge of the target organs of poisoning, the analysis of the toxicokinetic data, and the results of laboratory investigations, functional tests, and morphologic studies before harvesting the organs.

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Part II

Toxic Syndromes

The Assessment and Management of Hypotension and Shock in the Poisoned Patient

14

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While several large-scaled multicenter studies have changed the approach to the diagnosis and treatment of hypotension and shock in septic patients in recent years, the evidence base for the appropriate management of circulatory failure in poisoned patients is much more precarious. Toxicological research is often limited to case reports, small case series, or animal studies and most clinical recommendations or treatment guidelines are based on expert consensus or even personal experience rather than on criteria of evidence-based medicine [1]. Additionally, there may be a significant reporting bias from positive cases responding to different treatments, including extraordinary resuscitation measures. However, given the infrequency of many of these poisoning events, the likelihood of confirmatory randomized controlled trials to prove effectiveness will be low [2].

Most data regarding hemodynamics in critically ill patients are thus derived from nontoxicological populations, and it is often unclear if this evidence can uncritically be transferred to poisoned patients.

Current recommendations for the protocolized resuscitation of patients with sepsis-induced hypotension and shock suggest targeting a mean arterial pressure (MAP) of at least 65 mmHg, a central venous pressure (CVP) of 8–12 mmHg, a central venous oxygen saturation ($ScvO_2$) or mixed venous oxygen saturation (SvO_2) above 70% or 65%, respectively, and a urine output of at least 0.5 mL/kg per hour (1C) during the first

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6 h of resuscitation [3, 4]. Additionally, normalizing lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion has been suggested (2C) [4].

In contrast to the early-goal-directed therapy (EGDT) introduced by Rivers and colleagues in 2001 for the treatment of patients with septic shock [5], which has been both criticized and adopted during recent years [6, 7], a clear protocol-derived approach for poisoned patients with shock is still lacking.

In this chapter, pathophysiological aspects of hypotension and shock in poisoned patients will be discussed followed by discussion of appropriate diagnosis, and general and more invasive treatment options. Evidence of the proposed treatment modalities – if any – will be briefly discussed on the basis of the available literature. Detailed poison-specific management (e.g., antidotal therapy) is beyond the scope of this section but will be discussed in respective chapters of this textbook.

Epidemiology

Adverse cardiovascular events in poisoned patients are responsible for significant morbidity and mortality. Poisoning with cardiovascular drugs were involved in not more than about 4% of the 2.7 million reported overdoses in the USA in 2011, but accounted for about 11% of all reported drug fatalities [8]. While cardiac arrest and life-threatening hemodynamic instability are rather infrequent events of deliberate or accidental drug overdose, poisoning is the leading cause of nontraumatic death in patients under the age of 45 [9].

Although clear epidemiological data regarding cardiovascular complications in the course of poisoning are lacking, they account for significant morbidity and mortality in these patients. Drug-related adverse cardiovascular events occur with many drugs and mechanisms are diverse, depending on the underlying agent. The most common include dysrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsade de pointes), hypotension and circulatory failure, myocardial injury (evaluated with cardiac

biomarkers and the ECG), or cardiac arrest [10]. The incidence of adverse cardiovascular effects in hospitalized poisoned patients is reported to be as high as about 17% [11].

Poisoning with membrane stabilizing agents (i.e., antiarrhythmic drugs, certain beta-blockers, cyclic antidepressants, selective serotonin reuptake inhibitors, antiepileptics, antimalarial agents, and dopamine and norepinephrine uptake inhibitors) and calcium channel blockers are responsible for the majority of cardiovascular deaths [12]. According to reports of the American Association of Poison Control Centers, calcium channel blockers and beta-blockers account for approximately 40% of cardiovascular drug poisoning but represent more than 65% of deaths from cardiovascular medications [13].

Interference with cellular physiology, metabolism, or receptor blockade in these poisonings frequently result in diminished effectiveness of standard advanced cardiac life support (ACLS) protocols, so antidotes or alternatives such as calcium, glucagon, high dose of beta-receptor agonists, insulin/glucose, or intravenous lipid emulsion therapy may be necessary [1]. Patients suffering from ventricular fibrillation or pulseless electrical activity should immediately undergo cardioversion or defibrillation. A nonexhaustive list of agents causing bradycardia or tachycardia in the course of poisoning is shown in Table 1.

Definition of Hypotension and Shock

The term shock in the critically ill (including poisoned) patient is defined by a significant reduction of systemic tissue perfusion, which results in a decreased delivery of oxygen and substrates to tissues. This mismatch between oxygen consumption and delivery leads to cellular hypoxia and consequently to the disruption of essential biochemical processes at the cellular level and can progress to a systemic reaction [14]. At the cellular level, ion-pump dysfunction, membrane leakage, intracellular edema, and acid–base dysregulation may occur and progress to systemic alterations in the serum pH and endothelial dysfunction – triggering inflammatory or anti-inflammatory cascades.

Table 1 Frequent agents that may cause hemodynamic relevant bradycardia or tachycardia, ultimately leading to severe shock or (functional) cardiac arrest

Agents that may lead to bradycardia	Agents that may lead to tachycardia
Beta-receptor blockers	Sodium channel blockers such as tricyclic antidepressants, type I antiarrhythmics, local anesthetics, chloroquine, quinine
Calcium channel blockers	Other pharmaceuticals (e.g., theophylline)
Alpha ₂ -receptor agonists (e.g., clonidine, dexmedetomidine)	Drugs of abuse (e.g., amphetamines, cocaine)
Cardioactive glycosides (e.g., digoxin, fox glove, yellow oleander)	Cardioactive glycosides (e.g., digoxin, fox glove, yellow oleander)
Cholinergic agents (e.g., organophosphate compounds, carbamates)	Natural toxins (e.g., aconitine, night-shadow plants)
Potassium channel blockers (type III antiarrhythmics) (e.g., sotalol, amiodarone)	Potassium channel blockers (type III antiarrhythmics) (e.g., sotalol, amiodarone)
	Noradrenaline reuptake inhibitors (e.g., venlafaxine)

Sequential cell death with end-organ damage, even progressing to multi-organ failure, may then ultimately lead to death.

Before hypotension or even shock become clinically obvious, inadequate oxygen delivery with increased serum lactate may occur and is frequently called “cryptic shock” with normal blood pressure but hypoperfusion at the tissue level.

Hypotension can be defined as absolute (e.g., systolic blood pressure <90 mmHg) or relative (e.g., drop in systolic blood pressure >40 mmHg). The latter may partly explain why patients may be in shock despite high or normal blood pressure levels. Focusing mainly on traditional resuscitation endpoints such as blood pressure (and cardiac output) carries a high risk of overemphasizing systemic hemodynamics at the cost of tissue perfusion [15]. Focusing mainly on macrocirculatory parameters (such as the mean arterial pressure) additionally implies a high risk of overusing

vasopressors, which in turn may further aggravate tissue hypoperfusion.

For early diagnosis and adequate treatment, it is therefore of paramount importance to realize that shock is defined as an imbalance between oxygen (and substrate) delivery and oxygen consumption. The patient can therefore be in shock irrespective of the level of blood pressure, which can be low, normal, or even elevated. Several studies have revealed that, within the autoregulatory limits of the heart and brain, arterial blood pressure poorly correlates with tissue perfusion in critically ill patients [15, 16].

Pathophysiology

Mechanisms of hypotension and shock in poisoned patients are diverse and can be a combination of cardiac, central, and peripheral mechanisms. Systemic tissue perfusion and the maintenance of blood pressure are determined by adequate cardiac output (CO) in combination with appropriate systemic vascular resistance (SVR). CO may be reduced due to toxin-induced myocardial depression, arrhythmia (abnormal impulse formation, conduction disorders, or triggered rhythms), and relative (venous pooling) or absolute hypovolemia (true fluid loss or third-spacing). The CO itself is the product of heart rate and stroke volume, the latter being related to preload, myocardial contractility, and afterload. SVR may be reduced due to drug-induced vascular relaxation, central depression of central vasomotor tone or peripheral adrenergic receptor blockade, or a combination of each. SVR is dependent on blood vessel diameter, length, and viscosity of the blood [17].

Hypotension and/or shock are a consequence of a reduction in CO, SVR, or both; however, even an elevation of the one may be seen when the other is disproportionately low. Three types of shock are usually distinguished [18]:

- *True hypovolemic* (e.g., severe hemorrhage, third-spacing) is usually not seen primarily in the setting of poisoned patients,
- *Cardiogenic* which can be myopathic, arrhythmic, mechanical, or extracardiac obstructive

Table 2 Different types of shock with corresponding hemodynamic variables

Clinical classification	Preload (PCWP)	Cardiac output (CO)	Afterload (SVR)	Tissue perfusion (S_{cvO_2})
Hypovolemic shock	Decreased	Decreased	Increased	Decreased
Cardiogenic shock	Increased	Decreased	Increased	Decreased
Distributive shock	Decreased or normal	Increased	Decreased	Increased

PCWP pulmonary capillary wedge pressure [normal: 9 ± 4 mmHg], *CO* cardiac output varies with body size and is the product of stroke volume \times heart rate [normal: 4–8 L/min], *SVR* systemic vascular resistance, determined by vessel diameter and distensibility (compliance). It is calculated by: $SVR = (MAP - CVP) \times 80/CO$ with MAP is mean arterial pressure [in mmHg] and *CVP* = central venous pressure [in cm H₂O], usually measured in the superior vena cava [900–1500 dyn \times s/cm⁵]; S_{cvO_2} , Central venous oxygen saturation [normal: 72%], usually measured in the superior vena cava

(e.g., pulmonary embolism, cardiac tamponade, or tension pneumothorax)

- *Distributive* (e.g., septic, toxic, anaphylactic, endocrine).

Measurement of CO, SVR, and eventually the pulmonary capillary wedge pressure (PCWP) can assist in differentiating these shock types. The mixed venous oxygen saturation (S_vO_2) is a clinical parameter of reduced tissue perfusion.

Combined shock is a mixture of these three different types of shock, coexisting in one patient (e.g., distributive and cardiogenic shock in a patient with calcium channel blocker overdose).

Hypovolemic shock is a result of decreased preload due to intravascular loss of fluid volume. PCWP (a parameter for preload) is reduced, CO (a parameter for pump function and myocardial contractility) is reduced, and the SVR (a parameter for the myocardial afterload) is compensatory elevated. Tissue perfusion is reduced.

In *cardiogenic shock*, CO is decreased and both the SVR and the PCWP are compensatory increased and tissue perfusion is reduced.

Finally, in *distributive shock*, CO is increased, PCWP may be normal or reduced, and SVR is diminished, resulting in an increased tissue perfusion. Table 2 gives an overview of several quantitative hemodynamic variables and their change according to the type of shock.

A more conceptual model of poison-induced shock with its differential diagnosis and important treatment considerations is summarized in Fig. 1.

Development of hypotension and shock usually is a physiological continuum starting with preshock

(“warm shock,” clinically often compensated due to adaptive physiological mechanisms), manifest shock (compensatory mechanisms start to fail and symptoms of organ failure may appear), and the stage of manifest end-organ dysfunction. An overview of different shock types with echocardiography findings is shown in Table 3.

Diagnostic Approach

Any patient with suspected cardiovascular poisoning should be immediately evaluated for potential hemodynamic compromise. Minimal requirements are a continuous cardiac monitoring, including pulse oximetry, noninvasive blood pressure measurement, and a 12-lead ECG performed to evaluate for cardiac ischemia, arrhythmia, and the potential of QRS-widening or QT interval prolongation [10].

Medical history often cannot be provided in patients in profound shock and must instead be obtained from relatives or medical records available. The physical examination should be straightforward and directed toward uncovering the type, severity, and cause of hypotension or shock. Usually, patients in shock present universal (cardinal) findings and more specific findings that may suggest a particular type of shock.

Cardinal findings in patients with manifest shock and/or end-organ dysfunction include hypotension, abnormal mental status (e.g., as a sign of cerebral hypoperfusion), oliguria (as a sign of intravascular volume loss and/or shunting of renal blood flow), metabolic acidosis (often with elevated serum lactate due to both decreased

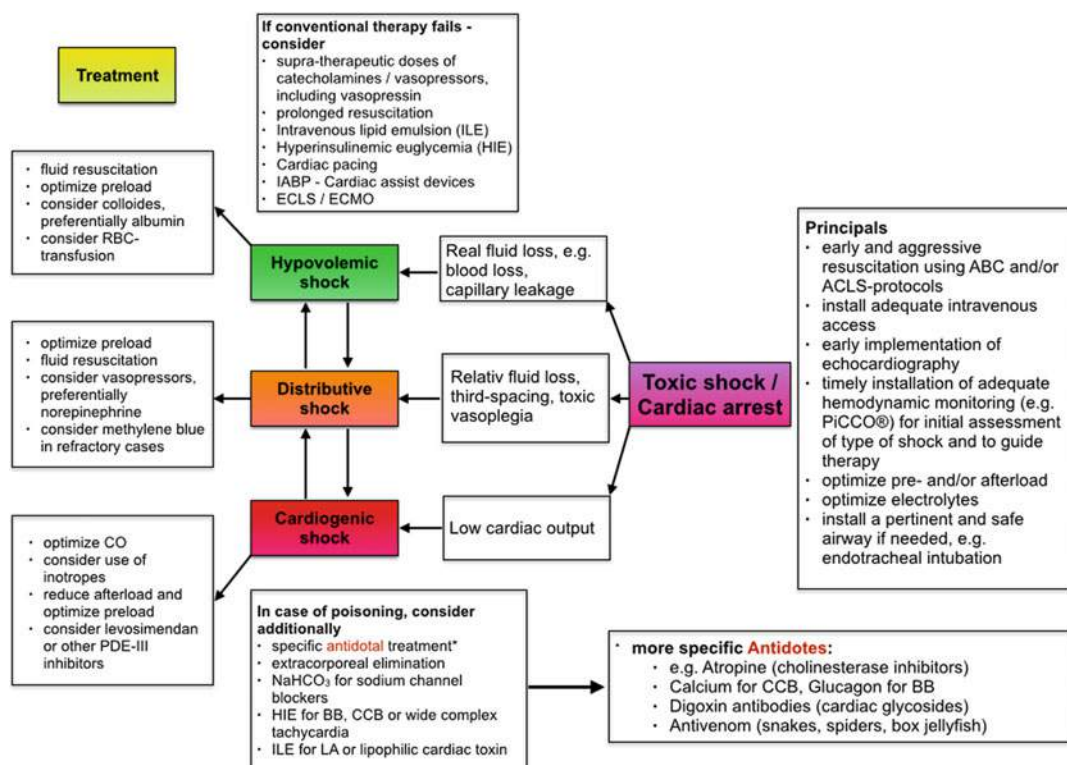


Fig. 1 Flowchart of pathophysiology and treatment options of different types of toxic shock. BB beta-receptor blockers, CCB calcium channel blockers, LA local anesthetics

lactate clearance and/or increased production due to anaerobic metabolism in hypoxemic tissues), and in some patients cool and clammy skin (not seen in hyperdynamic states of shock) [17]. Cardiogenic pulmonary edema may complicate the clinical picture and is typically characterized by increased PCWP >20 mmHg. Evaluation of skin hypoperfusion – the largest organ of the body – can indicate even early stages of hypotension and shock. The term skin “mottling” describes a red-lilaceous discoloration of the skin due to reduction of blood flow in small skin vessels. It involves vessels with a high density of noradrenergic receptors, such as the knee [19]. Associated with decreased urinary output and altered consciousness, mottling over the knee is a well-known clinical sign of circulatory shock [18]. Two recent small sample studies reported an incidence of mottling between 46% and 70% in patients admitted for septic shock, and this was associated with increased mortality at day 14

[20, 21]. In a much larger recent prospective study on 791 critically ill patients, the overall incidence of skin mottling was 29%, and it was 49% in a subset of septic shock patients. The independently associated in-ICU mortality was significantly different at 8% in patients without mottling, 30% in patients with a short mottling, and 40% in patients with persistent skin mottling [22]. Therefore, assessment of mottling may be a simple and reliable parameter allowing continuously identifying patients with impaired peripheral perfusion and increased mortality. Importantly, as with other parameters of impaired peripheral perfusion (e.g., prolonged capillary refill, high skin temperature gradient, or hyperlactatemia), the occurrence of mottling may, however, be seen also in patients without the need of vasopressors or a MAP greater than 65 mmHg [22, 23]. Several parameters reflecting tissue parameters and clinically targeted endpoints are summarized in Table 4.

Table 3 Different types of shock and typically echocardiographic findings

Type of shock	Cardiac output	Echocardiography
Hypovolemic shock	Low (CVP low)	Small cardiac chambers Contractility normal or high
Distributive shock	Normal or high	Normal cardiac chambers Preserved (normal) contractility
Cardiogenic shock	Low (CVP high)	Large cardiac ventricles Impaired contractility
<i>Obstructive shock^a</i>	<i>Low (CVP high)</i>	<i>Pulmonary embolism/ pneumothorax Dilated right ventricle, small left ventricle Pericardial tamponade Pericardial effusion, small right and left ventricle, dilated inferior vena cava</i>

CVP central venous pressure

^aFor a complete differential diagnostic approach, although this type of shock is usually not seen in poison-induced shock

In the toxicological setting, the appearance of specific toxidromes and/or analytical confirmation of toxins may be helpful in the diagnosis of shock, but these should not delay early and aggressive treatment of hypotension or shock. It is also important to note that analytical confirmation of toxins is not universally present or available, and even when they are available there will often be a significant delay in obtaining results. In every case, physical findings are neither sensitive nor specific for identifying the cause of shock.

Whenever possible, focused echocardiography should be performed as soon as possible in any patient presenting with shock. Echocardiography should include assessment for pericardial effusion, measurement of left and right ventricular size and function, respiratory variations in the vena cava, and measurement of stroke volume [18, 24]. See also Table 3 for echocardiography signs, differentiating types of shock.

Laboratory tests should be performed early in the evaluation of patients with shock including basic chemistry (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine,

Table 4 Parameters for tissue perfusion and suggested endpoints (Adopted from [15])

Class	Parameter	Endpoint
Peripheral perfusion	Tissue oxygen saturation Skin mottling Peripheral perfusion index Capillary refilling	≥70% Absence ≥1.4 ≤4.5 s
Venous oxygen saturation	Central (S _{CV} O ₂) Mixed (S _V O ₂)	≥65–70% ≥60–65%
Arterial lactate	Absolute Lactate clearance	≤2 mmol/L ≥20% decrease/2 h
Urine output	Quantitative	≥0.5 mL/kg/h

Peripheral perfusion index is derived from pulse oximetry signal and defined as the ratio between the pulsatile component of the light reaching the light-sensitive cell of the pulse oximetry probe; S_{CV}O₂ central venous oxygen saturation, S_VO₂ mixed venous oxygen saturation

liver function tests, lipase), coagulation studies (international normalized ratio, partial thromboplastin time), cardiac enzymes, arterial blood gas, toxicology screen, and lactate level. A complete blood count including a hemogram may differentially indicate a septic origin of shock. Venous whole blood lactate correlates with arterial lactate and is appropriate to screen for shock.

Catecholamines are well known to increase arterial lactate concentrations either by exaggerated stimulation of aerobic glycolysis [25] or induction of tissue hypoperfusion by inappropriate vasoconstriction [26, 27]. Although clearance of lactate is more delayed than the increase of MAP or CO, blood lactate level should decrease within hours and may indicate if therapy is effective [18]. Targeting a decrease of 20% in blood lactate within 2 h in patients with shock and an initial lactate level >3 mmol/L has been shown to be associated with reduced in-hospital mortality [28].

Hemodynamic Variables Assessing Severity of Hypotension and Shock

Since circulatory shock represents an imbalance between oxygen supply and requirement, maintenance of adequate oxygen delivery to the tissue is

essential and principally determined by CO. Absolute measures of CO are less important than monitoring trends in response to different treatment strategies and to target a predefined CO is not advisable since the CO needed will significantly vary, even in the same patient over time [18].

In a retrospective cohort study of 119 patients with cardiogenic shock (as a result of an acute coronary syndrome), cardiac index (CI) and cardiac power index (CPI) during the first 24 h after admission to intensive care unit were the most important hemodynamic variables separately associated with 28-day mortality. A CI of 3 L/min/m² and a CPI of 0.8 W/m² were most predictive of 28-day mortality [29]. The relative risk of death at day 28 substantially increased when CI dropped below 2 L/min/m² and CPI dropped below 0.4 W/m². Comparable cut-off values have been reported in other studies [30, 31]. Interestingly, no hemodynamic variable was associated with arterial lactate level however epinephrine and norepinephrine doses were [29]. Even though none of the hemodynamic variables commonly measured (e.g., MAP, CVP, SVR) were associated with outcome in this analysis, it is important to note that patients with cardiac shock due to acute coronary syndrome and patients with other causes of shock (i.e., vasodilatory shock, combination of central and peripheral circulatory failure due to poisoning, etc.) may differ substantially from a pathophysiological perspective.

Hemodynamic measurement can be helpful in determining the type of shock (see above and additionally in Table 2) and can also be used to titrate vasopressor therapy, assess hemodynamic effects of changes of respiratory settings, and guide fluid resuscitation. Hemodynamic optimization using, e.g., goal directed fluid therapy (GDFT) has been correlated with improved outcomes, at least in surgical patients [32]. The evidence supporting GDFT is sufficiently strong that national recommendations by the UK, France, and other European countries have embraced this approach [33].

Pulmonary artery catheterization (PAC) can obtain CO, PCWP, and SVR. However, it is

invasive, requires a certain level of operator skill and experience, and has potential hazardous side effects such as hemorrhage, rupture of pulmonary vessels, valvular erosions, dysrhythmia, line sepsis, and endocarditis [34]. Furthermore, it has never been shown to improve patient-important outcome parameters [35]. Other less invasive but accurate types of hemodynamic measurement are available and have more and more replaced PAC – which is now generally reserved for the perioperative monitoring of cardiac surgery patients. The less invasive PiCCO-system (PiCCO® Pulsion, Germany) generates CO, SVR, extra vascular lung water, and intrathoracic blood volume (a cardiac preload parameter). It can further add several mathematically derived hemodynamic variables by the means of changes in transpulmonary thermodilution. It needs an arterial catheter with a thermistor on the tip and can typically be placed in either the radial or femoral artery using Seldinger's technique. It can detect changes in temperature (dependent on hemodynamic properties) after injection of a bolus of ice-cold saline (typically 10–20 mL) via the central venous line. This system has been shown to accurately, reliably, and precisely predict hemodynamic variables, as compared to the “gold standard” PAC [36, 37].

While advanced hemodynamic monitoring has become more and more clinically routine in the assessment of hypotension, shock, or sepsis, its use in poisoned patients seems largely underrepresented, and its impact on patient outcome has never been evaluated. As a result, literature regarding this diagnostic approach in the poisoned patient is extremely scarce and limited to single case reports [34]. Consequently, no evidence about its accuracy or usefulness in this setting can be derived.

Furthermore, there is no evidence supporting the role of CVP (targeting between 8 and 12 mmHg) or S_{CV}O₂ (>70%) as an endpoint for fluid therapy [6, 38]. Evidence indicates that CVP does not correlate with volume status but is influenced by factors such as right ventricular function, intrathoracic pressure, and venous compliance, and protocols using the CVP as a guide to fluid therapy may result in over-resuscitation in a substantial number of patients [39, 40].

Adherence to the bundle of parameters as suggested by Rivers et al. [5], such as CVP above 8 mmHg or above 12 mmHg during mechanical ventilation, MAP >65 mmHg, diuresis >0.5 mL/kg/h, $S_{cv}O_2$ > 70%, and lactate <1.5 mmol/L or a decline in lactate levels have been repeatedly criticized in the recent years [41–43]. This holds true particularly for the CVP, the arbitrarily chosen MAP >65 mmHg, but also the $S_{cv}O_2$. The recently published ARISE study enrolling 1600 patients with early septic shock, which were assigned either to an EGDT-approach or an usual-care group, did not find a significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay. Moreover, the EGDT-approach did not reduce all-cause mortality at 90 days, critically questioning the value of such a protocol driven approach [6]. Volume and hemodynamic management should therefore no longer be based on unproven or imprecise surrogate parameters but should consider the actual hemodynamic situation of the individual patient. Evaluation of the cardiac pump function could be obtained easily and rapidly using echocardiography. Filling of the right ventricle and the vena cava can reliably be measured with little training. Surprisingly, the recent surviving sepsis campaign does not consider any methods of bedside hemodynamic evaluation, such as ultrasonography, in their guidelines [4]. The recently closed but not yet published ProMISe study investigating EGDT compared to standard care in targeted 1260 patients in 56 hospitals in the UK will hopefully add some new evidence on the appropriate diagnostic approach for diagnosis of shock. Needless to say, however, this evidence will relate to septic shock patients but not critically ill poisoned patients.

Management

Early and adequate hemodynamic support of patients in shock is crucial to prevent worsening of organ dysfunction and failure. The initial management of shock should be problem oriented and the initial targets are therefore the same,

regardless of the cause, although definitive treatments to reach the goals may differ [18]. The VIP rule is a simple mnemonic to describe essential components of resuscitation and includes [44]: ventilate (administration of oxygen), infuse (fluid resuscitation), and pump (administer vasoactive agents and/or inotropes).

Beyond specific toxicological treatment options, there are of course some important principal supportive and even more aggressive treatment modalities for patients with hypotension and shock, which will be discussed hereunder and are also depicted in Fig. 1.

Antidotal Therapy

Several agent specific antidotes along with the use of glucagon as an agonist of the class B G-protein coupled family of receptors with absence of peripheral vasodilatory effects (e.g., in beta-blocker poisoning) [45], high-dose insulin euglycemia (HIE) therapy (e.g., in beta-blocker or calcium channel blocker overdose, but also other types of shock), and rescue therapy with intravenous lipid emulsion (ILE) (e.g., local anesthetics, other lipophilic drugs) might be beneficial in the management of poisoning leading to severe hypotension or shock, although the clinical effectiveness of these antidotes is mostly based on low-level evidence. These specific treatment modalities, along with the suggested dosing, are discussed in the respective chapters of this textbook.

There are also more specific treatment modalities for poisonings with cardiovascular agents (e.g., Fab-antidotal therapy for digitalis poisoning; enhanced elimination procedures, including single-pass albumin dialysis, the molecular adsorbents recirculating system (MARSTM) technique, or plasma exchange therapy), which are discussed separately within the respective chapters of this textbook. Although the latter extracorporeal elimination techniques may have a role in very special settings of highly protein-bound drug-overdoses (where conventional hemodialysis fails) [46, 47], it is needless to say that most of these techniques require a minimum degree of hemodynamic

stability (i.e., sufficiently high CO) to be applicable – a prerequisite that essentially limits their use in patients with poison-induced severe hypotension, shock, or even cardiac arrest.

Fluid Resuscitation

Regarding cardiovascular stabilization in case of arterial hypotension or tissue hypoperfusion, early aggressive fluid resuscitation has been recommended, at least for the management of patients with severe sepsis and septic shock [3]. In an update of these international guidelines in 2012, initial fluid resuscitation with crystalloids (Level of Evidence [LoE] 1B) achieving a minimum of 30 mL/kg and consideration of the addition of albumin in patients who continue to require substantial amounts of crystalloids to maintain adequate MAP (LoE 2C) with the avoidance of hydroxyethyl starch formulations (1C) was recommended, based on the results of the VISEP [48], CRYSTMAS [49], 6S [50], and CHEST [51] trials. The latter studies are, however, questioned by the latest CRISTAL trial, which investigated the effects of fluid resuscitation with colloid versus crystalloid on mortality in 2857 mixed critically ill patients (sepsis, trauma, or hypovolemic shock without sepsis or trauma) presenting with shock. In this study, the use of colloid versus crystalloid did not result in a significant difference in 28-day mortality, and 90-day mortality was lower among patients receiving colloid rather than crystalloid, although this finding was considered exploratory and requires further research before reaching conclusion about efficacy [52]. A detailed review of the choice of resuscitation fluids was provided recently [53].

As stated in the surviving sepsis campaign, more rapid administration and greater amounts of fluid may be needed in some patients (LoE 1C). Fluid challenge techniques should be continued as long as hemodynamic improvement based on either dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables is observed [4].

Adherence to and variation in recommendations of the surviving sepsis campaign, however,

considerably varies between European intensive care units, as a cross-sectional survey between 145 ICUs of 16 European countries undertaken in 2009 demonstrated [54]. Particularly, the choice of fluid for resuscitation and the choice of the first-line inotropic drug differed significantly between centers, although norepinephrine was clearly the preferred vasopressor drug and nearly 50% of the respondents claimed to use supplementary vasopressin when norepinephrine dose exceeded a predefined level. The most commonly claimed hemodynamic variables to guide shock resuscitation were MAP (87%), $S_{CV}O_2$ (65%), CVP (59%), S_vO_2 (42%), and CI (42%) [54].

Fluid resuscitation in hypotensive patients, with or without shock, is the mainstay of therapy with the goal of obtaining adequate preload, ventricular filling, and tissue perfusion. Pragmatic endpoints for fluid resuscitation, however, are difficult to define. In general, the objective is for CO to become preload-independent (i.e., on the plateau of the Frank-Starling curve), but this is clinically difficult to assess [18]. Variations in the beat-by-beat stroke volume measured with CO monitors or indirectly observed variations in the pulse-contour wave in mechanically ventilated patients may be signs of fluid responsiveness but have some limitations [55]. A passive leg-raising test is an appropriate alternative method but requires a rapid response device since the effect is transient [18, 56].

Aggressive fluid resuscitation should, however, be used judiciously in patients at risk of fluid overload or pulmonary compromise (e.g., pulmonary edema, ARDS [acute respiratory distress syndrome], pneumonia) and optimally be adjusted using accurate hemodynamic monitoring (e.g., thermodilution including pulse-contour wave analysis, e.g., PiCCO[®]), or bedside echocardiography evaluating myocardial pump function, cardiac filling pressures, and the vena cava. Measures using the PiCCO[®] technique have been shown to adequately target the amount of volume needed, and to prevent side effects resulting from fluid overload, especially in patients with ARDS [57, 58].

In contrast, in a recently published study, patients with septic shock and/or ARDS were

randomized to a treatment algorithm based on parameters derived from PiCCO[®] or to a CVP-based algorithm. PiCCO[®]-based fluid management did not improve outcome based on the 28-day mortality [59], although it was somewhat unfortunate that patients in the PiCCO[®]-group had significantly higher baseline SOFA and APACHE II scores, both of them clearly having impact on the mortality [60].

A recent systematic review and meta-analysis including 36 clinical studies with 1224 patients investigated targets of perioperative fluid therapy and their effects on postoperative outcome. Three specific targets were identified: a systolic or pulse pressure variation <10–12%, an increase in stroke volume <10%, and a corrected flow time of 0.35–0.4 s. in combination with an increase in stroke volume <10%. Targeting one of these goals resulted in fewer postoperative complications and a shorter length of intensive care unit/hospital length of stay, but postoperative mortality remained unaffected [61]. It is, however, still to be defined whether all of the above mentioned surrogates to guide fluid resuscitation might also be reliably applicable to the subgroup of poisoned patients suffering from severe hypotension or shock.

Should a Target MAP >65 mmHg Generally Be Maintained?

Tissue and microcirculatory perfusion are physiologically regulated by blood flow and not the absolute arterial blood pressure itself. Consequently, the ideal MAP target in patients with shock remains a matter of debate [62–64]. In a recently published multicenter trial in 776 patients with septic shock, 388 underwent resuscitation with a high-target MAP (80–85 mmHg) and were compared to 388 patients with a conventional low-target MAP (65–70 mmHg). This study did not show differences in mortality at either 28 or 90 days, or in the overall rate of serious adverse events, although patients in the higher MAP group had significantly more episodes of atrial fibrillation. Of note, in a subgroup

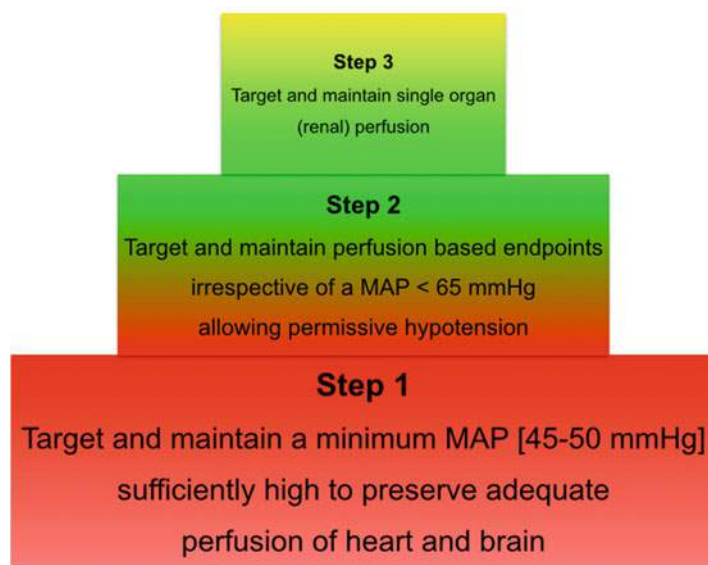
of patients with chronic arterial hypertension, a MAP of around 75–85 mmHg reduced the development of acute kidney injury [65]. In another very recent critical reappraisal of the literature, the authors concluded that a MAP of 65–75 mmHg is usually sufficient in patients with septic shock, but the time to achieve the target as well as the technique used to increase MAP needs further investigation [66].

In a post hoc analysis in 290 septic shock patients, MAP levels above 70 mmHg were not associated with 28-day mortality but higher catecholamine doses were significantly associated with adverse events, such as occurrence of acute circulatory failure, metabolic acidosis, renal failure, and thrombocytopenia [67].

The association between different arterial blood pressure values during the first 24 h after ICU admission, 28-day-mortality and organ function was evaluated in 274 septic patients. In this study, arterial blood pressure was associated with 28-day-mortality even when corrected for the impact of disease severity [68]. Currently, a MAP of 65–90 mmHg is a widely accepted and recommended blood pressure range for critically ill patients [69]. In the study of Dünser, there was no difference in the risk of death at 28 days between arterial blood pressure drops below MAP 65, 70, and 75 mmHg. However, a MAP of 60 mmHg during the first 24 h after ICU admission reflected a critical level as one or more episodes of MAP <60 mmHg increased the risk of death by 2.96 (CI 95%, 1.06–10.36; $p = 0.04$). The authors concluded that a MAP level equal or >60 mmHg may be as safe as higher MAP levels and may contribute to the use of lower doses of catecholamines, thereby reducing side effects and possibly increasing tissue perfusion [68].

Considering whether critical care physicians should strictly adhere to the recommendation to target a MAP above 65 mmHg and with regard to the published evidence to critically scrutinize these guidelines, a three-step approach of resuscitation endpoints based on growing evidence and physiological considerations was proposed recently [15]. Even though this algorithm has

Fig. 2 Stepwise approach to maintain sufficient organ (renal) perfusion, despite MAP <65 mmHg (Adopted from Ref. [15])



been suggested for septic shock patients only, it may be considered for poison-induced hypotension and shock as well (see Fig. 2).

1. In step one, a minimum individual and context-sensitive arterial blood pressure to preserve heart and brain perfusion should be targeted. A MAP between 45 and 50 mmHg rather than at least 65 mmHg is usually considered sufficient, respecting individual cardiac constellations, which may demand higher MAP values. Despite the fact that MAP does not accurately predict global tissue perfusion, it correlates well with coronary and cerebral blood flow.
2. In step two, tissue perfusion endpoints irrespective of MAP <65 mmHg (“permissive hypotension”) should be achieved considering: arterial lactate, peripheral perfusion, urine output, venous oxygen saturation (or a combination of these); see also [15].
3. In step three, markers of single-organ (mainly renal) perfusion should be targeted. Of all internal organs, the kidneys have the poorest capability to adjust to reductions in blood flow [70], therefore optimizing single-organ perfusion is in most patients equivalent to optimizing renal perfusion [15]. This can be achieved by increasing dose of norepinephrine (after

targeting step 1 and 2), critically weighing the potential risks of intensifying catecholamine therapy. This approach may be accompanied by ultrasonographic determination of the renal resistive index to optimally adjust vascular tone to improve kidney perfusion [71].

Vasopressors and Classical Inotropes

Adrenergic agonists have a rapid onset of action, high potency, and a short half-life, making them easy to dose, and they are therefore considered as first-line vasopressors. However, due to their potential harmful effects with myocardial ischemia, pure β -adrenergic agents – such as isoproterenol – should be limited to patients with severe bradycardia. On the other hand, the use of pure α -adrenergic agents – such as phenylephrine – is rarely indicated as they can decrease CO and impair tissue perfusion [18].

In their initial international surviving sepsis campaign, use of norepinephrine or dopamine as first-line vasopressor drugs or dobutamine as inotropic support has been recommended [3]. In the latest update, norepinephrine is still recommended as the first-choice vasopressor (0.1–2.0 $\mu\text{g/kg/min}$) to maintain a MAP

>65 mmHg (LoE 1B), adding epinephrine when an additional agent is needed to maintain adequate blood pressure. Vasopressin (0.03 U/min) can be added to norepinephrine to either raise MAP to target or to decrease norepinephrine dose, but it should not be used as the initial vasopressor (ungraded). Dopamine was recently associated with an increased mortality among patients with cardiogenic or septic shock and is no longer recommended in the surviving sepsis campaign, except for highly specific circumstances, e.g., patients with low risk of tachyarrhythmia and absolute or relative bradycardia (LoE 2C), and it should not be used for renal protection (LoE 1A) [4, 72, 73]. Dobutamine infusion (up to 20 µg/kg/min) administered or added to vasopressors in the presence of either myocardial dysfunction (e.g., elevated cardiac filling pressures and low CO) or ongoing signs of hypoperfusion (despite achieving adequate intravascular volume and adequate MAP) is recommended (LoE 1C). It was recommended not using a strategy of inotropic therapy to increase cardiac index to predetermined supra-normal levels (LoE 1B) [4]. Epinephrine, with predominantly β-adrenergic effects at lower doses and additional α-adrenergic effects at higher doses, did not show any beneficial effects over norepinephrine in septic shock patients and should reserve as a second-line agent for severe cases [4, 62].

It is unquestionable that catecholamines are highly effective to counteract cardiovascular instability, but they can be associated with numerous side effects, particularly at higher doses – with the most devastating negative effects on the heart [74]. For example, high doses of vasopressors (e.g., norepinephrine >0.5 µg/kg/min) in septic shock patients were associated with excessively high mortality [20]. Catecholamines have also repeatedly been associated with disease-related events on cardiac function ranging from tachycardia, ischemia to myocardial stunning, and apoptosis [74].

In a prospective observational study on 112 surgical intensive care unit patients with cardiovascular failure requiring catecholamine therapy, almost half of the patients (48.2%; 95% CI, 38.8–57.5%) developed 114 adverse cardiac events and these were related to both morbidity

and mortality. Specifically, the most frequent adverse events included new onset of tachyarrhythmia (49.1%), prolonged elevated heart rate (23.7%), and myocardial cell damage (17.5%), as reflected by increase in troponin T serum levels [75]. Both the extent and duration of catecholamine vasopressor therapy were independently associated with adverse cardiac events. Myocardial stunning, diastolic dysfunction, and increased ventricular afterload may all explain persistent reductions in systemic blood flow during treatment with (high doses of) vasopressors [76].

These negative effects might be reduced using a catecholamine-sparing treatment regimen whenever possible, including adequate fluid resuscitation or adding vasopressin, which has been shown to significantly reduce norepinephrine requirement without increasing the risk of serious adverse events in vasodilatory shock [77].

While there is no clear evidence to support the use of any vasopressor agent in poisoned patients with shock, both α-adrenergic vasoconstriction and β-adrenergic support of chronotropy and inotropy seems intuitive and should be the goal of therapy. For example, norepinephrine has been associated with improved outcomes in TCA-overdosed patients [78] and norepinephrine and epinephrine are recommended in current toxicological textbooks as the catecholamines of choice [79]. It should be noted, however, that there are some poisonings (e.g., overdoses with β-blockers/calcium channel blockers) where conventional or even high doses of α/β-agonists have proven to be less effective in the treatment. In these particular overdoses, alternative antidotal strategies may be required (e.g., high-dose insulin treatment, intravenous lipid emulsion, calcium salts) as discussed in more detail in chapters dealing with these specific poisonings [80, 81].

Use of high-dose vasopressor therapy in the management of drug-induced cardiovascular shock refractory to standard therapy has been discussed repeatedly. In the 1992 American Heart Association (AHA) guidelines, norepinephrine was recommended to be added if more than 20 µg/kg/min of dopamine was needed to maintain blood pressure. Epinephrine (2–10 µg/min)

was regarded as an alternative to be used in patients not in cardiac arrest (e.g., in symptomatic bradycardia), although it was not considered as a first-line agent. Norepinephrine was considered indicated in patients with severe hypotension (systolic blood pressure <70 mmHg) and a low systemic vascular resistance (SVR). Patients in refractory shock were deemed to require 8–30 $\mu\text{g}/\text{min}$ norepinephrine [82]. In the TOX-ACLS guideline from 2001 [83], a case report (LoE III) [84] and one animal study (LoE IIb) [85] supported the recommendation to use high-dose vasopressors in the management of drug-induced cardiovascular shock refractory to conventional therapy; these reports are discussed in more detail in the following paragraphs.

In the case report of Kalman et al., a 55-year-old man ingested 1200 mg atenolol together with 2880 mg slow-release verapamil. Vital signs at admission showed severe hypotension (systolic blood pressure 40–50 mmHg) and bradycardia (20/min). Treatment with atropine, prenalator, intravenous fluids, and calcium gluconate was ineffective, as was administration of dobutamine and isoprenaline. Only the combined infusion of epinephrine (up to 2.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$), norepinephrine (up to 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$), and dopamine (50 $\mu\text{g kg}^{-1} \text{min}^{-1}$) resulted in sustained cardiovascular stability and inotropes were discontinued 2 days after admission. No adverse events from the massive catecholamine infusion were reported, and the patient could be discharged at day 5 without sequelae [84].

In the study of Knudsen et al., the authors investigated different doses of epinephrine or norepinephrine (0.1, 0.5 or 5 $\text{mg kg}^{-1} \text{min}^{-1}$) in amitriptyline-intoxicated rats (0.625 $\text{mg kg}^{-1} \text{min}^{-1}$ amitriptyline by infusion throughout the experiment). Both epinephrine and norepinephrine appeared effective in reversing amitriptyline-induced cardiovascular shock, and they both significantly increased contractility, MAP, and heart rate, but epinephrine showed higher survival rates and had fewer arrhythmogenic properties compared to norepinephrine. The authors concluded that epinephrine may be the preferable inotrope for amitriptyline-induced cardiovascular shock [85].

In contrast, another good quality animal study (LoE IIb) in propranolol (30 $\text{mg kg}^{-1} \text{h}^{-1}$) intoxicated and spontaneously breathing rats did not show any beneficial effect on cardiovascular and respiratory variables or survival time, for the nonselective β -agonist isoprenaline (up to 50 $\mu\text{g kg}^{-1} \text{min}^{-1}$), the selective β_1 -agonist flerobuterol (up to 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$), or for the β_2 -selective lipophilic agonist clenbuterol (up to 50 $\mu\text{g kg}^{-1} \text{min}^{-1}$) [86].

High-dose vasopressors may, however, induce ventricular dysrhythmias in hearts already prone to dysrhythmia and close cardiac monitoring (including central hemodynamic measurement of CO and SVR), careful selection of agents, and titration of doses is mandatory. Vasopressors should be rapidly titrated until shock is adequately treated or until recurrent ventricular dysrhythmias, signs of peripheral vasoconstriction, or an above-normal SVR is observed (LoE IIb) [83]. In patients with underlying or toxin-induced cardiac dysfunction, any vasopressor-mediated increase in SVR augments left ventricular afterload and may thus reduce CO, which in turn means no or little benefit for the tissue perfusion [87].

It is thus very difficult to draw any conclusive recommendation about the usefulness of high-dose vasopressors or inotrope agents in toxin-induced cardiovascular shock, as protocols, investigated toxins, doses, class, and route of administration of vasoactive agents have varied between different studies.

Besides traditionally used vasopressor agents, there are some newer vasopressors, namely, 4-aminopyridine (4-AP), indicating positive responses in single human case reports and murine studies of intractable shock and hypotension resulting from calcium channel blocker overdose [88–91]. 4-aminopyridine indirectly influences calcium channels as it selectively blocks the potassium channels K1 on the cytoplasmatic side of the cellular membrane, thereby depolarizing the cell and opening voltage-dependent calcium channels [91, 92]. Rodent and feline models have demonstrated hemodynamic improvements of verapamil poisoning with infusion doses of 1–2 mg/kg 4-AP [89, 93, 94]. Cardiac output and blood pressure

were improved by 4-AP alone and in combination with levosimendan in a rodent model of verapamil poisoning [88, 92].

Metaraminol (Aramine®), a catecholamine with predominant alpha-adrenergic receptor activity, was successfully administered in a significant amlodipine overdose (560 mg) who failed to clinically respond to conventional treatment, including fluid resuscitation, administration of calcium salts, glucagon, and norepinephrine/epinephrine [95]. Metaraminol at a concentration between 0.5 and 1.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$ has potent peripheral vasoconstrictor activity with negligible effects on both myocardial function and cardiac output, thereby only minimally increasing myocardial oxygen demand [95, 96]. However, although widely used in Southeast Asia and Australasia, Metaraminol is infrequently used in Europe and the USA, and experience in drug-induced shock with this agent is very limited, so far.

Despite promising clinical effects of 4-AP and metaraminol in single cases or animal studies of calcium channel blocker overdose, further investigations are required to define whether these agents could enrich our armamentarium in the treatment of poison-induced shock.

Other Inotropes and Phosphodiesterase-III Inhibitors

The evidence for clinical meaningful benefits of newer inotropes in the treatment of severe hypotension or shock is weak. Data regarding the use of inotropes in poisoned patients are scarce and even in the specific cardiologic setting there are at present no robust or convincing data to support a distinct inotropic drug-based therapy as superior to reduce mortality in hemodynamic patients with cardiogenic shock or low CO as a complication of acute myocardial infarction – as stated in a recent comprehensive Cochrane Review [97].

Inotropes improve myocardial contractility and induce additional reduction of SVR for left ventricular afterload, thereby increasing cardiac output [98]. However, inotropes increase myocardial oxygen demand, induce cardiac arrhythmias, and may thus worsen heart function, especially in

the circumstances of myocardial infarction or cardiogenic shock [99]. In fact, clinical trials using classical inotropic agents (i.e., dobutamine, enoximone, or milrinone) suggest that both short-term treatment of acute heart failure without an essential requirement for inotropic support as well as long-term inotropic therapy in patients with severe chronic heart failure might increase arrhythmias and mortality [100, 101]. A retrospective analysis of 329 patients compared hemodynamic and clinical effects of milrinone (a PDE-III-inhibitor, also called inodilator) versus dobutamine. Despite more favorable hemodynamic effects in patients treated with milrinone, there was no statistically significant difference in in-hospital mortality between milrinone (7.8%) or dobutamine (10%) treated patients [102]. Although dobutamine led to more sinus tachycardia, both agents carried a significant risk of atrial and ventricular arrhythmias, probably related to increased intracellular calcium levels [103].

The use of vasodilators is furthermore often limited by hypotension and requires invasive hemodynamic monitoring to be administered safely. Moreover, in patients with severe hypotension or shock, even traditional inotropes (e.g., dobutamine or milrinone) may be poorly tolerated due to their vasodilatory effects. In these scenarios, peripherally acting agents (e.g., vasopressors) may be transiently required to increase blood pressure during the initiation of inotropic therapy [99]. In cases with potentially reversible insults (i.e., intoxication, acute myocardial infarction, and fulminant myocarditis), inotropes can serve as a bridge to a definitive therapy (e.g., revascularization) or recovery (e.g., falling levels of toxins).

Levosimendan

Levosimendan is a calcium sensitizer, enhancing myocyte sensitivity to calcium and thereby increasing force of contraction and improving CO. At higher doses, levosimendan also inhibits PDE-III, similar to other PDE-inhibitors such as milrinone. Finally, levosimendan has vasodilatory

properties through its action on adenosine triphosphate-sensitive potassium channels [99]. Levosimendan was found to have an additional distinct vasodilatory effect mediated by opening ATP-sensitive potassium channels (K_{ATP}) in vascular smooth muscle. A further postulated cardioprotective effect remains incompletely understood, but opening of mitochondrial K_{ATP} channels may play a crucial role [104]. The drug increases CO by 30–50% and decreases elevated filling pressures by a similar degree after a bolus dose of 6–12 $\mu\text{g/kg/min}$ followed by infusion of 0.2 $\mu\text{g/kg/min}$, as recommended by the manufacturer. According to a recent meta-analysis of randomized controlled studies (in nonpoisoned patients), the recommended dose range for levosimendan is 3–36 $\mu\text{g/kg}$ as intravenous bolus and 0.05–0.6 $\mu\text{g/kg/min}$ for continuous infusion [105].

Levosimendan as a vasodilator decreases both right and left ventricular preload and afterload. However, hypotension may limit or even lead to discontinuation of levosimendan, thus adequate fluid resuscitation along with low-dose vasopressors may be required in certain cases.

One key factor considered important in sepsis-induced (and probably toxin induced) myocardial depression is an alteration in calcium homeostasis within the cardiac myocyte secondary to circulating cytokines [106]. Other potentially beneficial effects include opening of K_{ATP} channels (resulting in improved tissue oxygenation and organ protection) along with anti-inflammatory properties of levosimendan and relaxation of vascular smooth muscle, which could lead to an improvement in perfusion, especially in hypoperfused areas such as the gastrointestinal tract [104, 107]. Levosimendan is, however, costly and has a half-life of several days, preventing timely dose adjustment in acute shock states which can limit its use in these circumstances [18].

In a small prospective, randomized open-label study comparing levosimendan and enoximone in refractory cardiogenic shock complicating acute myocardial infarction, survival rate at 30 days was significantly higher in the levosimendan-treated group (69% vs. 37%, $p = 0.023$); the latter

needed also a lower cumulative dose of catecholamines. However, only 32 patients were included in this study [108]. Effective use of levosimendan in Takotsubo cardiomyopathy has been also reported, and as a noncatecholamine inotrope, levosimendan may theoretically offer a rational treatment opportunity in this particular scenario [109].

Overall, although inotropes such as levosimendan in septic shock patients or patients with acute heart failure have been shown to improve cardiac parameters and despite promising single small studies, the proven evidence does not demonstrate improved overall survival [97, 110]. A currently recruiting randomized controlled trial (Levosimendan for the prevention of acute organ dysfunction in sepsis; LeoPARDS) will hopefully help to define its efficacy in septic shock patients. Whether levosimendan has a role in poisoned patients with severe hypotension or shock remains unclear. Importantly, hypotension in the overdose setting is frequently a result of a vasodilatory state – similar to the hyperdynamic state in the peripheral circulatory failure seen in septic patients. In this circumstance, a vasopressor such as norepinephrine (or vasopressin in certain circumstances) will still remain the most appropriate agent to improve blood pressure and systemic perfusion.

There are few reported cases with calcium channel blocker overdose that have been – along with extensive conventional therapy – successfully treated with levosimendan [111, 112]. Although results from animal models of calcium channel blocker and beta-blocker toxicity have shown that levosimendan improves CO, they have not shown that it increases blood pressure [113–116].

Vasopressin Analogues

Vasopressin physiologically mediates its cardiovascular effects via the V_1 receptor. It furthermore stimulates V_2 and V_3 receptors as well as oxytocin and purinergic receptors and thus has a wide range effect on several organ systems [117, 118]. Compared to norepinephrine, it may both modulate

immune function through V_1 receptors and have protective effects on endothelial function. Beside its well-known vasoconstrictive and antidiuretic properties, vasopressin has several other effects on substrate metabolism, mitochondrial function and oxidative phosphorylation, endocrine system, coagulation, liver function and bile flow, electrolytes, thermoregulation, immune function, endothelium, and intestinal motility. These may both explain typical and atypical side effects but also potential desirable effects.

Vasopressin analogues such as arginine vasopressin and terlipressin are increasingly used off-label and may be effective to increase MAP and reduce further catecholamine requirements in catecholamine-refractory (hyperdynamic) peripheral shock, although no overall survival benefit for patients in septic shock has been consistently demonstrated [119].

Experimental and clinical reports have demonstrated hypersensitivity against exogenous vasopressin receptor agonists in refractory peripheral shock, and their administration is associated with a marked increase of MAP and exaggerated elevation of SVR, even after small doses, while efficacy of catecholamines is markedly reduced [120].

In adult septic shock patients, vasopressin doses up to 0.04 IU/min are not reported to be associated with impaired CO or oxygen transport [121]. Furthermore, a multicenter, randomized clinical trial (vasopressin and septic shock trial, VASST) revealed no difference in mortality when comparing vasopressin doses of 0.03 U/min compared to norepinephrine alone, but it proved the safety and efficacy of vasopressin to reduce norepinephrine requirements [119]. The rationale for (additional) vasopressin therapy in vasodilatory shock is to reduce high and potentially toxic catecholamine dosages to ranges with a more reasonable benefit-risk ratio [122]. A cohort study indicated that 0.6 $\mu\text{g/kg/min}$ norepinephrine might constitute such a critical limit [123].

A retrospective analysis suggested that vasopressin doses up to 0.067 U/min may be as safe as a lower dose (0.03 IU/min) but more effective [124]. A more recent meta-analysis and systematic review of literature covering nine randomized

controlled trials with nearly 1000 participants investigated vasopressin and terlipressin in critically ill patients and concluded that vasopressin and terlipressin in vasodilatory shock are safe, associated with reduced mortality compared with norepinephrine, and facilitate weaning of catecholamines. In patients with septic shock, vasopressin compared with norepinephrine may also decrease mortality [125]. The long duration of action of terlipressin (several hours compared to minutes for vasopressin) is believed to offer no advantage over vasopressin and is therefore not recommended [18].

Vasopressin has been used as alternative for intractable hypotension in verapamil poisoning [126], but one animal study in verapamil-poisoned dogs demonstrated worsening of CI and no improvement in MAP [127]. Successful use of PDE-III inhibitors, as well as terlipressin, together with conventional antidotes and catecholamines has been reported in single cases of verapamil or angiotensin-II receptor antagonist overdose [128–130].

However, the use of vasopressin analogues may be linked to severe hemodynamic side effects, including reduced CO, diminished oxygen delivery, and consequently poor perfusion of the skin, gut, and liver [131]. Of note, global markers of impaired tissue perfusion such as lactate (or decreased capillary refilling or mottling) may remain constant and may indicate severe tissue hypoxia [132]. Hyponatremia in response to antidiuresis with water retention, decrease in platelet count, impairment of platelet aggregation, and elevation of liver enzymes and bilirubin may also occur [120, 133]. Dünser et al. reported a significant incidence of thrombocytopenia ($<50,000/\mu\text{L}$) in patients treated with vasopressin (0.067 U/min) but found no difference in the norepinephrine treated group [134]. Occurrence of thrombocytopenia during vasopressor therapy (beyond other reasons, i.e., septic patients) is thus frequent, but the clinical impact unclear.

Taken together, continuous application of vasopressin analogues is preferable over bolus doses, but the dose should not exceed 0.03 (-0.067) U/min for vasopressin or 2 $\mu\text{g/kg/h}$ for terlipressin, respectively [120]. Additional patient-tailored

Table 5 Effects of different catecholamines/inotropes/vasopressors on hemodynamic parameters

Catecholamine	CO	HR	SAP	LVEDP	SVR	CBF	MOD
Dobutamine	++	++	+/-	-	-	+	+
Dopamine	+	+	+/-	±0/+	(-)/+	+	++
Norepinephrine	+/-	-/±0	++	+	++	-	+
Adrenalin	++	++	+	+	+	-	++
Milrinone	+	+/++	±0/-	-	-	+	-
Levosimendan	++	+/++	+/-	-	-	+	±0
Vasopressin	±0	-	++	+	+++	-	+/-±0

CO cardiac output, HR heart rate, SAP systemic arterial pressure, LVEDP left ventricular end-diastolic pressure, SVR systemic vascular resistance, CBF coronary blood flow, MOD myocardial oxygen demand

aggressive fluid resuscitation may prevent adverse hemodynamic side effects of vasopressin analogues. Regular evaluation of ischemic skin lesions seems advisable although the incidence of skin necrosis does not appear to be higher in patients treated with vasopressin analogues compared to single catecholamines [135]. Electrolytes, platelets, and liver function tests together with lactate should be regularly (e.g., every 8–12 h) monitored. In cases of rapid deterioration, vasopressin analogues should be discontinued.

Table 5 shows a summary of typical effects of different catecholamines or inotropes on hemodynamic variables that can be quantified by enhanced hemodynamic monitoring.

Intravenous Lipid Emulsion Therapy

Intravenous lipid emulsion therapy is a proven, beneficial, and life-saving treatment of otherwise irretrievable situations in local anesthetic systemic toxicity (LAST) – however, several case reports, case series, and small studies suggest that it may also be beneficial in lipid-soluble poisonings with severe circulatory shock beyond this indication [136]. The most commonly reported nonlocal anesthetic drugs treated with ILE are tricyclic antidepressants and calcium channel blockers. ILE is recommended by the AHA and the American Society of Regional Anesthesia and Pain Medicine (ASRA) for use in LAST [137, 138] and recommended by the American College of Medical Toxicology for consideration in severe hemodynamic instability resulting from lipid-soluble xenobiotics [139]. Current dosing

recommendations from ASRA for 20% lipid emulsion therapy – which are frequently deduced for the ILE therapy for other xenobiotics – are: bolus 1.5 mL/kg (lean body mass) intravenously over 1 min, repeat the bolus for persistent cardiovascular collapse and continue infusion with 0.25 mL/kg/min for at least 10 min after hemodynamic recovery. The continuous infusion rate can be doubled for persistent hemodynamic instability. The upper limit of ILE recommended by ASRA is 10 mL/kg for the first 30 min, although higher doses of several successfully managed cases with no or minor side effects have been reported [137, 139].

The most commonly proposed mechanisms for the resuscitative effects of ILE are partitioning of the (lipid-soluble) xenobiotic and enhanced cardiac metabolism [140, 141]. The latter is suggested as fatty acids are known to increase cardiac myocyte calcium levels and thus ILE may act via direct inotropic action through increasing intramyocyte calcium concentration [142].

Potentially severe adverse effects such as the inability to obtain reliable complete blood count, interference with colorimetric laboratory tests, pancreatitis, respiratory distress syndrome, interference with vasopressors or other life-saving drugs, enhanced absorption of orally ingested lipophilic drugs, and clot formation during extracorporeal membrane oxygenation have to be carefully weighed against the possible benefits of ILE – even no contraindications are absolute in the setting of cardiovascular collapse [139, 143].

The evidence for the effectiveness of ILE in the overdose setting of xenobiotics other than LAST

in hypotensive patients, patients in severe shock or even cardiac arrest is limited and mostly derived from animal models and anecdotal or single case reports, case series, or small prospective studies. Additionally, it is as yet unclear whether hypotheses derived from LAST can be generalized to other agents of similar lipophilicity and/or inhibition to mitochondrial lipid metabolism [136]. Moreover, attributing causality to ILE in successfully resuscitated cardiac poisonings has been questioned given the confounding effects of numerous prior or concurrent interventions [136, 144]. Finally, there is a high probability of substantial publication bias toward positive effects of ILE. Unfortunately, there is no current prospective controlled randomized trial being undertaken to evaluate the efficacy of ILE [139]. This precludes the use of ILE as a first-line therapy for indications other than LAST.

This topic is discussed in greater detail in ► Chap. 152, “Lipid Resuscitation Therapy.”

High-Dose Insulin in Toxic Hypotension or Shock

There is increasing evidence that high-dose insulin (HDI) therapy (at doses between 1 and 10 units/kg/h) – classically recommended for severe beta-blocker or calcium channel poisoning (and discussed more in depth in the chapters related to these drugs) – may also be beneficial beyond these indications in individual scenarios [79, 81, 90, 145–147]. These reports include successful treatment of amitriptyline, citalopram, and amiodarone overdose when conventional treatment strategies have failed [148, 149].

Insulin has positive cardiac inotropic properties by promoting cellular glucose uptake, activating glucose transporters and both cardiac calcium- and potassium channels, and enhancing aerobic metabolism. It furthermore reactivates the phosphatidylinositol 3-kinase pathway – affecting the synthesis of glycogen and lipids – and it dilates systemic, coronary, and pulmonary vasculature via endothelial nitric oxide synthase [79, 146, 150, 151]. In several intact animal models, HDI (assuming the mechanisms mentioned above

may apply) was shown to be effective in enhancing CO and reducing SVR and thereby improving tissue perfusion [146, 152]. In a blinded, randomized controlled trial, HDI was statistically and clinically significantly superior to placebo in pigs with propranolol-induced cardiogenic shock. Moreover, higher insulin doses (10 vs. 5 vs. 1 unit/kg/h) were more effective at increasing CO than lower doses [80].

Beside the promising treatment option of HDI in cardiotoxic shock caused by beta-blocker or calcium blocker overdose, evidence of efficacy and safety so far is limited to animal models, case reports, small series, or prospective studies. As one size does not fit all, dose ranges of insulin have to be defined for overdoses with individual xenobiotics and as always, potentially severe side effects (including hypoglycemia and/or hypokalemia) have to carefully be outweighed against the potential benefits of this treatment strategy [153]. This especially holds true for the risk of severe hypoglycemia for indications other than calcium channel blocker overdose, as the latter cause insulin resistance, making unrecognized hypoglycemia less likely [154].

This topic is discussed in greater detail in ► Chap. 147, “Euglycemic Insulin Therapy.”

Methylene Blue

Traditionally, methylene blue (MB) has been used as an antidote for either hereditary or toxin-induced methemoglobinemia. It was also been considered for ifosfamide-induced encephalopathy, as an aniline dye derivative, and an antimalarial agent [155]. The use of MB has, however, most recently been advocated as a potential adjunct in the treatment of toxin-induced, anaphylactic, or sepsis-related severe hypotension or shock [156–158].

MB has an estimated terminal elimination half-life of 5.25 h and a volume of distribution of 0.2 L/Kg. Metabolism is predominantly via reduction to leucomethylene blue in peripheral tissues. It is eliminated through the kidneys in about 30% after intravenous and about 20% after oral administration [159]. Typical dosing for MB is

1–2 mg/kg of a 1% solution intravenously, with a repeat dose given if there is inadequate initial response [160]. A continuous infusion after the bolus dose has been described at ranges usually between 0.5 and 1 mg/kg/h. Despite its relatively short biological activity, MB can be present as discoloration in the urine for up to 5 days.

MB is thought to exert its main therapeutic effect in shock states by increasing SVR and reversing myocardial depression [161]. MB inhibits soluble guanyl cyclase (GC) and nitric oxide synthase (NOS) activity. Its inducible form (iNOS) is produced in cardiac myocytes, and vascular smooth muscle produces nitric oxide (NO). NO activates soluble GC producing cyclic guanosine monophosphate (cGMP). Elevated intracellular cGMP leads to relaxation of myocardium and vascular smooth muscle and increases vascular permeability. In summary, inhibition of GC by MB prevents relaxation of vascular smooth muscle (thereby increasing SVR), prevents relaxation of myocardium (reversing myocardial depression), and prevents increased vascular permeability (reversing third-spacing) [160]. In several dose-finding studies, MB has been shown to increase MAP, SVR, and pulmonary vascular resistance [162, 163].

The strongest evidence that MB may be a useful adjunct in raising blood pressure in septic shock patients is provided by two randomized controlled trials. MB, compared to saline, significantly increased MAP, although the effect was transient and MB did not have an impact on survival rates [164, 165].

In a recent case report, Jang et al. reported on the use of MB in the treatment of refractory shock from amlodipine [156]. After consuming 400 mg amlodipine, the patient became severely hypotensive and was treated with high doses of fluids, calcium gluconate, high-dose insulin, glucagon, dopamine, and norepinephrine without substantial effect on the MAP. After a bolus dose of 2 mg/kg of MB over 20 min followed by 1 mg/kg/h intravenously, MAP significantly improved and high-dose insulin together with all vasopressors could be weaned. Although the authors suggested MB as a rescue therapy in the treatment of refractory hypotension in calcium channel blocker

poisoning, a synergistic effect between all of the applied therapies and MB cannot be excluded.

Further evidence suggesting beneficial effects of MB in hypotensive or patients with shock in the overdose setting is limited to very few case reports. In all of these cases, MB was accompanied with other treatment strategies, including vasopressors [160]. This raises the question whether MB has beside synergistic also direct effects on increasing blood pressure – the pharmacodynamic action of MB would suggest the latter.

There are some potential severe adverse reactions of MB that should be considered. Due to an inhibitory effect on the monoamine oxidase, MB has been shown to potentially cause a serotonin syndrome – especially at higher doses of MB (5–7 mg/kg) [166]. MB should, therefore, not be administered in poisonings with serotonergic property [160]. At higher bolus doses (4–15 mg/kg), MB may cause paradoxically methemoglobinemia and due to its effect on pulmonary vasoconstriction, these effects of MB may limit its use in patients with ARDS [167].

MB is discussed further in the chapter on this agent.

Prolonged External Chest Compression Using Mechanical Resuscitation Devices

During cardiac no-flow situations (cardiac arrest, ventricular fibrillation) in the course of poisoning, successful resuscitation requires timely application of high-quality chest compression and/or defibrillation. In animal models of induced ischemic ventricular fibrillation, it has been demonstrated that even during effective and continuous external chest compression, systemic blood pressure did not rise above 40/10 mmHg within the first minute. Furthermore, it may be up to 2 min until adequate left ventricular and aortic pressure could be achieved for sufficient cardiac reperfusion – a prerequisite for successful resuscitation [168]. This implies a need for high-quality external chest compression, and it is questionable whether this could regularly be achieved in prolonged manual cardiac resuscitation

maneuvers that may be indicated for toxin-induced cardiac arrest [169, 170].

The most frequently used and best-evaluated systems are the load distributing band (LDB, AutoPulse[®], Zoll, USA) and the Lund University Cardiac Arrest System (LUCAS[™], Jolife AB/Physio-Control, Lund, Sweden).

Several studies demonstrate an advantage of external mechanical chest compression devices in cardiac arrested patients compared to standard chest compression, both in the preclinical and the clinical setting. However, two very recent randomized studies comparing external mechanical compression devices with standard thorax compression methods did not demonstrate improved survival or neurological outcome in patients treated with such mechanical devices compared to the standard group [171, 172]. A recent Cochrane review concluded that there is currently insufficient data to justify a routine use of mechanical compression devices [173].

It has, however, to be considered that the vast majority of patients in these studies suffered from direct cardiopulmonary complications (e.g., myocardial infarction, pulmonary embolism, or ischemic arrhythmia) and there are only very few single reports or series indicating that prolonged chest compression with mechanical devices may play a role in poisoned patients also [169, 174, 175]. Although uncommon, prolonged cardiopulmonary resuscitation using external mechanical devices has been associated with a favorable outcome in single cases of poisonings [176–178].

Unless more proven evidence about the impact on important clinical outcome parameters is available, the use of mechanical thorax compression devices, such as the LUCAS[™] and AutoPulse[®] system, should be considered if prolonged resuscitation in poisoned patients is indicated. These systems may enable the chance for endogenous and exogenous detoxification processes or may facilitate access to procedures such as extracorporeal life support (ECLS; see below) – with promising survival rates reported in small studies [179, 180]. It may additionally be indicated if the neurological outcome of the cardiac arrested poisoned patient seems promising and ethical issues for prolonged resuscitation seems also to be justified.

Extracorporeal Life Support (ECLS)

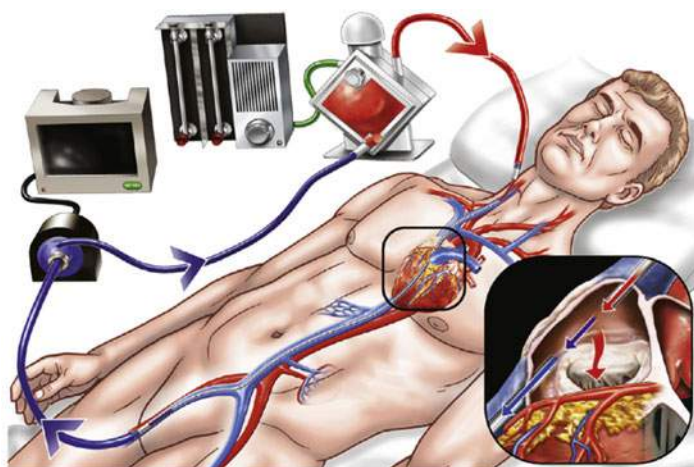
There are some cardiotoxics that might particularly be associated with severe hypotension, shock, or even cardiac arrest and the most severely cardiovascular-poisoned patients may not respond to any optimal conventional or reserve intervention as stated above. These patients may need special therapies such as ECLS [181]. ECLS is an umbrella term, including different active (pump driven) and passive (pumpless) techniques: i) the extracorporeal membrane oxygenation (ECMO), of these the veno-arterial (VA-ECMO) form being exclusively used for toxin-induced hemodynamic compromise, as the veno-venous (VV-ECMO) form does not support circulatory insufficiency; and ii) emergency cardiopulmonary bypass (ECPB) [182]. An exemplary simple ECPB/ECMO-configuration is shown in Fig. 3.

Venous blood is withdrawn from a central venous line (e.g., the femoral vein), pumped through a membrane oxygenator (providing gas exchange), and reinfused into a central artery (e.g., the internal carotid artery). This configuration allows – in contrast to veno-venous-ECMO, providing gas exchange only – also circulatory support. A typical recirculation problem occurs, if the drainage catheter and the reinfusion catheter are in close proximity. In this situation, oxygenated blood is being drawn back into the ECMO system without having entered the systemic circulation.

Despite promising results of ECLS performed in small patient groups, there is currently insufficient evidence to recommend the use of ECLS in a setting other than “experimental” [183, 184]. Several case reports and case series demonstrated good neurological outcomes in poisoned patients with prolonged (up to 4 h or longer) cardiopulmonary resuscitation, particularly in tricyclic antidepressant poisoning, beta-receptor, and calcium channel antagonist overdose [181, 185, 186].

Cardiac assist devices, intraaortic balloon pumps (IABP), ECPB, and ECMO have been successfully used to support poisoned patients to recovery and are also stated in the TOX-ACLS guidelines [83, 187–189]. The utility of these

Fig. 3 Exemplary configuration of a veno-arterial emergency cardiopulmonary bypass (ECPB also known as VA-ECMO with kind permission of JACC: Abrams D et al. 2014; 63 (25):2769)



measures will, however, depend finally on the causative agent, local resources, experience, and timing of their institution [190].

The experimental evidence that supports the use of ECLS was provided by six animal studies (LoE IIB) and more than 30 case reports. Few studies using control groups within different animal species, including dogs and swine, support evidence of the efficacy of extracorporeal life support in cardiovascular drug poisoning.

In one study, dogs received bolus doses of lidocaine. The control group (ACLS) was treated with antiarrhythmics, vasopressors, and cardioversion. Six of eight animals died within 30 min after infusion of lidocaine with standard treatment, while none of the dogs in the ECLS group died [191].

In another study with 12 dogs with desipramine-induced cardiac arrest, in addition to conventional measures, six were treated with ACLS using a thumper and six received ECLS therapy. In the ACLS group, return of spontaneous circulation (ROSC) occurred in only 1/6 dog, while 6/6 dogs in the ECLS group had ROSC. Moreover, surviving dogs in the ACLS group needed significantly higher doses of norepinephrine during the observation period [192].

In a third study, 20 swine were poisoned with i.v. amitriptyline (0.5 mg/kg/min) until systolic blood pressure dropped below 30 mmHg. The control group (ACLS) received conventional supportive therapy, including i.v. fluids, sodium

bicarbonate, and vasopressors. Animals failing to respond to ACLS therapy after 5 min additionally received open-chest cardiac massage for 30 min or until ROSC. Animals in the ECLS group received mechanical support only without pharmacological treatment. In the ACLS group, only 1/10 animal could be resuscitated while all 10 animals in the ECLS group had ROSC and nine of them could be easily weaned from bypass [193].

Patients presenting with severe hypotension, shock, or cardiac arrest following drug overdose are commonly younger, have no preexisting comorbidities such as myocardial or renal disease, and neurological outcome of timely and effective resuscitation is likely to be better than that expected in older patients suffering from different causes [2]. Vigorous resuscitation efforts maintaining minimal circulation until the toxin can be eliminated from the body seem therefore warranted and justified in individual situations. Many poisoning deaths are due to severe but potentially reversible depression of cardiovascular functioning and many patients may survive without end-organ damage if adequate perfusion can be maintained [83].

ECLS may further enable time for the normal detoxification methods or metabolism and excretion of the toxin through the liver and kidney. It is, however, yet not known whether ECLS affects drug metabolism or elimination, or whether it can be combined effectively with enhanced

elimination techniques, such as hemodialysis, albumin dialysis, or plasma exchange therapy – all of these requiring a minimal circulation [182].

If these invasive and partially heroic measures are to be effective, they must be implemented in a timely fashion before the stage of irreversible shock has been reached, and they require multidisciplinary expertise, including cardiology, cardiothoracic surgery, and cardiopulmonary perfusion experts (LoE IIb).

Intraaortic balloon pump or counterpulsation (IABP/IABC) provides limited support of CO, increasing it by about 20%. A recent randomized, controlled trial showed no beneficial effect of IABC in patients with cardiogenic shock, and its routine use for this indication is not currently recommended [18, 194]. Evidence for IABP use in poisoning events was provided by one animal study (LoE IIb) [191] and more than 10 case reports (LoE III). It has been used alone for the treatment of life-threatening overdose with quinidine [195], propranolol [196], dextropropoxyphene [197], antihistamines [198], and a combination of verapamil and atenolol [199]. In one case, IABP has been used together with ECLS in organophosphate poisoning [200]. IABP has, however, no role in cases of cardiac arrest, which is a major limitation for the treatment of cardiotoxic poisoning, where cardiac low- or no-flow situations may be observed due to ventricular tachycardia, ventricular fibrillation, electromechanical dissociation, or refractory cardiac arrest [201].

ECPB mainly provides circulatory support and requires always a membrane oxygenator. It further necessitates a sternotomy and both atrial and aortic cannulations. It is an invasive surgical procedure with a number of potentially life-threatening complications (e.g., coagulopathy, hemorrhage, pericardial tamponade). It has been used in single cases of aconitine, diltiazem, and verapamil poisoning [202–204].

ECLS also provides circulatory support but can be performed using peripheral cannulations of both arterial and venous vessels (most frequently the femoral vessels), in contrast to ECPB. As for ECPB, ECLS requires additionally a membrane oxygenator (ECMO). ECLS can

provide flow rates from 1.5 up to 6 L/min and can thus bridge a failing or even arrested heart. Beside several complications of either percutaneous or surgical cannulation, the large diameter of the cannula (15–17 Gauge) can cause critical limb ischemia, which can, however, be prevented by peripheral bypass surgery [205].

ECLS was clinically used in single cases of imipramine, desipramine, carbamazepine, propranolol, acebutolol, disopyramide, quinidine, flecainide, verapamil, diltiazem, carbamate, paroxetine, digoxin, and chloroquine poisoning [181]. For a brief summary, see also [201].

Clinical evidence and efficacy of the extracorporeal assist methods mentioned above is limited to single case reports and small series [181, 206]. A recently published retrospective cohort analysis from two centers in France including 62 patients compared outcome between 14 poisoned patients (mainly antiarrhythmics with membrane stabilizing activity) treated with ECLS and 48 patients treated with conventional therapies. Baseline parameters such as poisoning severity score, simplified acute physiology II-score, sequential organ failure assessment score, and GCS-score were comparable between the groups. Surviving of ECLS-treated patients (12/14; 86%) was significantly higher compared to the conventionally treated group (23/48; 48%) and this result remained significant, even after adjusting for confounders in multivariate analysis [181]. Important to note is that the use of ECLS was complicated by severe ischemia or bleeding, requiring immediate vascular surgery in one third of the cases. There was a trend toward better survival in the subgroup of patients with severe shock (52/62) compared to those with persistent cardiac arrest (10/62). As reported by others, none of the patients with persistent cardiac arrest survived without ECLS [181]. Survival rates of patients within cardiac arrest treated with ECLS seem to be higher (33–71%) compared to conventional treatment without ECLS, where survival rates have been reported as low as 4.5–7.5% [183, 190].

Even though all these case reports and series suggest that ECLS may be promising in patients poisoned with cardiotoxics, they do not allow

drawing any definite conclusions and it is likely that there is a meaningful underreporting of cases that have failed from this invasive procedures. Furthermore, prognostic indicators able to predict refractoriness to conventional treatment are largely unknown.

Finally, utilization and implementation of ECLS is associated with significant financial costs (average total cost approximately US \$ 100,000), and this financial impact has to be considered by the health care community and society [182, 207].

For a further discussion of this topic please see

► Chap. 4, “Extracorporeal Membrane Oxygenation and Cardiopulmonary Bypass in the Poisoned Patient.”

Conclusion

In cases of poison-induced refractory cardiac arrest or refractory heart failure, exceptional therapies may be considered [201], such as:

- (Ultra-) high-dose catecholamines, ILE, HDI, levosimendan, or other PDE-III-inhibitors
- Prolonged external chest compression with the use of mechanical devices, e.g., AutoPulse® or Lund University Cardiopulmonary Assist System (LUCAS 2®) in cases of cardiac arrest
- ECLS if heart failure, multi-organ failure, or cardiac arrest develops
- ECPB in patients with history of severe arteritis or lower limb ischemia if ECLS with the need for arterial cannulation is not feasible

In cases of refractory peripheral vasoplegia:

- Increased doses of vasopressors (e.g., epinephrine or norepinephrine, consider vasopressin)
- Consider application of methylene blue

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The constancy of the internal environment is the condition for free and independent life.

Claude Bernard, 1813–1878

Acid–base disorders are a major source of morbidity and mortality among patients in the intensive care unit (ICU). An observational cohort study of 9,799 ICU patients found that nearly two thirds of critically ill patients suffered from acute Metabolic Acidosis. Mortality among those with metabolic acidosis was 45% compared with 25% for those without it. For those with lactic acidosis, the mortality rate was 56% [1]. It is difficult to directly extrapolate these findings to poisoned patients who generally have a significantly lower mortality rate than the average ICU patient. We do know, however, from studies of poisonings with specific substances, such as metformin, ethylene glycol, and methanol, that the presence of severe metabolic acidosis is associated with a relatively poor prognosis [2]. A review of 22 cases of metformin overdose revealed a median pH nadir of 7.30 and median plasma lactate of 10.8 mmol/L among survivors compared with pH 6.71 and median plasma lactate of 35.0 mmol/L among non-survivors [2]. Among 18 ethylene glycol poisoned patients, non-survivors had a mean admission pH of 7.05, compared with 7.31 in survivors [3]. No patient with a pH less than 7.10 survived. Not surprisingly, most of the non-survivors presented to the hospital late after ingestion (from 6 h to >24 h). In a review of one-time methanol exposures with

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known time of ingestion, 22 patients presented for care <6 h after ingestion and had an early methanol level. Sixteen of these were acidotic on arrival [4]. Blood methanol concentrations ranged from 10 to 570 mg/dL (3–178 mmol/L), and initial arterial pH ranged from 6.90 to 7.42. All underwent treatment with alcohol dehydrogenase inhibitors (with or without hemodialysis). One patient with pH 6.99 died. Three patients with pH ranging from 7.26 to 7.32 suffered optic neuropathies but survived. One patient with pH 6.90 was described as “alive” on discharge, with the remaining 11 (pH range 7.09–7.42) noted as having a full recovery. In summary, it appears that severe metabolic acidosis is associated with a poor prognosis in representative poisonings and that time of presentation plays a significant role in outcome. A larger study of the prognostic value of acid–base disturbances in poisoning in general among ICU patients would be edifying.

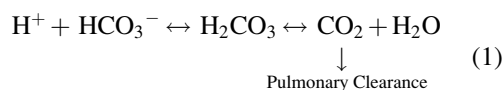
In poisoning, alterations of acid–base balance may result from exogenously administered ions, metabolic production of organic acids, impaired mitochondrial function, renal injury, hypoventilation, or inadequate tissue delivery of oxygen because of respiratory or circulatory insufficiency. Poisoned patients may suffer acid–base disturbances due to underlying illness or complications of their hospitalization, including acute or chronic kidney or pulmonary disease, side effects of therapy (crystalloids, diuretics, hyperalimentation, vasopressors), and sepsis. Determining which disorders of acid–base balance are present, and which are due to the toxic exposure versus underlying illness or complications, is not always straightforward. Thus, it is incumbent on critical care physicians caring for poisoned patients to be well versed in the evaluation and management of disorders of acid–base equilibrium.

In the last edition of this text, a “quiet revolution” was ongoing in acid–base disorder analysis, as exemplified by increasing attention to the work of Stewart with respect to electroneutrality and the strong ion gap. In the intervening period, numerous evaluations of the Stewart method have been undertaken, rendering examples of complex acid–base disorders discerned by quantitative

acid–base chemistry that might have been missed by the standard approach using base excess. It is fair to say that this issue remains highly controversial, with two very staunch camps, the “bicarbonate-based camp” and the “Stewart camp.” According to Rastegar, the Stewart approach has been largely ignored by nephrologists and renal physiologists while being embraced by anesthesiologists and intensivists [5]. He opines that the Stewart method provides no advantages over the traditional method in terms of prognosis. While numerous small prospective studies have compared these methods, large multicenter comparisons are lacking, and so the argument is not likely to be settled soon. It may be said, however, that the Stewart approach has led even the traditionalists to reexamine the importance of the influence of nonvolatile buffers, such as albumin, as well as the effects of dilution on the standard base excess and on the anion gap, resulting in new corrective formulas even in the “traditional camp.” On the quantitative acid–base side, investigators have attempted to distance themselves from tedious formulas and exhaustive analyses, offering simplified formulas and confining their components to plasma elements that most often undergo significant alteration. Al-Jaghbeer and Kellum argue that the two approaches are complementary and not contradictory [6]. Both approaches to acid–base analysis are discussed in this chapter.

Rapid Review of Key Factors in Acid–Base Equilibrium

Acid–base balance under physiological conditions is the simple sum of the production of organic acids occurring in metabolism and their elimination or neutralization by the body’s buffer systems. The first line of defense is the respiratory buffer system. Carbon dioxide, produced by the metabolism of carbohydrates, forms carbonic acid (H_2CO_3) when combined with water:



This is considered an “open system” because moderate increases in CO_2 are normally eliminated by a compensatory increase in minute volume. Acidosis stimulates respiratory chemoreceptors to produce an increase in ventilation, hence shifting this equation to the right and thus reducing the acidosis. However, severe acidosis may actually impede ventilation and lead to a vicious cycle that may result in death unless rapidly corrected.

Plasma proteins and phosphate stores in the bone serve as a second line of defense against acid–base abnormalities. The important role of these buffer systems will be discussed further with the “strong ion” approach. A strong ion refers to one that generally exists in a dissociated or nearly dissociated form (Na^+ , K^+ , Cl^- , and others). The kidneys play a critical role in acid–base balance via regulation of strong ions.

All forms of acid–base disorders may be observed in a poisoned patient. However, given its frequent presence in serious poisonings, the majority of this chapter will be devoted to metabolic acidosis.

Toxicant-Induced Respiratory Alkalosis and Acidosis

Respiratory alkalosis and acidosis are direct reflections of increased and decreased ventilation, respectively. Ventilation may be altered through changes in tidal volume, respiratory rate, and gas exchange across the alveoli or by combinations thereof. These disorders may be of central or peripheral origin. Stimulation of the central nervous system may result in tachypnea or hyperpnea and subsequent respiratory alkalosis. Salicylates [7], nicotine [8], and caffeine [9] are examples of agents that stimulate respiratory centers. Opiates decrease the respiratory rate by depressing the central respiratory and brainstem regulatory centers, [10] but also reduce ventilation through peripheral effects, such as non-cardiogenic pulmonary edema and increases in thoracic muscle tone [11]. Benzodiazepines and barbiturates likewise have both central effects (γ -aminobutyric acid-mediated depression in the medulla

oblongata) and peripheral effects (muscle weakness resulting in upper airway obstruction and/or respiratory muscle inefficacy); however, the peripheral effects appear to be of greater clinical importance [12]. Inadequate ventilation may also result in inadequate oxygenation and thereby lead to anaerobic glycolysis and lactate production. Thus, combined respiratory and metabolic acidosis is not uncommon in poisoning by toxicants that interfere with ventilation. Clinical diagnosis of these disorders is rather straightforward and based on physical examination and arterial blood gases, particularly PaCO_2 .

Toxicant-Induced Metabolic Alkalosis

Chemical-induced metabolic alkalosis is relatively rare. The milk-alkali syndrome, characterized by hypercalcemia, metabolic alkalosis, and renal failure, was common in the early to mid-twentieth century, when a common remedy of peptic ulcer disease consisted of hourly administration of milk with a “Sippy” powder (sodium bicarbonate with calcinated magnesia or bismuth subcarbonate) [13]. Nowadays, it is seen most often in elderly women taking calcium supplements for osteoporosis and among patients taking calcium antacids and is rightfully known as calcium-alkali syndrome [13, 14]. It has also been reported in betel nut chewers who use calcium-rich oyster shell paste in its preparation [15]. Laxatives taken in excess can give rise to hypokalemia and metabolic alkalosis [16, 17], as can diuretics [18, 19] and licorice [20, 21]. A non-exhaustive list of toxicants responsible for metabolic alkalosis is found in Table 1.

Toxicant-Induced Metabolic Acidosis

Acute metabolic acidosis is found in 64% of critically ill patients. Its presence is associated with an almost twofold rise in mortality [1]. Al-Jaghbeer and Kellum divide the causes of acidosis into (1) increased anion gap and (2) non-anion gap, consisting of renal, gastrointestinal, and iatrogenic causes (Box 1). While

Table 1 Toxicants reported to cause metabolic alkalosis

Agent	Classification	Selected references
Amikacin	Aminoglycoside antibiotic	[22]
Calcium carbonate	Antacid	[23]
Chlorthalidone	Diuretic	[24]
Ethacrynic acid	Diuretic	[19, 25]
Furosemide	Diuretic	[25]
Gamma-hydroxybutyrate	Anesthetic	[26]
Gentamicin	Aminoglycoside antibiotic	[27, 28]
Laxative	Laxative	[16, 17]
Licorice (glycyrrhizin)	Candy	[20, 21]
Neo-Mull-Soy (removed from market)	Soy-based infant formula	[29]
Potassium sodium citrate	Antiurolithiasis agent	[30]
Sodium acetate	Antacid, electrolyte solution	[31]
Sodium bicarbonate	Antacid, electrolyte solution	[32]
Sodium lactate	Antacid, electrolyte solution	[33]
Tobramycin	Aminoglycoside antibiotic	[34]

poisoned patients may suffer from any of these causes of metabolic acidosis, we will primarily focus on toxicant-induced etiologies.

Box 1 Causes of Metabolic Acidosis (Modified from Al-Jaghbeer and Kellum [6])

Increased anion gap

Renal failure

Ketoacidosis

Diabetic

Alcoholic

Starvation

Metabolic errors

Lactic acidosis

Toxicants (see also Table 2)

Methanol
Ethylene glycol
Paraldehyde 5-oxoproline (pyroglutamic acid)
Sepsis
Hyperchloremic (non-anion gap)
Renal tubular acidosis
Gastrointestinal
Diarrhea
Small bowel/pancreatic drainage
Iatrogenic
Parenteral nutrition
Saline
Carbonic anhydrase inhibitors
Anion-exchange resins

Many toxicants provoking acidosis increase the anion gap. Ingested mineral acids (toilet bowl cleaners, battery acid) may serve as exogenous sources of metabolic acidosis. Toxic alcohols and glycols, including methanol and ethylene glycol, are notable causes of metabolic production of organic acids. Interference with mitochondrial function results in lactate production. Anti-retroviral medications and cyanide are well known for their ability to induce lactic acidosis. Agents causing profound cardiovascular collapse, such as chloroquine and colchicine, may give rise to acidosis through diminished perfusion, as well as other mechanisms. In Table 2, the reader is provided with selected references for a non-exhaustive list of toxicants that may induce metabolic acidosis. In-depth discussion of individual toxicants is beyond the scope of this chapter. Related chapters in this text pertaining to specific substances should be consulted.

Clinical Suspicion of Acid–Base Disorders

Vigilance is required to promptly detect and treat acid–base disorders. The finding of altered mental status or abnormal vital signs should always invoke

Table 2 Toxicants reported to cause metabolic acidosis

Agent	Classification	Selected references
1-Benzylpiperazine (BZP)	Sympathomimetic, stimulant drug of abuse	[35]
2,5-Dimethoxy-4-bromoamphetamine (DOB)	Sympathomimetic, stimulant and hallucinogenic drug of abuse	[36]
3,4-Methylenedioxymethamphetamine (MDMA)	Sympathomimetic, stimulant drug of abuse	[37, 38]
Acetaminophen (paracetamol)	Analgesic, antipyretic	[39]
Acetazolamide	Carbonic anhydrase inhibitor	[40]
Acetonitrile	Solvent, chemical intermediate	[41]
Acetylene	Welding gas	[42]
Aminocaproic acid	Hemostatic	[43]
Amphetamine and substitutions	Sympathomimetic, stimulant drugs of abuse	[37, 44]
Arginine	Amino acid	[45]
Aspirin (acetylsalicylic acid) and salicylates	Analgesic, antipyretic	[7]
Azide, sodium	Herbicide, fungicide, fumigant, bactericide, chemical intermediate, preservative, propellant	[46, 47]
Boric acid	Insecticide	[48]
Carbon monoxide	Asphyxiant, chemical	[49–52]
Cathinones, substituted	Stimulant drugs of abuse	[53]
Chlorine	Disinfectant, halide	[54]
Citalopram	Antidepressant	[55]
Cocaine	Anesthetic, sympathomimetic, stimulant drug of abuse	[56, 57]
Cyanide (HCN and salts)	Asphyxiant, chemical	[58–61]
Detergent sacs, single use (SUDS)	Detergent, laundry and surfactants	[62, 63]
Diazepam	Sedative hypnotic	[64]
Dicamba	Herbicide	[65]
Didanosine	Antiviral, nucleoside analogue	[66, 67]
Diethylene glycol/triethylene glycol	Glycol, solvent, brake fluid	[68–71]
Endosulfan	Organochlorine insecticide	[72, 73]
Ethanol	Alcohol	[74]
Ethylene glycol	Antifreeze, solvent	[70, 75, 76]
Ethylene glycol monobutyl ether (EGBE, butoxyethanol, butyl cellosolve)	Solvent, glass cleaner	[70, 77–79]
Ethylene glycol monomethyl ether (EGME, methoxyethanol, methyl cellosolve)	Solvent, antifreeze	[80]
Etomidate	Anesthetic	[81–84]
Fialuridine	Antiviral, nucleoside analogue	[85, 86]
Flumequine	Antimicrobial, fluoroquinolone	[87]
Formalin (40% formaldehyde in water)	Tissue fixative, embalming fluid	[88]
Formic acid	Organic acid	[89, 90]
Hydrogen sulfide	Petroleum production, decomposition of sulfur-containing organic matter	[91, 92]
Iron	Mineral supplement	[93, 94]
Isoniazid (INH)	Antimicrobial, antitubercular	[95, 96]
Lorazepam	Sedative hypnotic	[97–99]
Mephedrone	Sympathomimetic, stimulant drug of abuse	[100]

(continued)

Table 2 (continued)

Agent	Classification	Selected references
Methamphetamine	Sympathomimetic, appetite suppressant, stimulant drug of abuse	[101]
Methyl alcohol (methanol)	Solvent, antifreeze, chemical intermediate, paint remover	[70, 102]
Methylone	Sympathomimetic, stimulant drug of abuse	[103]
Nalidixic acid	Antimicrobial, quinolone	[104]
Neem oil	Tree oil used in cosmetics, organic gardening	[105, 106]
Nitroprusside, sodium	Antihypertensive, vasodilator	[107]
Nortriptyline	Cyclic antidepressant	[108]
Olanzapine	Antipsychotic, atypical	[109]
Parathion	Pesticide, organophosphate	[110]
Phenol	Disinfectant, aromatic organic solvent	[111, 112]
Phentermine–topiramate	Appetite suppressant drug combination	[113]
Phosphoric acid	Metal cleaner, toilet bowl cleaner	[114]
Phosphorus, elemental	Pesticide, fireworks	[115]
Potassium chloroplatinite	Photographic toner solution	[116]
Propionitrile	Cyanogen	[117, 118]
Propofol	Anesthetic	[119]
Propylene glycol	Solvent, pharmaceutical adjuvant	[71, 98, 99]
Smoke, fire (see cyanide and carbon monoxide above)	Environmental toxicant	[58, 61, 120]
Sodium chloride	Electrolyte	[121–123]
Stavudine	Antiviral, nucleoside analogue	[124]
Teniposide	Anticancer chemotherapeutic agent	[125]
Theophylline	Thioxanthine bronchodilator	[126]
Thiamine deficiency	Vitamin	[127]
Toluene	Solvent, aromatic organic, paints, thinners, lacquers, adhesives	[128]
Topiramate	Anticonvulsant	[129]
Treosulfan (dihydroxybusulfan)	Anticancer chemotherapeutic agent	[130]
Trimethoprim/sulfamethoxazole	Antimicrobial, sulfonamide	[131]
Valproic acid	Anticonvulsant	[132]
Xylenol	Phenolic detergent	[133]
Zidovudine	Antiviral, nucleoside analogue	[134, 135]

consideration of an acid–base disturbance. Clinical findings may be subtle early in the pathophysiologic process, so habits as elemental as truly counting the respiratory rate may make the difference in early recognition of these disorders. A thorough examination may detect sentinel breath odors (ketones, paraldehyde, and cyanide), altered respiration (hyperpnea, Kussmaul respirations), cyanosis, pressure sores or bullae suggestive of

rhabdomyolysis, etc. Clinical signs and symptoms are insensitive, however, so laboratory screening is necessary in all critically ill patients. While point-of-care diagnostic devices have simplified life for the clinician, a multitude of conditions can alter their readings [136–139]. Definitive evaluation of acid–base disorders is based on carefully selected data provided by the chemistry and toxicology laboratories.

Laboratory Diagnostic Tools in Acid–Base Balance

Gaps in Our Knowledge of Acid–Base Disturbances

This double entendre is not original [140] but reflects our incomplete comprehension of acid–base disorders in spite of years of studies and discussions regarding the use of various gaps – base excess, anion, delta, and osmol. Each of these tools, their potential utility, and their shortcomings will be discussed, followed by a discussion of the quantitative approach to acid–base balance, which introduces the more recent strong ion gap.

Given the ubiquity of its use in clinical medicine, the most frequently available laboratory indicator of acidosis is the serum electrolyte panel. For this reason, anion and delta gaps will be discussed before base excess and osmol gaps.

Anion Gap

The serum anion gap (AG) remains a useful but only moderately sensitive tool in the initial evaluation of potential acid–base disturbances. It suffers from numerous limitations, which will be discussed. If the clinician is aware of these limitations and adjusts for them accordingly, the AG provides one of the most rapidly available tools in the evaluation of acid–base disorders.

In its most basic form,

$$\text{AG} = \text{Measured serum cations} \\ - \text{Measured serum anions}$$

Because the most important anions after chloride and bicarbonate (protein, inorganic phosphate, and sulfate) are not routinely measured in a serum electrolyte panel, a “normal” AG exists. The presence of additional unmeasured anions (often organic acids) creates an “increased” AG. The most commonly used calculation for AG is (using mmol/L units for the anions/cations)

$$\text{AG} = \text{Na}^+ - (\{\text{Cl}^-\} + \{\text{HCO}_3^-\}) \quad (2)$$

An alternative, though less frequently used, equation adds $[\text{K}^+]$ to the first term. Extremes of potassium may affect the AG and should be kept in mind; however, the discussion that follows will be based on (Eq. 2). Although its calculation is remarkably simple, its interpretation is not always straightforward.

Because of the body’s requirement for electroneutrality, an increase in unmeasured anions (the AG) should be compensated by an equal decrease in serum bicarbonate or chloride, although in almost all circumstances, the compensation is reflected in a decrease in the bicarbonate concentration [141]. Thus, the first evaluation of the calculated AG should be its relationship to serum bicarbonate. In the simplest case, AG increases in an amount equivalent to the fall in bicarbonate. However, this does not always occur. For example, in the case of diabetic ketoacidosis (DKA), a discordance is often found [142], with AG being smaller than predicted based on the decrease in bicarbonate. Extensive tubular elimination of ketone bodies, along with concomitant retention of chloride, may result in a component of hyperchloremic metabolic acidosis, thus decreasing the AG. The hyperchloremic component of acidosis increases over the course of DKA [143], probably in part due to the large amount of sodium chloride typically administered in DKA. Large-volume fluid resuscitation with isotonic saline can induce acidosis because the equimolar concentrations of sodium and chloride in normal saline (155 mmol/L) will increase plasma chloride to a greater extent than plasma sodium, thus decreasing the serum bicarbonate concentration [144]. A review of several studies on acidosis induced by chloride-rich crystalloids appears in the discussion on treatment [123].

The limitations of the AG fall into two general categories: (1) analytic and (2) physiologic.

Analytic Limitations and Errors

Early published normal ranges of AG values, 12 ± 4 mmol/L [145], continue to be used by

many clinicians. However, these values now represent, in many hospitals, a significant overestimate because of changes in technology that occurred in the 1980s. Ion-specific electrode methodology has largely replaced flame photometry for measurement of sodium and chloride, leading to an increase in normal values of chloride of 2–6 mmol/L, with a concomitant decrease in the normally expected AG. Winter and colleagues [146] found a normal AG of approximately 6 mmol/L, with 95% confidence intervals of 3–11 mmol/L in a group of 120 blood donors. This difference from previous normal values may seem small, but as the authors point out, if the true normal AG is 6 mmol/L, a patient with 10 mmol/L of added organic acid and thus an AG of 16 mmol/L would, by generally accepted standards, have a normal AG. In a group of 222 patients with normal renal function and albumin, Sadjadi [147] found an AG of 6.6 ± 2 mmol/L, almost identical to that demonstrated in the study of Winter and coworkers. Failure to take this change into account may result in failure to diagnose acidosis. Using a “normal” range of 12 ± 4 mmol/L, Iberti and colleagues found that 50% of critically ill patients with lactic acidemia in the range of 5–9.9 mmol/L and 79% of those with lactate concentrations 2.5–5 mmol/L had AG values less than 16 mmol/L. Applying the current lower ranges of AG would clearly improve sensitivity. Sadjadi and colleagues more recently retrospectively reviewed the charts of 409 veterans with a glomerular filtration rate ≥ 60 mL/min/1.73 m² body surface area and serum albumin ≥ 4 g/dL. They found a mean anion gap of 7.2 ± 2 mEq/L. This compares with 299 patients in the same study with lactic acidosis (lactate ≥ 4 mEq/L) and 68 patients with end-stage renal disease on dialysis, in whom the mean anion gaps were 12.5 mEq/L and 12.4 mEq/L, respectively [148]. A word of caution is in order, however. Lolekha points out that to interpret the anion gap accurately, one must use an analyzer-specific reference range. He and his colleagues found slightly differing anion gaps on four auto analyzers, using blood samples from healthy volunteers [149]. Anion gap values may also vary significantly according to the laboratory

providing the measurements [150]. Finally, clinicians must also be aware that some laboratories have altered the calibration of the chloride-measuring instrument so that the normal ranges of chloride and AG in those institutions remain closer to “classic” published values. Thus, it is imperative that clinicians discuss this issue with laboratory medicine specialists in their own institutions to ensure that the normal ranges provided by the laboratory have, in fact, been verified in that laboratory.

Kraut and Nagami [151] attempted to determine the sensitivity of the AG in detecting lactic acidosis through a literature review. Unless the AG is corrected for serum albumin, the sensitivity ranged from 39% to 63% for serum lactate greater than 2.5 mmol/L. With correction for albumin, the sensitivity range improved to 75–94% demonstrating two salient points: (1) if the anion gap is to be useful, it should be corrected for serum albumin and (2) if one is truly concerned about lactic acidemia, a serum lactate should be obtained. One last word about the anion gap, which applies to lab tests in general: a single, normal AG is just that – a unique, not analytically infallible, test obtained at a point in time. In contrast, poisonings are dynamic processes which may radically modify the kinetics of absorption, distribution, metabolism, and excretion. Jacob et al. recently reported two cases of life-threatening salicylate poisoning with apparently normal anion gap due to a false increase of measured chloride in the presence of high serum salicylate levels on some analyzers [152]. Herres and colleagues reported a fatal case of salicylate poisoning who presented with a deceptively mild elevation in anion gap and initially undetectable serum salicylate concentration. Failure to repeat the anion gap in a timely manner, to trend salicylate concentrations until they were clearly declining, and to carefully observe the patient in an acute medical setting contributed to his ultimate demise [153].

Physiologic Limitations

Serum albumin. Whereas the potential for abnormal proteins (such as cationic multiple myeloma proteins) to alter the AG is widely appreciated, the

critical role of normal proteins such as albumin remains largely ignored. Albumin constitutes the largest component of unmeasured anions under normal physiologic conditions, with inorganic phosphate and sulfates representing most of the remainder. Calculation of the AG without consideration of serum albumin may be justifiable in normal healthy patients, but it is certainly not acceptable in the critically ill. Figge and coworkers found marked hypoalbuminemia in 96% of 152 critically ill patients, with values < 20 g/L (normal range 44 ± 3 g/L) in 49%. Each g/L decrease in serum albumin caused the observed AG to underestimate the total concentration of unmeasured anions by 0.25 mmol/L [154]. A severely malnourished patient may have a significant AG virtually obscured because of the influence of hypoalbuminemia [155]. The AG may be corrected for hypoproteinemia as follows:

$$\begin{aligned} \text{AG}_{\text{corrected}} = & \text{Na}^+ - (\{\text{Cl}^-\} + \{\text{HCO}_3\}) \\ & + 0.25 \times (\{\text{Normal albumin g/L}\} \\ & - \{\text{Observed albumin g/L}\}) \end{aligned} \quad (3)$$

If albumin values are reported in grams per deciliter, the factor is 2.5. Hyperalbuminemia from severe dehydration (cholera) may reach significant enough concentrations to contribute to metabolic acidosis [156].

Water excess/deficit. Significant loss or gain of free water will alter serum sodium and chloride by the same percentage but not by the same absolute amount, which will clearly alter the AG [140]. The effect of hyponatremia (water excess) on the AG has been clinically documented [140, 157]. Decaux and Musch compare the electrolytes and anion gap in various states of hypoosmolality (Table 3) [158]. Corrections for the effects of water excess/deficit are taken into account in calculation of the strong ion gap (to be discussed) but have not generally been applied to the AG. A prospective look at the value of such a correction in patients with metabolic acidosis is needed.

Assumptions regarding lactate in the anion gap. The presence of an increased AG acidosis

not explained by the presence of ketoacids, renal failure, or historical and laboratory evidence of toxicant ingestion is often assumed to be due to lactate. However, Gabow and colleagues found that a measured increase in lactate of greater than 4 mmol/L was present in only 9 of 21 patients (43%) meeting these criteria, thus illustrating the potential for error in such an assumption [145]. Conversely, Dorwart and Chalmers found normal AGs in 32 of 45 patients with plasma lactate levels between 2.5 and 9.9 mmol/L [159]. Thus, if lactic acidemia is in the differential diagnosis, lactate should be quantified. This is particularly important in poisoning, where measurement of exogenous anions such as oxalate or formate is not always readily available. Quantification of lactate may not only provide clues to the diagnosis but also increase or decrease the suspicion of the presence of other unmeasured anions and should thus be considered an integral part of the laboratory evaluation.

Readers should be aware of other worrisome analytical problems related to lactate. Multiple authors have reported falsely elevated plasma lactate in the setting of glycol poisonings. In the case of ethylene glycol overdose, the glycolate metabolite can cross-react with the recombinant L-lactate oxidase, resulting in a marked false increase in measured lactate [160–165], potentially obscuring the diagnosis of ethylene glycol poisoning. D-lactate, a by-product of propylene glycol, can also be falsely recognized by lactate analyzers as L-lactate [166].

Role of potassium in the anion gap. Serum potassium, as mentioned earlier, is often “discarded” in calculating the AG because the range of serum potassium in most patients is small enough that potassium variations cause only a minimal change in the calculated gap. Nonetheless, there are circumstances (e.g., digitalis and toluene poisoning or acute renal failure) in which extremes of serum potassium may occur and render its consideration in calculation of the AG more important. Furthermore, a reduction in “normal” mean AG (absent the potassium) from 12 to 6 mmol/L renders the variation in potassium of greater importance in terms of percent change

Table 3 Clinical and biological data generally allowing differentiation between appropriate and inappropriate Anti-DH secretion in patients with hypoosmolality^a (Adapted from Decaux and Musch [158] with permission)

Parameter	Appropriate diuresis		Inappropriate diuresis
	Hypervolemic (↑ECV; ↓EABV)	Hypovolemic (↓ECV; ↓EABV)	Euvolemic (↑ECV; ↑EABV)
History	Chronic heart failure, cirrhosis, nephrosis	Extrarenal losses (e.g., gastrointestinal, sweating, burns, third space) Renal losses (e.g., Addison, diuretics, bicarbonaturia, salt-losing nephropathy, cerebral salt-wasting syndrome)	Drugs (e.g., carbamazepine, SSRI) Neurologic diseases (e.g., encephalitis, strokes) Pulmonary diseases (e.g., tuberculosis, pneumonia) Cancer (e.g., oat cell carcinoma) Endocrine (e.g., hypothyroidism, pituitary hypocorticism)
BP	Low	Low	Normal
Edema	+	—	—
Plasma anti-DH	↑	↑	↑ (↓ ^b)
Plasma sodium	↓	↓	↓
Plasma urea	NL-↑	NL-↑	NL-↓
Plasma anion gap	NL-↑	NL-↑	NL-↓
Urine osmolality	↑	↑	↑
Urine sodium (mEq/L)	<30	<30 ^c	>30 ^d
Fractional excretion of sodium (%)	<0.5	<0.5 ^c	>0.5 ^d

^aAnti-DH antidiuretic hormone, ECV extracellular volume, EABV effective arterial blood volume, NL normal, SSRI selective serotonin reuptake inhibitor

^bAnti-DH is low in nephrogenic syndrome of inappropriate antidiuresis (nephrogenic syndrome of inappropriate antidiuresis or syndrome of inappropriate secretion of antidiuretic hormone type D)

^cUnless salt depletion is of renal origin

^dIf salt intake is normal

in AG. Regardless of whether potassium is included in the calculation used, it exerts an electrical force as a strong ion.

Hyperphosphatemia. Because the contribution of inorganic phosphates to the normal AG is moderate and because normal phosphate concentrations are generally about 1.0 ± 0.2 mmol/L, hypophosphatemia results in a negligible change in the AG. On the other hand, conditions that result in hyperphosphatemia, such as phosphate enema intoxication, may result in an increased AG [167, 168]. Thus, hyperphosphatemia must be added to the differential diagnosis of an increased AG.

Delta Gap

Another method of evaluating acid–base disorders is to compare the change in AG with the change in alkaline reserve [141]. This relationship is expressed as the “delta gap,” which is defined as:

$$\Delta\text{Gap} = \Delta\text{AG} - \Delta\text{HCO}_3^- \quad (4)$$

where ΔAG is the observed AG minus the upper normal limit of the AG and ΔHCO_3^- is the lower normal HCO_3^- minus the observed HCO_3^- . The normal range for the delta gap is 0 ± 6 . As

mentioned previously, the body must maintain electroneutrality, so an increase in unmeasured anions (the AG) should be compensated by an equal decrease in serum bicarbonate [141]. Therefore, for a simple increased AG acidosis, the delta gap should be 0. A significantly positive (greater than +6) delta gap suggests the presence of metabolic alkalosis. A significantly negative (less than −6) delta gap suggests hyperchloremic acidosis. Because normal values for electrolytes (and AGs) vary among hospitals, depending on the methodologies used, it is imperative to calculate these values on the basis of local norms. Wrenn demonstrated through a series of clinical cases that the delta gap can assist in the detection of mixed acid–base disorders that would go unsuspected on the basis of evaluation of the AG alone. It is not foolproof, however, as illustrated by one case in which a patient with a normal AG (4 mmol/L), a normal delta gap (−2 mmol/L), and a bicarbonate concentration of 19 mmol/L actually had a combination of anion gap metabolic acidosis, HCMA, and metabolic alkalosis from volume contraction [141]. While this simple calculation remains a useful screening tool for distinguishing and mixed acid–base disorder from isolated anion gap acidosis [169], one should not rely entirely on either the AG or the delta gap in the evaluation of potential acid–base disorders [140].

Base Excess

Base excess (BE) was the first “gap” to be proposed as a useful approach to the evaluation of acid–base disturbances [170]. It is calculated as follows, but is often provided with the results of the blood gas analyzer:

$$\text{BE} = 1.2(\{\text{HCO}_3^-\} - 22.9) \quad (5)$$

The multiplier 1.2 takes into account the approximately 25% of buffer capacity not provided by the carbon dioxide/bicarbonate system. HCO_3^- is the “standard” bicarbonate, which is the concentration of bicarbonate in plasma when whole blood has been equilibrated at a PaCO_2 of

40 mmHg, oxyhemoglobin saturation of 100% and temperature of 37 °C. Once the pH is measured, the standard bicarbonate can be obtained directly from (Eq. 6), the Henderson–Hasselbalch equation:

$$\text{pH} = 6.10 + \log \frac{\text{HCO}_3}{\text{PaCO}_2 \times 0.030} \quad (6)$$

The normal mean of standard bicarbonate is 22.9 mEq/L, so this value is subtracted in (Eq. 5) from the product to obtain the BE. A BE less than −5 mEq/L is thought to be consistent with metabolic acidosis. Salem and Mujais have warned against the use of this theoretical bicarbonate concentration when calculating the AG (in lieu of total CO_2) because rapidly changing conditions in apparent values of pK' (the pH at which equal concentrations of the acid and base forms of a buffer are present – range: 5.8–6.3) may result in calculated errors in HCO_3^- as high as 50% [140]. Others have likewise called attention to this problem [171, 172]. Furthermore, excess heparin in blood gas samples may decrease PaCO_2 by up to 25% which also distorts the calculated bicarbonate value [140]. The effects of heparin volume on PaCO_2 have recently been shown to vary with syringe volume, needle size, and sample volume [173]. It stands to reason that the BE, determined on the basis of calculated bicarbonate, also risks misinterpretation. In addition to the risk of analytical and calculated errors, the BE is dependent on a number of other factors “assumed” to be normal in this simple calculation: normal water content, electrolytes, and albumin. As pointed out by Balasubramanyan and colleagues, changes in these values will alter the calculated BE independent of changes in lactate, bicarbonate, or unmeasured anions [174].

Quantitative Acid–Base Analysis: The Strong Ion Gap

The strong ion approach to acid–base management appears to be the most fundamentally sound from the perspective of physical chemistry

[175]. This method, originally described by Stewart [176] and refined by Fencel and Leith [177], relies on the fact that systems operate under a number of restraints imposed by physical laws that must always and simultaneously be met:

1. Electroneutrality must always exist: the sum of all positive charges must always be equal to the sum of all negative charges.
2. Dissociation equilibria of all incompletely dissociated substances must always be satisfied.
3. Mass is conserved; that is, the total concentration of an incompletely dissociated substance can always be accounted for as the sum of the concentrations of its dissociated and undissociated forms. The hydrogen ion concentration in blood is held within a very tight range, 36–43 nmol/L, because this range is critical to the maintenance of appropriate protein function (enzymes, pumps, etc.) and thus cellular function [175]. The source of hydrogen ions is the dissociation of water. Dissociation of water into hydrogen and hydroxyl ions is determined by three independent determinants (each can be changed independently of the others): the strong ion difference [SID], PaCO_2 , and the total weak acid concentration (A_{TOT}).

The first independent variable is [SID], or the net electrical charge difference of the strong ions (i.e., those that are completely or nearly completely dissociated). This variable comprises the strong cations (Na^+ , K^+ , Ca^{2+} , Mg^{2+}) and the strong anions (Cl^- and other strong anions of low pK_a such as lactate and ketoacids), which are likewise almost completely dissociated at physiologic pH. The second independent variable is PaCO_2 , which, of course, varies with ventilation. The third independent variable is A_{TOT} , the sum of weak acids [HA] and their anions $[\text{A}^-]$. The weak acids are primarily composed of proteins (mainly albumin) and inorganic phosphates $[\text{Pi}^-]$. Kellum and coworkers [178] point out that weak acids [HA] without their anions are not an independent variable because their equilibrium with A^- changes with alterations in [SID] and PaCO_2 . Looking at Fig. 1, one observes that the [SID] can also be calculated by adding the $[\text{HCO}_3^-]$ to

Table 4 Classification of primary acid–base disturbances

	Acidosis	Alkalosis
I. Respiratory	$\uparrow \text{PaCO}_2$	$\downarrow \text{PaCO}_2$
II. Nonrespiratory (metabolic)		
1. Abnormal [SID] ^a		
a. Water excess/deficit ^b	$\downarrow [\text{SID}]$, $\downarrow [\text{Na}^+]$	$\uparrow [\text{SID}]$, $\uparrow [\text{Na}^+]$
b. Imbalance of strong ions		
i. Chloride excess/deficit	$\downarrow [\text{SID}]$, $\uparrow [\text{Cl}^-]$	$\uparrow [\text{SID}]$, $\downarrow [\text{Cl}^-]$
ii. Unidentified anion excess	$\downarrow [\text{SID}]$, $\uparrow [\text{SIG}]$	–
2. Nonvolatile weak acids		
a. Serum albumin	$\uparrow [\text{Alb}]$	$\downarrow [\text{Alb}]$
b. Inorganic phosphate	$\uparrow [\text{P}_i]$	$\downarrow [\text{P}_i]^c$

Adapted with permission from Fencel and Leith [177]

^aChanges in acid–base balance are controlled by changes in three independent variables – PaCO_2 , the strong ion difference, and total weak acids. As such, these disorders may be classified on the basis of their underlying cause or causes. Assessment of these three variables can explain even complex acid–base disorders

^bDiscerned by abnormal $[\text{Na}^+]$

^cBecause inorganic phosphate concentrations are normally low (≈ 1 mmol/L), hypophosphatemia has a negligible effect on acid–base balance

Alb plasma albumin concentration, $[\text{P}_i]$ plasma inorganic phosphate concentration, $[\text{SID}]$, difference between the sums of all the strong (fully dissociated, chemically nonreacting) cations (Na^+ , K^+ , Ca^{2+} , Mg^{2+}) and all the strong anions (Cl^- and other strong anions), $[\text{SIG}]$ plasma concentration of unidentified strong anions

the $[\text{Alb}^-] + [\text{Pi}^-]$. *The central tenet of the strong ion approach is that neither $[\text{H}^+]$ nor HCO_3^- can change without a change in one or more of these three independent variables.* Neither H^+ nor HCO_3^- is a strong ion. Strong ions cannot be created or destroyed to satisfy electrical neutrality, but hydrogen ions can be generated or consumed by changes in water dissociation [178]. Likewise, bicarbonate production or consumption is a result of changes in the three independent variables. Thus, the “classic” approach of looking at HCO_3^- is in a sense backward, in that we are examining the end result rather than the underlying cause of the disturbance. Acid–base disturbances may be classified according to the underlying change in these three independent variables (Table 4).

Fig. 1 Electroneutrality must be maintained in blood plasma; thus, the sum of positive charges must equal the sum of negative charges. Hydroxyl, carbonate, and protons are not shown because their concentrations are in the nanomolar to micromolar range. [SIG] represents unidentified strong anions (lactate, sulfate, keto acids, others). [SID], strong ion difference (Adapted from Fencel et al. [155])

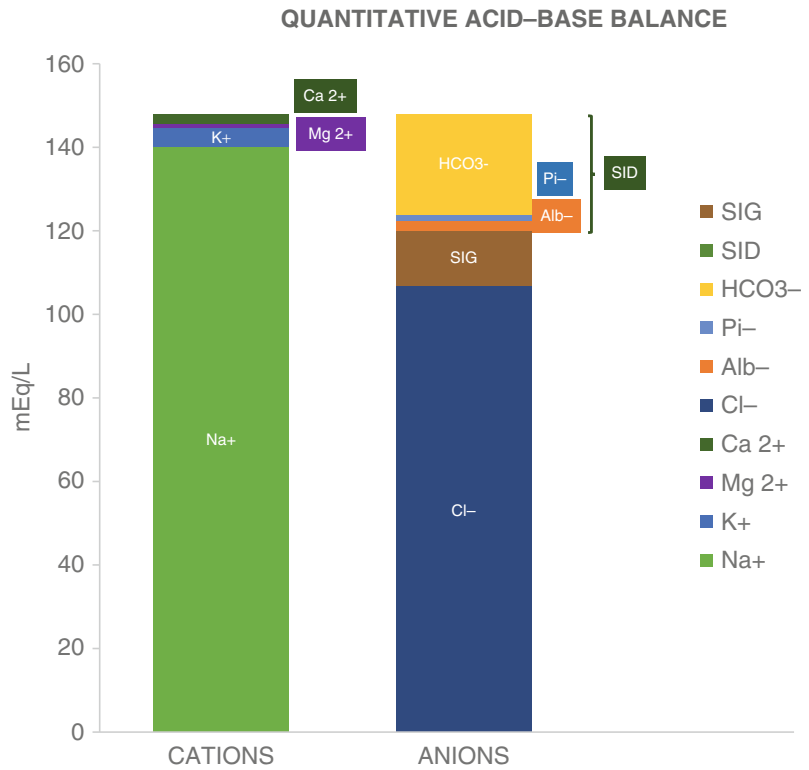


Figure 1 demonstrates that [SID] is equivalent to the following:

$$[\text{SID}] = [\text{HCO}_3^-] + 0.28 \times [\text{Alb}^-, \text{g/L}] + 1.8 \times [\text{Pi}, \text{mmol/L}] \quad (7)$$

$[\text{HCO}_3^-]$ is obtained from arterial blood gas measurements, and the effects of albumin (g/L) and inorganic phosphate (mmol/L) are based on their direct measurement in serum. This formula is a simplification and uses factors of 0.28 and 1.8 to correct for the actual charge (in mEq) provided by albumin and inorganic phosphates. If your laboratory provides [Pi] in mg/dL, the factor for [Pi] is 0.6 rather than 1.8.

The strong ion gap [SIG], sometimes expressed as $[\text{XA}^-]$, is comparable to the anion gap in that it consists of strong anions other than Cl^- (lactate, ketoacids, and other organic anions such as toxic metabolites or sulfate), some of which are not readily measured in plasma. [SIG] is thus derived as

$$[\text{SIG}] = [\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] - [\text{Cl}^-] - [\text{SID}] \quad (8)$$

where [SID] is obtained from (Eq. 7). Water excess or deficit, determined on the basis of an abnormal $[\text{Na}^+]$, will alter $[\text{Cl}^-]$ and [SIG], both of which must be corrected:

$$[\text{Cl}^-]_{\text{corrected}} = [\text{Cl}^-]_{\text{observed}} \times ([\text{Na}^+]_{\text{normal}} / [\text{Na}^+]_{\text{observed}}) \quad (9)$$

Correction of chloride allows one to determine the plasma excess or deficit in chloride.

$$[\text{SIG}]_{\text{corrected}} = [\text{SIG}]_{\text{calculated}} \times ([\text{Na}^+]_{\text{normal}} / [\text{Na}^+]_{\text{observed}}) \quad (10)$$

Although this series of steps is a bit more demanding in time and cost than is the calculation

of AG, it allows recognition of complex acid–base disturbances that might be missed by simple examination of BE or AG [155]. Through Monte Carlo simulation, Antsey estimated the 95% confidence interval of normal [SIG] to be 3.9 ± 6.4 mEq/L [179]. Gunnerson and colleagues have shown that the [SIG] is substantially higher in stable ICU patients compared with healthy controls, possibly representing occult acid–base disorders or simply metabolic differences among the critically ill. In this small study of 15 healthy adults and 15 stable adult patients just before ICU discharge, the mean [SIG] was 1.4 ± 1.8 mEq/L versus 5.1 ± 2.9 mEq/L, respectively [180]. Like the anion gap, it appears the [SIG] varies from one laboratory to another and from one instrument to another, so that local norms must be established.

There are now several approaches to using quantitative acid–base chemistry clinically. In the first approach, one calculates the strong ion gap [SIG], which, similar to the AG, identifies the presence of unmeasured anions. This multi-equation approach has been criticized as too complex for the bedside such that simplified equations have been developed. Examples of these will follow. The second approach provides corrections to BE based on strong ion theory. Each approach has been shown to provide advantages over the use of the classic AG and BE.

Fencel and colleagues [155] compared the Stewart method to classic methodology (calculation of the anion gap and base excess) in a study involving nine healthy subjects ([SIG] mean \pm S. D. = 8 ± 2) and 152 intensive care unit patients. 96% of patients had serum albumin concentrations less than or equal to three standard deviations below the mean of the control subjects. In 20 and 22 patients, respectively, the base excess and plasma bicarbonate were normal. The Stewart method detected complex acid–base disturbances among many of these, in some cases grave. The authors conclusively demonstrated that reliance on the AG (particularly if not corrected for albumin) or BE results in false interpretation of the acid–base status of critically ill patients. The strong ion approach, though requiring a few more direct laboratory measurements, is comprehensive and thus more sensitive.

Durward et al. obtained arterial blood samples on admission and at 24 h in 85 children undergoing surgery for congenital heart disease. An elevated strong ion gap (>3 mEq/L) was present in 41% of children on admission and 52% at 24 h. Both the strong ion gap and lactate increased with surgical complexity. [SIG] was superior to lactate in predicting mortality [181].

Moviat et al. conducted a prospective, observational multicenter study in Dutch ICU patients. 137 of 312 consecutive patients (44%) who had normal pH, normal base excess, and normal PaCO₂ underwent arterial blood sampling. Strong ion gap was calculated from three consecutive arterial blood samples. These patients were found to have mixed acid–base disorders due to hyperchloremia and hypoalbuminemia, in spite of normal blood gas parameters [182].

Zheng and colleagues [183] studied 78 patients with metabolic acidosis with or without acute kidney injury (AKI). They analyzed physicochemical parameters at 24 and 72 h, at 1 week, 1 month, and 3 months on survival after AKI. Mortality was higher in AKI group with higher anion gaps and strong ion gaps. The AG was strongly associated with mortality at 1 and 3 months after acute kidney injury. However, an elevated [SIG] most strongly predicted mortality at 24 h, 72 h, 1 week, 1 month, and 3 months post acute kidney injury.

Applying Strong Ion Theory to the Base Excess

The corrected base excess approach to using clinical quantitative acid–base chemistry is illustrated by Balasubramanyan and colleagues [174]. They used three equations of Fencel and Leith [177] to calculate a corrected BE that takes into account the fact that free water, changes in chloride concentration, and albumin all affect BE. First, the effect on BE caused by free water (BE_{fw}) is calculated as

$$BE_{fw} = 0.3 \times (\{Na^+\} - 140) \quad (11)$$

Changes in BE accounted for by chloride are calculated as

$$BE_{Cl} = 102 - Cl_{corr}^- \quad (12)$$

where $\text{Cl}^-_{\text{corr}}$ is the corrected chloride: $\text{Cl}^- \times 140/\text{Na}^+$. Finally, the effect of albumin on BE (BE_{alb}) is calculated as

$$\text{BE}_{\text{alb}} = 3.4 \times (4.5 - \text{albumin}) \quad (13)$$

where albumin is reported in grams per deciliter.

The “classic” BE, as calculated from plasma bicarbonate, is really the sum of these three components plus a component attributable to unmeasured anions, BE_{ua} :

$$\text{BE} = \text{BE}_{\text{fw}} + \text{BE}_{\text{Cl}} + \text{BE}_{\text{alb}} + \text{BE}_{\text{ua}} \quad (14)$$

If one subtracts the first three from reported BE, one obtains BE_{ua} or BE caused by unmeasured anions:

$$\text{BE}_{\text{ua}} = \text{BE} - (\text{BE}_{\text{fw}} + \text{BE}_{\text{Cl}} + \text{BE}_{\text{alb}}) \quad (15)$$

In his study of 255 children in whom arterial blood gases, electrolytes, and albumin were measured simultaneously, Balasubramanyan demonstrated that BE_{ua} predicts increases in plasma lactate concentration better than BE and, furthermore, that it is a better predictor of mortality than either BE or the lactate concentration [174].

Story et al. [184] further simplified the FencI–Stewart methodology based on the premise that a change in the sodium-chloride component of the [SID] will change the base excess directly. Assuming a normal median sodium of 140 mEq/L and a normal median chloride of 102 mEq/L, the median difference is 38 mmol/L. The simplified version of the equation for sodium minus chloride effect on base excess is thus

$$\begin{aligned} \text{Sodium} - \text{chloride effect (mEq/L)} \\ = [\text{Na}^+] - [\text{Cl}^-] - 38 \end{aligned} \quad (16)$$

The albumin likewise has a direct effect on the base excess as the principal contributor to plasma total weak acid concentration. The simplified FencI–Stewart equation for albumin effect is as follows:

$$\begin{aligned} \text{Albumin effect (mEq/L)} \\ = 0.25 \times [42 - \text{albumin (g/L)}] \end{aligned} \quad (17)$$

This was tested prospectively in a non-randomized ICU study of 300 patient samples. In the samples, they compared the agreement between the more complex FencI–Stewart equations and their simplified versions using Bland–Altman analyses. They concluded that the simplified equations agreed well with the more complex equations. The authors proposed analysis of blood gases using the following four steps: (1) obtain standard base excess (mmol/L) from a blood gas machine; (2) calculate sodium-chloride effect (mEq/L) = $[\text{Na}^+] - [\text{Cl}^-] - 38$; (3) calculate albumin effect (mEq/L) = $0.25 \times [42 - \text{albumin (g/L)}]$; and (4) calculate unmeasured ion effect:

$$\begin{aligned} \text{Unmeasured ion effect (mEq/L)} \\ = \text{standard base excess} - \text{sodium} \\ - \text{chloride effect} - \text{albumin effect.} \end{aligned} \quad (18)$$

Employing these four steps, Ahmed and colleagues performed a randomized, prospective, interventional trial among 300 patients with “abdominal sepsis.” Patients were randomized to receive 20 mL/kg of either normal saline or Ringers lactate over 30 min. Patients in the normal saline arm had a significant drop in pH and base excess, whereas Ringers lactate patients did not. See Fig. 2. This was largely explained by the sodium-chloride effect on base excess. Dilution of serum albumin caused a partial correction of acidosis, creating a metabolic alkalosis. This mixed acid-based disorder would not have been recognized by the standard base excess approach or the anion gap approach but was detected by the FencI–Stewart method [185].

The studies of Balasubramanyan [174], FencI [155], and their colleagues provide evidence that critical care patients warrant an aggressive evaluation of acid–base status.

Osmol Gap

Osmolality is an expression of the number of particles in a given weight of solvent. Thus, each molecule of a substance, regardless of its molecular weight, contributes exactly the same as a

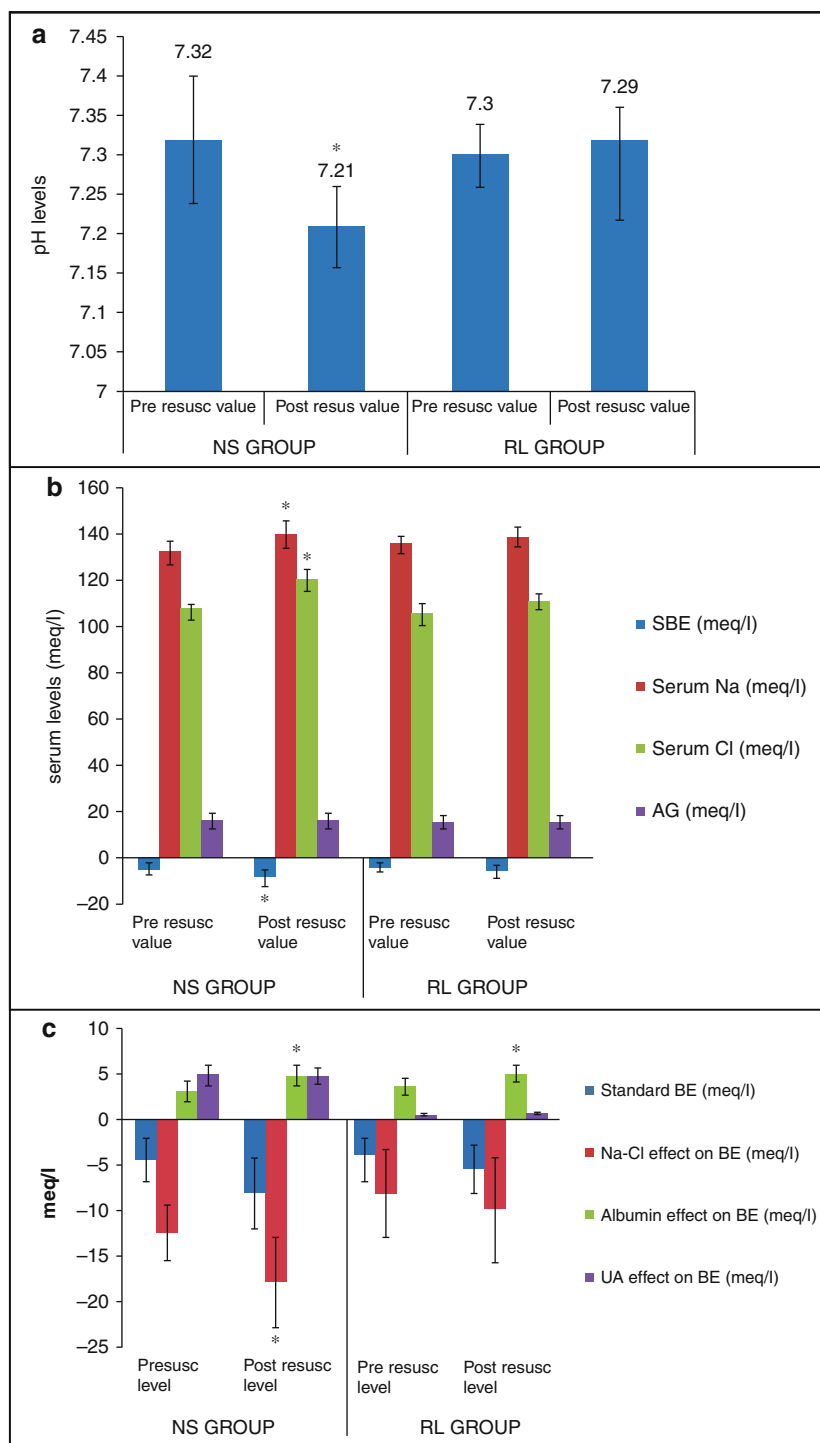


Fig. 2 Infusion of electrolyte solutions of varying SID will, according to the strong ion theory, variably alter the pH, base excess, and the concentrations of the strong ions themselves. These panels represent the effects of

infusion of 20 ml/kg of either normal saline (NS) or Ringer's lactate (RL) over 30 min. NS has an [SID] of 0 mmol/L ($[\text{Na}^+] - [\text{Cl}^-] = 154 - 154 = 0$ mmol/L), whereas RL has an SID of 28 mmol/L ($[\text{Na}^+] + [\text{K}^+] +$

molecule of another substance to osmolality. The vast majority of circulating osmols consist of sodium (and its associated anions), glucose, and urea. The presence of unanticipated osmols (osmol gap) is a potentially useful signal of the presence of a toxic alcohol. The true utility of the osmol gap in poisoned patients has been questioned, perhaps unfairly, on the basis of poor sensitivity [186]. However, in true clinical circumstances, the sensitivity of the osmol gap for “toxic alcohol” poisoning is 90% [187]. The osmol gap is calculated as

$$\text{OG} = \text{MO} - \text{CO} \quad (19)$$

where MO is the measured osmolality and CO the calculated (anticipated) osmolality. The small difference between osmolality and osmolality is ignored in the calculation of the osmol gap. There are normally a limited number of unmeasured osmols, so a small gap is expected. In the context of a poisoned patient, the OG is most commonly measured in an attempt to determine whether substantial concentrations of circulating exogenous osmols are present. Generally, the presence of excess measured osmols in a poisoned patient will be due to alcohols or glycols, such as ethanol, methanol, isopropanol, ethylene glycol, or propylene glycol, the last often present because of its widespread use in therapeutically administered medications. Since alcohols are volatile, MO for them should be determined by freezing-point depression to ensure that they are not liberated during determination of osmolality. This is not as much of a concern with glycols. The relative contributions of several molecules of interest to MO are indicated in Table 5. It should be

emphasized that the figures in this table are theoretical and should be used only as a rough guide to expected changes in osmolality or, conversely, plasma concentration. Osmolality is measured in mOsm/kg H₂O. Numerous formulas have been used for calculation of this gap, and one popular formula for the predicted serum osmolality, proposed by Dorwart and Chalmers, [159] follows:

$$\begin{aligned} &\text{Standard International [SI] units} \\ \text{CO} &= 1.86 [\text{Na}^+] + [\text{Glucose}] + [\text{BUN}] + 9, \end{aligned} \quad (20a)$$

where concentrations of sodium, glucose, and blood urea nitrogen (BUN) are expressed in mmol/L.

$$\begin{aligned} &\text{Mass Units} \\ \text{CO} &= 1.86 [\text{Na}^+] + [\text{Glucose}/18] \\ &\quad + [\text{BUN}/2.8] + 9, \end{aligned} \quad (20b)$$

where sodium is expressed in mmol/L and glucose and urea in mg/dL [159].

Purssell and colleagues [189] derived an osmol gap formula using linear regression with the blood ethanol concentration taken into account and then validated it in convenience samples from 128 patients. This formula is based on that of Mahon et al. [190], who used a multiplier of 2 for Na⁺ rather than 1.86. Purssell added a correction factor of 1.25 in SI units for the contribution to osmolality by ethanol. Given the frequency with which ethanol is found in poisoned patients, its presence should be confirmed and included in the calculation. Thus, adding the Purssell ethanol correction factor,

Fig. 2 (continued) $[\text{Ca}^{2+}] - [\text{Cl}^-] = 130 + 4 + 3 - 109 = 28 \text{ mmol/L}$. **Panel A.** Changes in pH following infusion of normal saline or Ringer’s lactate. **Panel B.** Changes in serum base excess, sodium, chloride, and anion gap following infusion of normal saline or Ringer’s lactate. **Panel C.** Changes in standard base excess, sodium minus chloride effect, albumin effect, and unmeasured anion effect on base excess following infusion of normal saline or Ringer’s lactate (Adapted from Ahmed et al. [185])

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Table 5 Contributions of some solutes to serum osmolality

Substance	Molecular weight	1 mg/dL blood or plasma concentration of substance will increase the osmol gap by approximately (mOsm/kg)	CF ^b	AIOG ^c	1 mOsm/kg increase in the osmol gap corresponds to an estimated concentration of (mg/dL)	1/CF ^d	AIEC ^e
Acetone	58.1	0.17			5.8		
Ethanol ^a	46.1	0.22	1.20	0.26	4.6	0.83	3.82
Ethylene glycol	62.1	0.16	1.00	0.16	6.2	1.0	6.20
Isopropanol	60.1	0.17			6.0		
Methanol	32.1	0.31	1.07	.033	3.2	0.93	2.98
Propylene glycol	76.1	0.13			7.6		

Serum concentration (mg/dL) = (osmol gap) × molecular weight/10. These calculated figures may be misleading and should be interpreted carefully

^aSee the text for revised calculations of ethanol concentration

^bConversion factors, as proposed by Khajuria and Krahn [188]

^cAdjusted estimate of increase and osmol gap (multiply column 3 by column 4)

^dReciprocal of conversion factors, as proposed by Khajuria and Krahn [188]

^eAdjusted estimate of increase in concentration (multiply column 6 by column 7)

one arrives at a formula for CO, corrected for measured blood ethanol (CO_{corrected}):

SI units
$$\text{CO}_{\text{corrected}} = 2\{\text{Na}^+\} + \{\text{Glucose}\} + \{\text{BUN}\} - 1.25 \times \{\text{Ethanol}\}$$

(21a)

If mass units (mg/dL) are used for the latter three, the following formula is used:

Mass Units
$$\text{CO}_{\text{corrected}} = 2\{\text{Na}^+\} + \{\text{Glucose}\}/18 + \{\text{BUN}\}/2.8 - \{\text{Ethanol}\}/3.7$$

(21b)

Two more recent studies have studied the effect of ethanol on the osmol gap [191, 192]. Carstairs and colleagues gave ten healthy volunteers up to 140 mL 100% ethanol in sugar-free soda (n = 8) or plain sugar-free soda (n = 2). The Dorwart formula was used. The osmol gap was divided by the blood ethanol to determine the mean coefficient of ethanol’s contribution to serum osmolality, yielding 4.25 (95% CI, 4.13–4.38). This divisor is smaller than that predicted by molecular weight of ethanol, indicating that it contributes

more to total osmolality than predicted for an ideal solute [191]. The study has been criticized for proposing a mean coefficient when the underlying individual subjects had coefficients that were substantially inconsistent [193]. In a much larger study of 603 emergency department patients, Garrard and colleagues retrospectively reviewed patients who had concurrent ethanol, basic metabolic panel, and measured serum osmolality results available [192]. The median ethanol concentration was 166 mg/dL (36 mmol/L). The mean osmol gap was 47, with a significant proportional relationship between ethanol and osmol gap. The authors concluded that the contribution of ethanol to the osmol gap is defined by the ethanol concentration (mg/dL)/4.0 [192].

Dozens of formulas of varying performance have been proposed for the plasma osmolality calculation. Not surprisingly skepticism about the value of the osmolal gap as a predictive tool for the presence of toxic alcohols has arisen [186]. Nonetheless, many hospitals do not have access to immediate confirmation for the presence and quantity of toxic alcohols in the blood. They thus depend on the anion and osmol gaps for determining the likelihood of a toxic alcohol exposure.

Khajuria and Krahn [188], in an effort to derive a formula that can be used in normal patients, as well as in those who are hyperglycemic and/or intoxicated, performed a series of *in vitro* experiments and tested several formulas for the calculated osmol gap. They demonstrated that glucose and alcohols don't accurately predict osmolality on the basis of their molecular weights alone. The experiments demonstrated the need for correction factors for glucose, ethanol, methanol, and ethylene glycol of 1.15, 1.20, 1.07, and 1.00, respectively, in order to accurately predict osmolality. The authors then tested two formulas against data from 37 healthy volunteers (without ethanol) and 129 emergency department patients with mean ethanol concentrations of 41.5 ± 27.0 mmol/L. Both formulas predicted osmolality well, in the presence or absence of ethanol. One of the two formulas, a modification of the Dorwart formula [159], with potassium added follows:

$$\begin{aligned} \text{SI units} \\ \text{CO} &= 1.86[\text{Na}^+ + \text{K}^+] + 1.15[\text{Glu}] \\ &+ [\text{Urea}] + 1.2[\text{Ethanol}] + 14 \end{aligned} \quad (22a)$$

This formula yielded a mean osmol gap of 0.77 ± 3.80 mOsm/kg in healthy volunteers (without ethanol). The mean osmol gap in patients with ethanol present was -0.2 ± 5.00 mOsm/kg, with a reference interval of -8.04 – 6.50 mOsm/kg [188], substantially narrower than that reported by Hoffman and colleagues (-5 – 15 mOsm/kg, using a different formula) [186]. This formula and that of Siervo (see below) utilize urea in SI units rather than BUN. However, there is 1 mmol of nitrogen in 1 mmol of urea, so the conversion is the same as usual if BUN is employed (i.e., divide by 2.8 to obtain mmol/L from mg/dL):

$$\begin{aligned} \text{Mass Units} \\ \text{CO} &= 1.86[\text{Na}^+ + \text{K}^+] + 1.15[\text{Glu}/18] \\ &+ [\text{BUN}/2.8] + 1.2[\text{Ethanol}/4.6] + 14 \end{aligned} \quad (22b)$$

One notes that the correction factor for ethanol in this case resolves to $4.6/1.2 = 3.8$, almost precisely the correction factor proposed by Pursell [189].

Siervo and colleagues [194] subsequently compared 38 predictive equations, including the Khajuria formula (minus the ethanol correction), in a group of 186 frail older people with and without diabetes. They found four equations which showed reasonable agreement with measured osmolality, but that the formula with narrowest limits of agreement was the following:

$$\text{CO} = 1.86[\text{Na}^+ + \text{K}^+] + 1.15[\text{Glu}] + [\text{Urea}] + 14.$$

One immediately notes that this is the same formula as that of Khajuria (Eq. 22a) minus the correction for ethanol.

Martin-Calderon and colleagues [195] independently compared 14 calculated osmolality equations, comparing goodness of fit of the calculation with osmolality measured by freezing-point depression among 146 healthy volunteers (96 males/50 females). They warned that the original Dorwart-Chalmer equation should not be used for osmolality calculations. Like Siervo, they did not include ethanol in their calculations. The best fit was obtained by the same equation adjusted for use of mass units:

$$\begin{aligned} \text{CO} &= 1.86[\text{Na}^+ + \text{K}^+] + 1.15[\text{Glu}/18] \\ &+ [\text{BUN}/2.8] * + 14 \end{aligned}$$

* BUN/2.8 was substituted for urea/6 for use in the USA, where measurement of urea is uncommon. Thus, while prospective confirmation of its validity in a wide variety of patients with normal values, hyperglycemia, elevated blood ethanol, and/or toxic alcohols is needed, this formula (adding the correction for ethanol) clearly looks promising.

One other issue of importance to the calculation of the osmol gap is that of "pseudohyponatremia" associated with hyperglycemia. Pseudohyponatremia is an accurate description of the volume exclusion effect of very elevated triglycerides or protein when sodium is measured by indirect methods. The move to specific ion electrodes has largely eliminated this issue. The decrease in sodium seen with hyperglycemia is not pseudohyponatremia, but rather a shift of water from the intracellular space to the plasma induced by the osmotic effect of glucose, such that the sodium in the vascular compartment is indeed

decreased by dilution. The specific ion electrode for sodium provides accurate measurements even in the presence of elevated glucose; thus, there is no reason to “correct” the sodium for elevated glucose in calculating the osmol gap [196].

So, what is one to do with these different equations for calculated osmols? First, inquire from your laboratory whether they have determined the normal osmol gap in your patient population. As Pursell warns, the calculation of the osmolal gap at the bedside without knowledge of how the calculation works in that environment is poor practice and subject to serious error [189]. Of the published equations, the Khajuria (Eqs. 22a and 22b) appear to offer very close correlation with measured osmols. In the end, it is important to remember that assuming the presence or absence of a toxic alcohol on the basis of the osmol gap, regardless of formula, is not ideal. It is imperative to understand that the range of “normal” osmol gaps will vary significantly, depending on the calculation chosen and on laboratory equipment used for the analysis. The osmol gap appears to be most reliable when it exceeds 25 mOsm/kg [197], although a more recent paper reports excellent sensitivity down to 10 mOsm/kg [187]. Because of variations in the results (and normal values) obtained depending on the formula used, the relatively small number of osmols produced by a toxic concentration of ethylene glycol (a blood concentration of 25 mg/dL [4 mmol/L] is equivalent to only ≈ 4 mOsm/kg see Table 5), and the possibility of missing even *severe* very early or late manifestations of ethylene glycol or methanol toxicity, the osmol gap should be interpreted with caution. Small or absent anion or osmol gaps may be obtained after severe toxic alcohol poisoning, depending on the extent of absorption and metabolism that have taken place since the ingestion. Therefore, both anion and osmol gaps must be viewed with prudence and do not completely rule out such poisonings. If any clinical suspicion exists, a direct measurement of the possible offending alcohols or glycols should be obtained and strong consideration given to initiation of blockade of alcohol dehydrogenase (ADH). When the osmol gap is elevated in the case of methanol poisoning, the osmol gap may be

followed to assess treatment progress. Jacobsen and colleagues have reported on 28 patients from a recent methanol outbreak, in whom the osmol gap predicted in a linear fashion the methanol concentration, with a correlation coefficient of 0.94 [198]. This same group demonstrated good correlation between serum methanol and osmol gaps during hemodialysis, concluding that, in the absence of serum methanol analyses, the osmol gap is useful to assess indication for and duration of dialysis in methanol poisoned patients [199].

An unvalidated algorithm in which the various gaps are used for evaluation of acid–base disorders is presented in Fig. 3. Suggestions for use of the anion and delta gaps are found in Figs. 4 and 5, respectively. A side-by-side comparison of the Stewart and modified anion gap–base excess methodologies is found in Fig. 6.

Arterial Blood Gases

Interpretation of arterial blood gases in a poisoned patient does not differ significantly from that in other patients and is therefore not discussed in detail here. It is worthwhile, however, to note that according to the strong ion theory, the change in pH induced by a change in PaCO_2 will vary depending on $[\text{SID}]$ and A_{TOT} , thus indicating that PaCO_2 is important not only in respiratory acidosis but also in metabolic acidosis and reinforcing the importance of evaluation of all three independent variables [176]. The compensation formulas for simple acid–base disorders proposed by Narins and Emmett [200] are provided in Table 6. The caveats discussed above with regard to “standard” bicarbonate hold.

Treatment of Acid–Base Disorders

The *sine qua non* of therapy for acid–base disorders is correction of the underlying cause of the disorder. Attention to the patency of the airway and adequacy of ventilation and oxygenation cannot be overemphasized.

In terms of metabolic derangements, the strong ion theory significantly simplifies the task of

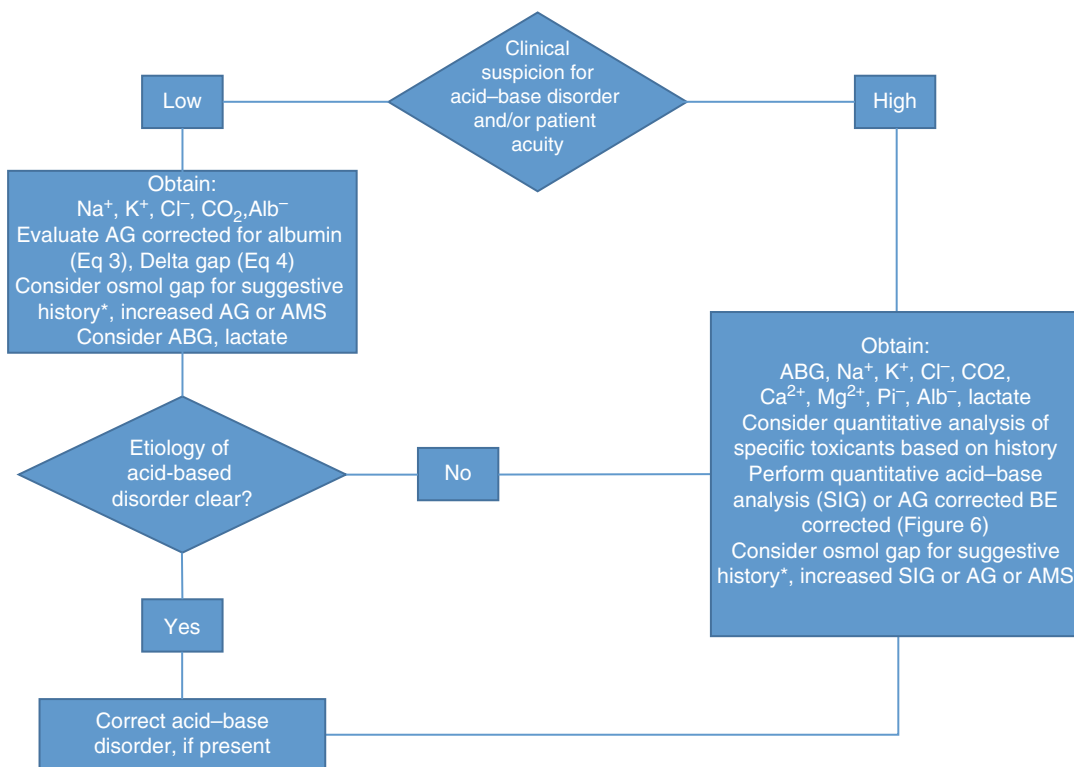


Fig. 3 An unvalidated algorithm (level of evidence III) for the evaluation of acid-base disorders based on clinical suspicion of a disorder or patient acuity. While simple acid-base evaluation, using classic laboratory studies and calculation of “gaps,” may suffice where suspicion of acid-base derangements and acuity is low, quantitative “strong ion” analysis is indicated where there is high suspicion of acid-base disorder or high acuity. Failure to clarify the etiology of the disorder with simple gaps and

ABG analysis should also indicate the need for quantitative acid-base analysis. See text and Fig. 6 for details on calculation. Abbreviations: *ABG* arterial blood gas, *AG* anion gap, *ALB*⁻ serum albumin, *AMS* altered mental status, *BE* base excess, *LOE* level of evidence, *Pi* inorganic phosphate, *[SIG]* strong ion gap. Level of evidence: Corrected anion gap-II-2, Delta gap-III, *[SIG]*-I, *BE* corrected-II-1

correction. A careful evaluation of strong ions will determine the need for electrolyte replacement, so reflexive administration of large volumes of solutions that alter *[SID]*, such as sodium chloride, is avoided in the treatment of metabolic acidosis. Hypoperfusion persisting in spite of correction of vascular water and electrolyte deficits may require the use of vasoactive substances. It must be appreciated that their use may often worsen acidosis via the production of lactate, so careful attention to the risk-benefit ratio of their use is of utmost clinical interest [201, 202].

Since the advent of the Stewart approach, increasing attention has been directed at correction of strong ion differences through the use of

various crystalloid solutions. Morgan and colleagues studied the relationship between the strong ion difference of a diluting crystalloid and its acid-base effects on *in vitro* blood dilution [203]. They tested three solutions of varying chloride content (120, 110, and 100 mmol/L (*[SID]* equals 20, 30, and 40 mEq/L respectively), as well as 0.9% saline (*[SID]* equals 0) and Hartmann solution (*[SID]* equals -4 mEq/L). With the exception of the solution of 40 mEq/L *[SID]*, for which *[SID]* did not change, plasma *[SID]* decreased during hemodilution. For solutions with higher *[SID]*, base excess increased during hemodilution. The relationship between hemoglobin concentration and both plasma *[SID]* and a

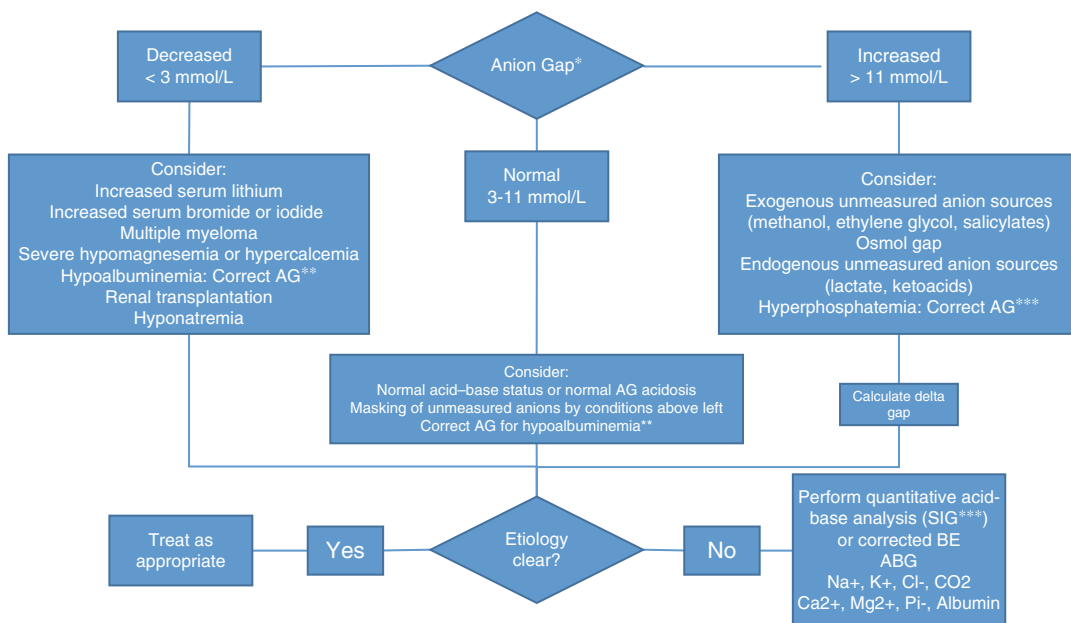


Fig. 4 Evaluation of the anion gap (AG). *AG is calculated as $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$. The normal range of AG is 3–11 mmol/L but will vary according to individual hospital laboratories. **Correction for hypoalbuminemia: $\text{AG observed} + 0.25 \times ([\text{Albumin, nL}] - [\text{Albumin observed}]) = \text{AG corrected}$, where normal albumin is considered to be 45 g/L. ***Correction for

hyperphosphatemia: $\text{AG observed} - 0.32 \times ([\text{Phosphate observed}] - [\text{Phosphate, nL}]) = \text{AG corrected}$, where the upper normal phosphate level is considered to be 5 mg/dL. If phosphate is reported in mmol/L, simply drop the multiplier of 0.32. ABG, arterial blood gases; [SIG], strong ion gap. Level of evidence: Corrected anion gap-II-2

whole blood base excess were linear. Linear regression revealed the [SID] of crystalloid producing a 0 base excess/hemoglobin concentration slope during blood dilution (in other words no acid–base change) was 23.7 mEq/L. This same group demonstrated in rats undergoing normovolemic hemodilution that there is a linear relationship between the crystalloid [SID] and the postdilutional metabolic acid–base status [204]. The [SID] of a crystalloid balance for normovolemic hemodilution is 24 mEq/L, identical to the standard bicarbonate.

Omron and Omron performed clinical simulations of modeled acid–base and fluid compartment parameters in a 70 kg test participant at standard physiologic state [205]. Comparing simulated infusions of up to 10 L of normal saline ([SID] equals 0), Ringers lactate ([SID] equals 28), Plasma-Lyte 148 ([SID] = 50), half normal saline +75 mEq sodium HCO_3^- ([SID] = 75) and 0.15 mole/L sodium ([SID] = 150) with a

hypothetical crystalloid solution of [SID] = 24.5 mEq/L, the authors demonstrated that a crystalloid [SID] equivalent to standard-state actual HCO_3^- (24.5 mEq/L) results in a neutral metabolic acid–base status or standardized base excess approximately equal to 0 mEq/L for infusions up to 10 L. The larger the infused volume, the greater the displacement of SBE from 0 mEq/L when crystalloid [SID] and actual HCO_3^- are discordant. The lower the [SID] relative to actual HCO_3^- , the greater the standard base deficit; the greater the crystalloid [SID] relative to actual HCO_3^- , the greater the SBE. A 1 L normal saline infusion resulted in metabolic acidosis, whereas the same infusion of Ringers lactate resulted in metabolic alkalosis.

In 2013, Morgan [123] reviewed the subject of the “balanced” crystalloid in the context of quantitative acid–base chemistry. Noting that the [SID] of isotonic saline is 0 (equal concentrations of sodium and chloride), Morgan makes the case

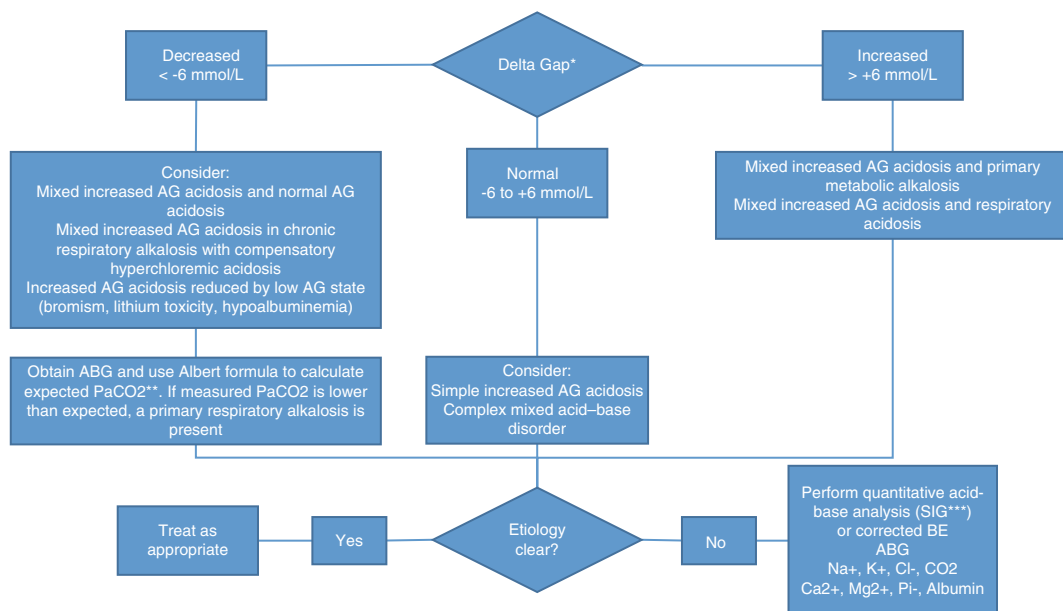


Fig. 5 Evaluation of the delta gap. *The delta gap is calculated as $\Delta\text{gap} = \Delta\text{AG} - \Delta\text{HCO}_3^-$, where ΔAG = observed AG – the upper normal limit of the AG and ΔHCO_3^- = lower normal HCO_3^- – observed HCO_3^- . The normal range for the delta gap is 0 ± 6 . **Albert

formula: Expected $\text{PaCO}_2 = 1.5 [\text{HCO}_3^-] + 8 + 2$.
***See text and Fig. 6 for calculation of [SIG] (XA^-)
(Adapted from Wrenn [141]). Level of evidence: Delta gap-III

that administration of large volumes of saline over a relatively short period of time forces reductions in [SID], leading to hyperchloremic metabolic acidosis, while at the same time reducing Atot through dilution of plasma proteins and phosphate, which gives rise to metabolic alkalosis. The net result however is metabolic acidosis. Admittedly, saline-induced acidosis is relatively mild to moderate. Nonetheless, he underscores that there are data suggesting that hyperchloremic metabolic acidosis is pro-inflammatory, causing multiorgan dysfunction. He reminds us that reduced chloride exposure may lessen kidney injury with a possible mortality benefit [206]. To achieve exact balance from an acid–base perspective, it is sufficient to reduce the strong ion difference to 24 mEq/L. This can be done by replacing chloride in an isotonic saline solution with HCO_3^- or a substitute such as acetate. He points out that Ringer’s acetate solution is as close to a balanced solution that exists currently, both from acid–base and tonicity perspectives. He suggests that a large, randomized clinical trial is necessary to

establish definitively the benefits of using a balanced crystalloid solution [123].

Ragunathan and colleagues carried out a retrospective cohort study of patients admitted with sepsis, comparing those who received only “no-balanced fluids” (i.e., isotonic saline with or without dextrose 5% [SID] = 0) against patients who received some (widely variable) quantity of “balanced” solutions such as Ringers lactate in 53,448 patients among 360 US hospitals [207]. While the patients treated with balanced fluids were younger and less likely to have heart disease or chronic renal failure, they were more likely to receive mechanical ventilation, invasive monitoring, colloids, steroids, and larger crystalloid volumes. The authors then applied propensity matching to arrive at two comparison groups of 3,396 matched subjects. Receipt of balanced fluids was associated with lower in-hospital mortality (19.6% vs. 22.8%) with mortality progressively decreasing among patients receiving larger proportions of balanced fluids [207]. While these findings are of interest, there are clearly methodological issues.

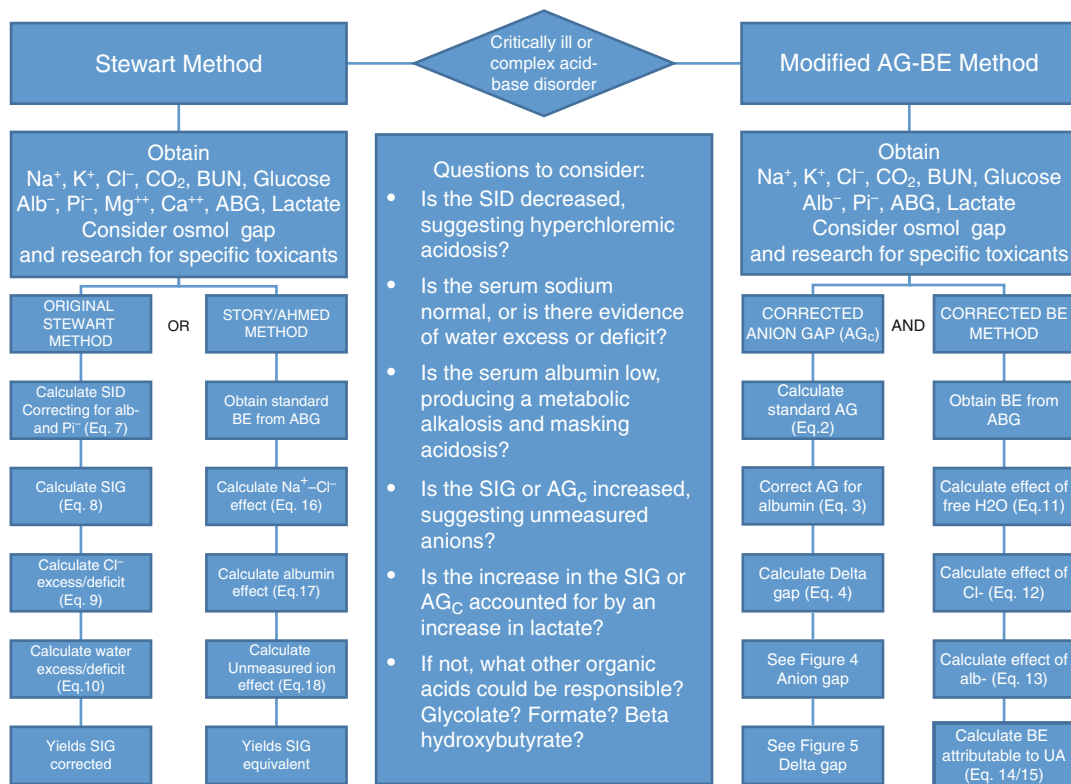


Fig. 6 Evaluation of patients with perceived complex acid–base disorders. Both Stewart physicochemical methods and modifications of the anion gap and base excess methodology have been proposed in recent years. The choice of methodology remains controversial, so multiple methods of acid–base analysis are provided here.

Abbreviations: Alb^- albumin, ABG arterial blood gas, AG_c corrected anion gap, BUN blood urea nitrogen, [SID] strong ion difference, [SIG] strong ion gap, UA unmeasured anions. Level of evidence: Corrected anion gap-II-2; Delta gap-III; [SIG]-I; BE corrected-II-1

Thus, a large randomized controlled trial of well-defined balanced versus unbalanced fluids is clearly needed.

The comparison of Ringers lactate to normal saline and abdominal sepsis patients by Ahmed and colleagues has already been cited. Figure 2 demonstrates significant differences in pH and base excess induced by relatively modest (20 mL/kg) infusion volumes of 0 [SID] solutions such as normal saline.

The specific (i.e., other than supportive) treatment of acid–base disorders remains controversial. For many years, the cornerstone of treatment of metabolic acidosis, with the exception of DKA, was the administration of bicarbonate, sometimes in very large quantities. Correction of abnormal pH (excess H^+) via administration of bicarbonate

appears logical on the surface. However, Graf and colleagues [208] pointed out evidence that administration of bicarbonate may actually worsen intracellular acidosis, which led to proposals by some that we should “ban bicarbonate” in the treatment of acidosis [209]. Whether this rapid swing of the pendulum in the opposite direction was warranted depends on the belief that all metabolic acidosis is alike and should therefore be treated similarly. One might question, however, whether the acidosis produced by metabolic conversion of methanol is equivalent to the lactic acidosis produced in septic shock. Kellum has pointed out that when treatment is based on [SID], the need for bicarbonate therapy becomes clear [175]. If the disorder involved is characterized by decreased or normal sodium, administration of sodium in the

Table 6 Formulas for expected compensation in simple acid–base disorders

Disorder	Formula
Metabolic acidosis	Change in $\text{PaCO}_2 = 1.2 \times \text{change in } \text{HCO}_3^-$
Metabolic alkalosis	Change in $\text{PaCO}_2 = 0.6 \times \text{change in } \text{HCO}_3^-$
Acute respiratory acidosis	Change in $\text{HCO}_3^- = 0.1 \times \text{change in } \text{PaCO}_2$
Acute respiratory alkalosis	Change in $\text{HCO}_3^- = 0.2 \times \text{change in } \text{PaCO}_2$
Chronic respiratory acidosis	Change in $\text{HCO}_3^- = 0.35 \times \text{change in } \text{PaCO}_2$
Chronic respiratory alkalosis	Change in $\text{HCO}_3^- = 0.5 \times \text{change in } \text{PaCO}_2$

Adapted from Narins and Emmett [200]

Changes represent differences from normal values for PaCO_2 (40 mmHg) and HCO_3^- (24 mEq/L). See text for cautions regarding standard HCO_3^-

form of bicarbonate may in fact be warranted. However, it is in reality the sodium concentration (the strong ion) that is being addressed. If one accepts the Stewart theory, bicarbonate will actually be determined by the three independent variables (strong ions, PaCO_2 , and weak acids/salts). Only by increasing sodium relative to chloride can sodium bicarbonate “repair” metabolic acidosis. Thus, when sodium is already increased, there is no role for bicarbonate therapy [175]. Other considerations make the use of sodium bicarbonate potentially appropriate in metabolic acidosis of toxic origin. Alkalinization of the urine has a demonstrated beneficial effect on the distribution of salicylates and barbiturates by hastening elimination and diminishing CNS penetration. Sodium administration (as bicarbonate or hypertonic saline) appears to be effective as well in the treatment of cyclic antidepressant-related dysrhythmias, which may be associated with metabolic acidosis [210–212]. In summary, although bicarbonate should no longer be viewed as the “universal antidote” for metabolic acidosis, its use should not be summarily abandoned in all cases of acidosis. Kraut and Madias have recently provided recommendations for calculation of

bicarbonate requirements in severe lactic acidosis ($\text{pH} \leq 7.10$), diabetic ketoacidosis ($\text{pH} \leq 7.0$), and non-gap metabolic acidosis ($\text{pH} \leq 7.20$) when attempts at correcting the underlying disorder have been unsuccessful:

$$\begin{aligned} \text{Bicarbonate requirement} &= \text{desired } [\text{HCO}_3^-] - \\ &\quad \text{present serum } [\text{HCO}_3^-] \times \text{bicarbonate space,} \\ &\quad \text{where bicarbonate space} = [0.4 + (2.6/\text{HCO}_3^-)] \\ &\quad \times \text{body weight (kg)} \end{aligned} \quad (23)$$

The authors further recommend that, in order to minimize potential complications of bicarbonate administration, therapy should be initiated based on calculation using bicarbonate space of 50% body weight (kg); if this is not successful in achieving desired serum $[\text{HCO}_3^-]$, administer larger quantities of bicarbonate based on bicarbonate space calculated from the above formula [213].

The use of the strong ion approach allows us to not only recognize the often multiple underlying causes of acid–base disorders but also correct them. Hypoalbuminemia contributing to severe metabolic alkalosis may warrant replacement therapy. Chloride excess leading to acidosis may be addressed by hemofiltration or the use of a weak base such as tris(hydroxymethyl) aminomethane (THAM, or tromethamine). The presence of a strong ion gap (excess unmeasured anions) calls for therapy to reduce their production or facilitate their removal [175].

THAM has been proposed as an alternative to sodium bicarbonate, because it reduces arterial hydrogen ion concentration without producing CO_2 and penetrates cells easily, reducing intracellular acidosis [214]. Weber and colleagues studied THAM in 12 patients undergoing permissive hypercapnia for ARDS [215]. Patients who received THAM experienced less myocardial depression and lessened effects of hypercapnia on arterial pressure and mean pulmonary arterial pressure. Marfo and colleagues reported the case of a patient with severe lactic acidosis secondary to highly active antiretroviral therapy successfully treated with THAM [216]. Several studies have shown promising results in selected patient populations [217, 218], but additional studies are

needed. Kraut and Madias recommend consideration of THAM in patients with lactic acidosis, diabetic ketoacidosis, or non-gap metabolic acidosis in patients when CO_2 retention is present or incipient. They estimate THAM requirements using the following formula:

$$\begin{aligned} &0.3 \text{ M THAM requirement (in ml)} \\ &= \text{body dry weight (kg)} \\ &\times \text{base deficit (mEq/l)} \times 1.1, \end{aligned} \quad (24)$$

where base deficit = desired serum $[\text{HCO}_3^-]$ – actual serum $[\text{HCO}_3^-]$ [213].

Finally, extracorporeal treatments may be of interest in acidosis of toxic etiology [219–221]. Hemodialysis can correct not only the plasma bicarbonate (the result of the underlying disturbance in strong ion imbalance) but also some strong ion abnormalities (hyperkalemia). Furthermore, it has the capacity to remove a number of endogenous (lactate, pyruvate) and exogenous (methanol and metabolites, ethylene glycol and metabolites) compounds of low molecular weight and limited volume of distribution.

Based on admittedly limited data (mostly case reports), the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup has recommended extracorporeal removal of metformin in the case of severe poisoning (plasma lactate > 20 mmol/L [180 mg/dl], $\text{pH} \leq 7.0$, shock, failure of standard support measures, and decreased level of consciousness) [222]. EXTRIP has also recently released recommendations for extracorporeal treatment for valproic acid (VPA) poisoning. Intermittent hemodialysis is recommended for valproic acid poisoning when at least one of the following criteria for severe poisoning is present: VPA concentration > 1,300 mg/L (9,000 $\mu\text{mol/L}$), the presence of cerebral edema, or shock; suggestions for extracorporeal treatment include a VPA concentration > 900 mg/L (6,250 $\mu\text{mol/L}$), coma or respiratory depression requiring mechanical ventilation, acute hyperammonemia, or $\text{pH} \leq 7.10$ [223]. Note, however, that some degree of hyperammonemia is common with even minor VPA toxicity. Thus, the hyperammonia should be significant if that is the only reason the patient is

being considered for extracorporeal drug elimination. Cessation of extracorporeal treatment (ECTR) is indicated when clinical improvement is apparent or the serum VPA concentration is between 50 and 100 mg/L (350–700 $\mu\text{mol/L}$). Intermittent hemodialysis is the preferred ECTR in VPA poisoning. If hemodialysis is not available, then intermittent hemoperfusion or continuous renal replacement therapy is an acceptable alternative. EXTRIP has recommended extracorporeal treatment for acetaminophen (APAP) poisoning in the case of mitochondrial dysfunction as reflected by early development of altered mental status and severe metabolic acidosis preceding liver failure [224]. They point out that extracorporeal treatment should be reserved for those rare situations when the efficacy of N-acetylcysteine (NAC) cannot be definitively demonstrated. Specific recommendations for extracorporeal treatment include: an APAP concentration over 1,000 mg/L (6,600 $\mu\text{mol/L}$) if NAC is not administered, signs of mitochondrial dysfunction and an APAP concentration over 700 mg/L (4,630 $\mu\text{mol/L}$) if NAC is not administered, and signs of mitochondrial dysfunction and an APAP concentration over 900 mg/L (5,960 $\mu\text{mol/L}$) if NAC is administered (level of evidence [LOE] = III). Intermittent hemodialysis (HD) is the preferred ECTR modality in APAP poisoning [LOE] = III.

Summary

Acid–base disorders in poisoned patients may be of multiple toxic and nontoxic etiologies. A careful history and physical examination are necessary to suspect the disorder, and a thorough laboratory evaluation is required to distinguish the probable etiology. Reliance on simple calculations such as anion or osmol gaps may result in errors, including missed diagnosis. A systematic approach using multiple diagnostic tools, including the quantitative (strong ion) method, will decrease the likelihood of errors. Treatment is largely supportive. Bicarbonate or THAM therapy is useful in selected cases but should be based on a quantitative analysis of acid–base derangements rather than being a rote response to abnormal

laboratory values. Hemodialysis may also be of benefit in selected patients, again relying on the patient's clinical condition as a guide to therapy.

Acknowledgment This chapter is dedicated to the memory of Professor Chantal Bismuth, whose contributions to medical toxicology are innumerable and lasting. With her sharply analytical mind, incisive wit, and charming smile, she mentored hundreds of toxicologists-in-training, challenged the status quo, and brought focus to many nebulous concepts in toxicology. She will be missed.

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Treatment of Acute Respiratory Distress Syndrome in the Poisoned Patient

16

Dylan W. de Lange

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Lung-Damaging Toxicants

Lung-damaging toxicants may be defined as chemicals that induce pathological changes in the lung following absorption [1, 2]. The acute respiratory distress syndrome (ARDS) is a clinical syndrome which might be caused by direct damage to the respiratory cells at the alveolar level or indirectly through inflammation mediators in a severely exposed patient.

The true incidence of people being exposed to lung-damaging toxicants is unknown. The incidence that can be deduced from case reports, case series, and (inter)national registries is likely to represent only a minute fraction of the true incidence as the majority of patients do not seek medical attention. Furthermore, where medical treatment is necessary, many physicians do not inform poison information centers. Either they know how to treat such patients and do not need advice, or, more likely, they are unaware that an exposure is causing the respiratory effects.

The burden of inhalatory toxicants is unknown. However, the ubiquitous nature of these gasses (e.g., chlorine from household products, swimming pools) and its use in industry put many at risk. Due to the accidental nature of many of these intoxications, often many people are exposed simultaneously. A devastating example of such industrial exposure with numerous civilian fatalities is the infamous gas leak of Bhopal (India). In 1984, an exothermic reaction in a carbaryl producing factory plant caused the release of approximately 30 metric tons of methyl isocyanate in a densely populated area. This resulted in over 2500 deaths and 200,000 injuries [3]. Arguably, this is the largest industry evoked exposure of lung-damaging toxicants. While most of these acute inhalatory intoxications are the result of accidents, intentional exposure as a result of warfare or terrorist acts is an persisting threat (see Box 1).

In this chapter we will discuss the treatment options of patients with chemically induced ARDS.

Box 1: Warfare Use of Poisonous Gasses

A typical example of mass exposure and multiple deaths is the use of chemical gasses during warfare. Toxic fumes were used in the war between the Athenians and the Spartans in 428 BC, when the Athenians used a combination of pitch and sulfur to incapacitate their opponents. It can be assumed that during the many wars hereafter many were exposed to “toxic fumes.” However, one of the most well-known and best documented wars that used chemical gasses was the First World War. During this war, all parties used chemical gasses to injure, demoralize, and kill opponents. In 1914, irritant gasses were used (so-called tear gasses, like ethyl bromoacetate). These gasses were intended to induce irritation and thus handicap soldiers. The first lethal gas to be employed in the trenches is said to be xylyl bromide [4]. However, in the cold weather, the chemical froze and did not have the desired effect. Additionally, bromine was hard to obtain causing the Germans to switch to chlorine. This chemical gas was a by-product of the German dye manufacturing and could be produced in sufficient amounts. Chlorine is a powerful irritant and in high and prolonged exposures, it may also cause pulmonary injury. This is discussed in greater detail in ► [Chap. 100, “Irritant and Toxic Pulmonary Injuries.”](#) Although many soldiers perished in these poisonous gas attacks, chlorine was not a very effective warfare agent. Soldiers who stood on high ground and kept their exertion to a minimum often survived. Injured soldiers that lay on the ground (prolonged exposure to a dense and heavy gas) or fled in the gas clouds (exertion) were at risk of pulmonary involvement and even death. Chlorine gas is easy to detect (visible greenish clouds with a strong odor) and

(continued)

several counter measures were applied. Chlorine is moderately water soluble and covering the nose and mouth with a moist cloth was somewhat effective. This quickly developed into more sophisticated gas masks.

In 1915, phosgene gas was introduced. It was colorless and difficult to detect, making it a more effective weapon than chlorine. However, phosgene had one major drawback, it took several hours before the symptoms became manifest. Therefore, there was a delay between exposure and incapacitation of the opposing troops.

In 1917, mustard gas was introduced by the Germans. Mustard is a vesicant (meaning blister provoking) that is not extremely lethal, although in high enough doses it might be fatal. However, it was used to disable the opponents. The skin of victims of mustard gas blistered, their eyes became inflamed, and they developed emesis. Mustard caused internal and external bleeding and attacked the bronchial tubes, denuding their mucous membrane. This was extremely painful. Fatally injured victims sometimes took 4 or 5 weeks to die of mustard gas exposure [5, 6]. The combination of chlorine, phosgene, and mustard gas continued to be used throughout the First World War; however, its effectiveness diminished against well-trained and well-equipped soldiers. The use of chemical gases was widespread in subsequent wars. In 1925, a treaty was conceived banning the use (but not stockpiling) of chemical weapons. Many countries ratified this, although some countries took more than 50 years to finally agree with this prohibition.

In 1988, Iraqi Air Forces dropped chemical weapon canisters on the town of Halabja. More than 5,000 people died of the immediate attack, and another 7,000 were injured or suffered long-term sequelae [7]. The attack was said to include vesicant

mustard gas as well as several nerve agents, such as tabun, sarin, and VX (quite lethal although not producing pulmonary symptoms). However, this has been denied by other sources.

For more information, see also ► [Chaps. 135, “Nerve Agents,”](#) and ► [136, “Sulfur Mustard.”](#)

Three Types of Acute Inhalation Exposures

Several elements of the respiratory tract contribute to the protection of the respiratory system from lung-damaging toxicants and inhaled particles (e.g., smoke). In the upper respiratory tract, particles larger than 5–10 μm (microns) are trapped through turbulence in the mucosal surfaces of the nose and mouth. In the conducting airways, ciliated and mucus-secreting epithelial cells move particles upward. It is estimated that this “mucociliary escalator” can move inhaled particles up the respiratory tract at approximately 1–4 cm per hour [8]. In the more distal airways, alveolar macrophages and neutrophils play an important role. They phagocytose particles and destroy them through hydrolyses containing lysosomes. Lymphatic clearance of particles is another, less important, mechanism of pulmonary clearance. The downside of macrophage and neutrophil involvement is the potential for activation of the inflammatory cascade.

The lung parenchyma is capable of metabolizing some inhaled toxins, but this is only a minor contributor to biotransformation of inhaled toxins. The majority is either exhaled or absorbed and subsequently excreted through other mechanisms (e.g., renal or hepatic clearance).

Three fundamental parameters determine the extent of involvement of lung-damaging toxicants: water solubility, duration of exposure, and minute ventilation. Water solubility plays a significant role in determining the location of toxic inhalation injury. Clinically, three types of

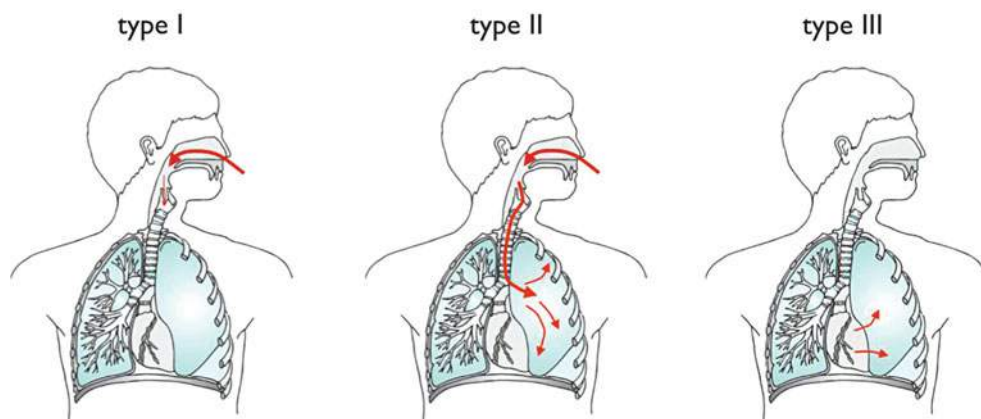


Fig. 1 Three types of reactions to inhaled toxins. There are three routes by which lung-damaging toxins can cause pulmonary damage. In type I exposure, the (often hydrophilic) lung-damaging toxin does not penetrate deep into the lung and causes irritation to the upper membranes. In type II exposure, the (often lipophilic) lung-damaging

toxicant penetrates deeper into the lung and causes damage at the alveolar level. In type III exposures, the toxicant is not or only minutely damaging the lung, but the effects after exposure and absorption are exerted elsewhere in the human body

inhalation injury are described, which are related to the physical properties of the inhaled toxin [1, 2, 9]. The first type (type I) consists of inhalation of a water-soluble toxicant, which causes direct irritation to the membranes of the upper respiratory tract. The second type (type II) reflects exposure to toxicants that are poorly soluble in water, which penetrate deeper into the lungs and cause damage at the alveolar level. The third type (type III) involves a toxic agent that does not directly cause damage to the lungs, but is absorbed and causes damage elsewhere or after metabolism (Fig. 1). An alternative, but important, route of exposure to lung-damaging toxicants is through non-pulmonary absorption. This often involves absorption through the gastrointestinal tract or skin.

Type I Inhalation Injury

Generally, agents that are soluble in water (see Table 1) are easily dissolved in the mucus of the upper airways. This results in a chemical process (oxidation, reduction, or pH change) in the mucosal membranes. After cessation of the initial exposure, this chemical reaction terminates, although an inflammatory response may continue.

Symptoms occur instantly after exposure and the nose and eyes are usually also involved. The symptoms are pain in the upper airways while breathing, nasal discharge, and lacrimation. In more severe cases, dyspnea due to bronchospasm, bronchial edema, glottis edema, and increased mucus production may be present; hemoptysis and cyanosis may become manifest. Although pulmonary edema might occur after exposure to water-soluble agents, it will never be the sole manifestation.

Type II Inhalation Injury

Shortly after inhalation of poorly water-soluble compounds (see Table 1), symptoms are not usually present in the first few hours after exposure (level of evidence [LoE] grade III) [9]. Examples of agents that cause such a delayed response are listed in Table 1. Consequently, examination directly after exposure may not provide information regarding the full extent of the severity of the intoxication. Rarely, minor irritative effects in the upper airways or nausea are present but generally bronchospasm is not prominent. After several hours, depending on the concentration of the agent and the duration of exposure, ARDS may

Table 1 Classification of lung-damaging toxicants and their site of action. This is not an exhaustive list, but it does give some examples of lung-damaging agents (LDAs) causing inhalation injuries. Partially based upon De Lange DW et al. Ref. [2], copyrights © (2013), Informa Healthcare. Reproduced with permission of Informa Healthcare

Water-soluble toxic agents (type I exposure)
Chlorine [10]
Chloramine [11]
Ammonia [12, 13]
Anhydrides [14]
Aldehydes of lower molecular weight (acrolein, formaldehyde, acetaldehyde) [15]
Sulfur dioxide [16, 17]
Hydrogen chloride [18]
Hydrogen fluoride [19–21]
Hydrogen bromide [22]
Dimethylamine hydrazine [23]
Zinc chloride [24, 25]
Poorly water-soluble toxic agents (type II exposure)
Nickel [26]
Nitrogen dioxide [27, 28]
Phosgene [29, 30]
Phosphine [31]
Ozone [32, 33]
Non-pulmonary exposure to toxins associated with ARDS
Amiodarone [34, 35]
Aluminum phosphide [36, 37]
Amitriptyline [38]
Ampicillin [39]
Aprotinin [40]
Arsenic [41, 42]
Aspirin [43, 44]
Bleomycin [45]
Carbofuran [46]
Chemotherapeutics [47]
Cocaine [48]
Cyclosporine [49]
Desferrioxamine [50]
Detergents [51]
Dextran [52, 53]
1,3-dichloropropene [54]
Diphenhydramine [55]
Elinogrel [56]
Ethchlorvynol [57]
Ethylene glycol (ingestion) [58, 59]
Fluorocarbon resin [60]
Gemcitabine [61, 62]

(continued)

Table 1 (continued)

Heroin [63, 64]
Ibuprofen [65, 66]
Hydrocarbon [67–73]
Hydrofluoric acid [74]
Lidocaine [75–78]
Lithium [79, 80]
Methadone [63, 64, 81, 82]
Methotrexate [83–85]
3,4-methylenedioxy-methamphetamine (MDMA) [86]
Mercury vapor [37, 87]
Nickel [88]
Nitrofurantoin [89–91]
Nitrogen dioxide [92]
Opioids [63, 64, 93, 94]
Organophosphates [95, 96]
Paraquat [97–101]
Phenol-formaldehyde resin [15]
Phenothiazines [102, 103]
Propylthiouracil [104–106]
Phosgene (inhalation) [29, 30, 107]
Protamine [108, 109]
Quinine and chloroquine [110, 111]
Radiocontrast material (injectable) [112]
Rapeseed oil (denaturated) [113]
Selenious acid [114]
Sodium oleate [115]
Streptokinase [116, 117]
Sulfuric acid fume [118]
Ticagrelor [56, 119]
Transretinoic acid [120]
Tricyclic antidepressants [38, 121, 122]
Welding on metals with galvanized coating or containing zinc chloride or nickel [123, 124]
Zotepine [125]

become evident. Agents that cause a delayed response dissolve poorly in water and therefore penetrate deeper into the lung. Consequently, the process causing symptoms is situated lower in the respiratory tract, which is in the alveoli and the terminal bronchioli.

Type III Inhalation Exposure

In a third type of response to inhalator toxicants, substances are absorbed through the lung but exert

their toxic effect elsewhere in the body. Usually such a toxicant only gives minor irritation in the lung itself. Typical examples of such substances are carbon monoxide or organic solvents, like toluene and xylene [9]. This type of inhalation exposure infrequently gives ARDS. If pulmonary symptoms occur, a type I or type II inhalation injury should be considered. Alternatively, non-pulmonary absorption of lung-damaging toxicants might play a role.

Non-pulmonary Absorption of Lung-Damaging Toxicants

Another important route of pulmonary injury represents lung-damaging toxicants that are absorbed elsewhere in the human body, but, through the circulation, exert their toxic effect in the lungs (indirect injury). This route of exposure is as important as type I and type II exposures but is more difficult to diagnose. A typical example is paraquat intoxication. Paraquat is a synthetic herbicide and when ingested can cause serious damage to various organs, including the lungs. Types I and especially II pneumocytes appear to selectively accumulate paraquat by actively taking up paraquat against the concentration gradient. This results in an additional distribution compartment (the so-called third “toxic effect” compartment) from which paraquat is only slowly eliminated. Biotransformation of the paraquat in these cells results in free-radical production with resulting lipid peroxidation and cell injury (LoE II-3) [126]. While acute pulmonary edema and early lung damage may occur within a few hours of severe acute exposures to paraquat, the delayed toxic damage of pulmonary fibrosis, the usual cause of death, most commonly occurs 7–14 days after the ingestion.

Pathophysiology of ARDS

The normal alveolar epithelium is composed of two types of cells. Flat type I cells make up 90% of the alveolar surface area and are easily injured [127]. Cuboidal type II cells make up the

remaining 10% of the alveolar surface area and are more resistant to injury; their functions include surfactant production, ion transport, and proliferation and differentiation to type I cells after injury. The loss of epithelial integrity in ARDS has a number of consequences. First, under normal conditions, the epithelial barrier is much less permeable than the endothelial barrier [128]. Thus, epithelial injury can contribute to alveolar flooding. Second, the loss of epithelial integrity and injury to type II cells disrupt normal epithelial fluid transport, impairing the removal of edema fluid from the alveolar space [129]. Third, injury to type II cells reduces the production and turnover of surfactant, contributing to the characteristic surfactant abnormalities [127]. Finally, if injury to the alveolar epithelium is severe, disorganized or insufficient epithelial repair may lead to fibrosis (LoE II-3) [130].

The innate immune system plays an important role in the pathophysiology of ARDS. Multiple immunologic processes involving neutrophils, macrophages, and dendritic cells are involved in mediating tissue injury. Toxicological insults affect bronchial epithelium, alveolar macrophages, and vascular endothelium, causing accumulation of protein-rich edema fluid into the alveoli and, consequently, hypoxemia due to impaired gas exchange [127, 131, 132]. Alveolar macrophages play a pivotal role in orchestrating inflammation (LoE II-2) [131, 132]. Once alveolar macrophages are stimulated, they recruit neutrophils and circulating macrophages to the pulmonary sites of injury. These recruited cells secrete a diverse array of bioactive mediators, including proteases, reactive oxygen species, eicosanoids, phospholipids, and cytokines, which subsequently stimulate further inflammatory responses. One of the most notable effects of these mediators is the damage done to adjacent cells, specifically alveolar type 2 epithelial cells [1]. Type 2 alveolar cells serve vital functions by synthesizing and secreting pulmonary surfactant, which is an indispensable material that lines the inner lung surface to lower alveolar surface tension. Type 2 alveolar cells also actively transport electrolytes to control lung fluid. Damage to these cells results in histological changes typical of an

acute exudative phase that results in significant impairment of lung mechanics and gas exchange [127].

Importantly, ARDS is not limited to the lungs, rather it's a systemic inflammatory disease with bidirectional involvement between the lungs and other organ systems [133]. Inflammatory cytokines, such as IL-1 β , TNF- α , IL-6, and IL-8, are elevated both in bronchoalveolar lavage fluid and in the systemic circulation (LoE II-2) [134].

Pattern recognition receptors (PRRs) are essential to the innate immunity, detecting components of foreign pathogens (referred to as pathogen-associated molecular patterns, PAMPs). However, some of these receptors are also able to detect damage-associated molecular patterns (DAMPs) after toxic injury. Toll-like receptors (TLRs) are PRR proteins which appear to be highly conserved molecules throughout vertebrates [135]. Currently, ten functional TLRs have been identified in humans [136]. They recognize PAMPs and DAMPs and trigger a subsequent pro-inflammatory signaling. Development of ARDS appears to be related to TLR signaling pathways. For example, hyaluronan, an extracellular matrix glycosaminoglycan produced after tissue injury, functions as a DAMP for TLR [137]. TLR4 was described as playing a pivotal role in the induction of ARDS in various murine models, TLR2 is implicated in hemorrhage-induced ARDS (LoE III) [138, 139].

In addition to the transmembrane TLRs, nucleotide-binding oligomerization domain-like receptors (NLRs) are cytosolic PRRs that respond to the various PAMPs and DAMPs and trigger pro-inflammatory responses. NLRs are responsible for the sterile inflammation in ARDS. One of them, NLRP (NLR family, pyrin domain containing) is an important component of the inflammasome, a large multiprotein complex. This complex is activated by pore-forming toxins or hypoxic cellular injury and is associated with poorer outcome in patients with ARDS (LoE II-2) [140, 141].

Other molecules, which can be freed into the surrounding tissues or in the circulation after toxic injury, might act as DAMPs as well. For example, mitochondrial DNA and ubiquitin are associated

with ARDS in experimental studies (LoE III) [142–144]. Ubiquitin is a small regulatory molecule found universally in most tissues in eukaryotic organisms. Ubiquitination is a posttranslational modification process whereby ubiquitin is attached to a substrate protein, usually serving as the signal for its degradation via the proteasome or lysosome [145, 146].

The pro-inflammatory signaling of pulmonary macrophages results in influx of neutrophils. Several chemokines, including interleukin 1 β (IL-1 β), IL-6, IL-8, and tumor necrosis factor (TNF), play a central role in regulating neutrophil recruitment and consequent tissue damage, as well as altered alveolar–capillary permeability in both human and animal studies (LoE II-2) [147].

Indeed, histological studies of lung specimens obtained early in the course of ARDS have shown a marked accumulation of neutrophils [127]. Neutrophils predominate in the pulmonary edema fluid and bronchoalveolar lavage fluid obtained from affected patients (LoE II-2) [148]. However, ARDS might develop in patients that are devoid of neutrophils (e.g., profound neutropenia) indicating that neutrophils are important but not critical to the development of ARDS [149].

Macrophages and neutrophils cause (collateral) damage to the pulmonary epithelium (clinically and pathologically presenting as diffuse alveolar damage), which results in filling of the alveoli with protein-rich fluids, cellular debris, and hyaline membranes. Additionally, the alveolar–capillary distance is increased by the formation of collagen [127]. The clinical picture is that of a patient in acute respiratory distress with hypoxia, cyanosis, tachypnea, and radiological manifestations. Arterial hypoxemia that is refractory to treatment with supplemental oxygen is a characteristic feature. Radiographically, the findings are indistinguishable from those of cardiogenic pulmonary edema.

Clinical Definition(s) of ARDS

Clearly, ARDS is not a disease with a well-defined pathophysiology. It should be considered as a set of effects (hence the term “syndrome”) of

Table 2 Different acute respiratory distress syndrome (ARDS) definitions throughout the years. AECC means the American-European Consensus Conference. PaO₂ denotes the partial arterial pressure of oxygen. FiO₂ means the fraction of inspired oxygen. ALI is acute lung

injury. ARDS means acute respiratory distress syndrome. PAOP means pulmonary artery occlusion pressure (also called wedge pressure) which is measured by a pulmonary artery catheter

ARDS definition (1967)					
1. Severe tachypnea, severe dyspnea					
2. Cyanosis that is refractory to supplemental oxygen					
3. Loss of lung compliance					
4. Diffuse alveolar infiltrates of chest radiograph					
Murray score (1988)					
Points	0	1	2	3	4
PaO₂ with F_iO₂ of 100% oxygen (mmHg)	>300	225–299	175–124	100–174	<100
Chest radiograph	Normal	One point for each quadrant involved			
PEEP (cmH₂O)	≤5	6–8	9–11	12–15	≥15
Compliance (ml/cmH₂O)	≥80	60–79	40–59	20–39	≤19
Severe lung injury if average ≥2.5 points					
The AECC definition (1992)					
Oxygenation abnormality					
	ALI	PaO ₂ /F _i O ₂ < 300			
	ARDS	PaO ₂ /F _i O ₂ < 200			
Chest radiograph		Bilateral infiltrates and pulmonary edema			
PAOP < 18 mmHg (or no clinical evidence of left atrial hypertrophy)					
The Berlin definition (2012)					
Timing	Acute onset within 1 week of a known clinical insult or new/worsening respiratory symptoms				
Chest radiograph	Bilateral opacities, not explained by effusions, lobular collapse, nodules				
Origin of edema	Respiratory failure not explained by cardiac failure or fluid overload				
	Need of objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor is present				
Severity					
Hypoxemia	Mild	Moderate		Severe	
	PaOPaO ₂ /F _i O ₂ 200–300 mmHg with PEEP ≥ 5 cmH ₂ O	PaO ₂ /F _i O ₂ 100–200 mmHg with PEEP ≥ 5 cmH ₂ O		PaO ₂ /F _i O ₂ < 100 mmHg with PEEP ≥ 5 cmH ₂ O	

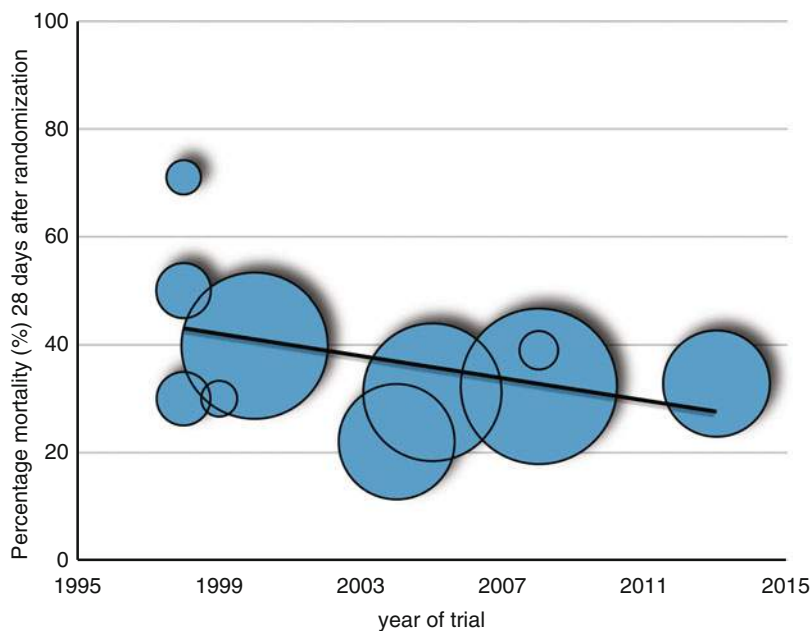
incompletely understood pathophysiology. As a consequence, the clinical definition of ARDS has changed through the ages.

The first description of ARDS was published in 1967 by Ashbaugh and colleagues and combined clinical and laboratory results (LoE III) [150]. The original clinical pattern included severe tachypnea, cyanosis that was refractory to oxygen supplementation, the loss of lung compliance, and diffuse alveolar infiltrates on a chest radiograph. Despite the fact that this definition of ARDS was

nonspecific and was dichotomous, it was used for many decades (see Table 2).

In 1988, Murray and colleagues elaborated on this model and added a grading system to the definition [151]. This so-called Murray score introduced the ratio of partial pressure of arterial oxygen (PaO₂) and inspired fraction of oxygen (F_iO₂) as a measure of severity of ARDS (see Table 2). If the patient had an average Murray score exceeding 2.5 points, the ARDS was considered severe (LoE III).

Fig. 2 Slowly declining 28-day mortality in the control arms of the randomized controlled trials on ARDS. The size of the dots represents the amount of patients in the control arm only [160–169]



In 1992, the American-European Consensus Conference came up with a distinction between acute lung injury (ALI) and ARDS depending on the severity of the $\text{PaO}_2/\text{F}_i\text{O}_2$ ratio (LoE III). An important improvement was the exemption of cardiogenic edema as a cause of respiratory failure. By definition, the patient needed to have a pulmonary artery occlusion pressure (PAOP) of less than 18 mmHg; otherwise, it is considered congestive pulmonary edema. The severity of the ALI/ARDS was correlated with mortality outcome. Mortality of severe ARDS ($\text{PaO}_2/\text{F}_i\text{O}_2$ ratio < 100 mmHg) exceeded 50% in some studies, although the ARDS-associated mortality declined throughout the years (LoE II-1) [152].

However, distinction in severity (ALI vs. ARDS) was dismissed with the introduction of the Berlin criteria 2012. What used to be called ALI is nowadays called “mild ARDS.” The added value of the latest definitions is a distinction between “moderate ARDS” and “severe ARDS” ($\text{PaO}_2/\text{F}_i\text{O}_2$ ratio < 100 with a positive end-expiratory ventilation pressure of at least 5 cmH_2O) (LoE III) [153, 154].

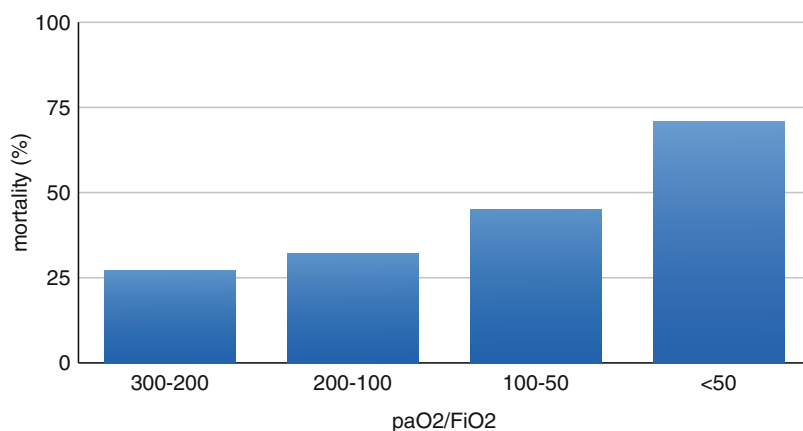
None of the consensus definitions were able to discern different types of ARDS, nor was it possible to separate distinct pathophysiological

pathways. At present, the lack of knowledge of the underlying pathophysiological processes makes it impossible for clinicians to separate different forms of ARDS. However, it is unlikely that ARDS resulting from an infectious origin is completely the same as ARDS from a toxicant. Unfortunately, at present we still have to assume that they are all the same and the pathophysiological pathway in infection (PAMPs) is the same as in toxic injury (DAMPs).

Mortality of ARDS

Differences in definitions and study populations throughout the years make it virtually impossible to compare mortality rates of ARDS patients. In the 1980s, the mortality of ARDS was 60–80% and this slowly declined to a mortality of 30–40% in the 2000s (see Fig. 2) (LoE I) [155, 156]. Patients with more severe respiratory failure had higher associated mortality rates (see Fig. 3). Obviously, mortality might be associated with factors other than ARDS itself. Some studies suggest that the mortality is related to the development of multi-organ failure or sepsis. In patients with ARDS, the primary cause of death was sepsis

Fig. 3 Mortality of ARDS based upon severity ($\text{PaO}_2/\text{FiO}_2$). See text for more details



and multi-organ failure (49%), refractory hypoxia (16%), cardiac failure (15%), and neurologic failure (10%) (LoE III) [157]. Patients with ARDS as a result of sepsis had a higher mortality than patients with other causes of ARDS. However, most of these ARDS mortality rates are derived from studies in which most patients have sepsis-associated ARDS rather than toxin-induced ARDS. Information on toxic ARDS is limited to case reports and observational studies and is often intertwined with patients with toxic circulatory shock. Mortality rates are therefore difficult to extrapolate, but are reported to be as high as 48% (LoE III) [2, 158, 159].

Treatment of ARDS

The ultimate goal of treatment in ARDS patients is to provide the other organs sufficient oxygen to prevent secondary organ damage, or even organ failure, and to prevent unnecessary damage to the already damaged lungs.

Although this seems obvious, there are no absolute cutoff points that define severity of ARDS. Certain patients are moderately ill with $\text{PaO}_2/\text{FiO}_2$ ratios <300 , while others at this same ratio are severely respiratory compromised and need immediate mechanical ventilation. The consensus definitions have aided in the identification of ARDS, but the treatment remains individualized. However, the common goal of ARDS treatment is “do no further harm,” and this has been merged into the “lung-protective ventilation”

strategy, which consists of low tidal volumes, high positive end-expiratory pressure (PEEP), recruitment maneuvers, and prone positioning of the patient (see next paragraphs for more details).

Lung-Protective Ventilation

Gattinoni and coworkers were among the first to notice three distinct regions in ARDS-affected lungs: normal lung tissue, a region densely consolidated, and a region that collapses during expiration and is recruitable during inspiration (LoE II-2) [170]. When these heterogeneous lungs are ventilated (even at low tidal volumes) in the absence of PEEP, they present a repetitive opening and closing of airways and lung units [171]. This type of injury is called “atelectrauma” [171]. However, if these heterogeneous lungs are ventilated with higher tidal volumes, over distension of alveoli may occur, leading to “barotrauma,” which causes complications such as pneumothorax (LoE II-2) [172]. A third form of ventilator-induced lung injury is called “biotrauma,” which is a systemic inflammatory response syndrome as a consequence of a release of lung cytokines (e.g., $\text{TNF-}\alpha$, IL-6, IL-8) (LoE II-2) [173]. Clearly, mechanical ventilation poses potential harm to patients, and therefore mechanical ventilation should be as “protective” as possible.

Amato and colleagues were the first to show that smaller tidal volumes while being ventilated were associated with improved outcome (LoE I)

[160]. Up to this study, most patients were usually ventilated with higher tidal volumes (~ 12 ml/kg of ideal body weight or more). This study showed that mortality from ARDS could be reduced from 71% to 38% by applying a lower tidal volume approach (~ 6 ml/kg ideal body weight). However, the mortality in the control arm of this study was disproportionally high in comparison to the background mortality of ARDS (30–40%) at that time period (see Table 2). Hereafter, several randomized controlled trials have attempted to show that lower tidal volumes that prevent mortality have had varying results [160–164, 174]. A meta-analysis summarizing the clinical effects of ventilatory components on the outcome of patients with ARDS [175] found that mechanical ventilation strategies that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes, and higher PEEP can improve survival, but the relative importance of each component has not been established (LoE I). In this study, all individual patients from nine previous randomized clinical trials were reassessed. They found that small tidal volumes per se were not associated with better outcome, but lower driving pressures were (pressure needed to achieve a tidal volume) [175, 176]. When patients were matched according to PEEP level, higher peak pressures were associated with increased mortality. However, if patients were matched for driving pressure, higher levels of PEEP were not associated with decreased mortality. Further, if they matched patients with the same level of plateau airway pressures, higher levels of PEEP (and, inversely, lower driving pressures) were associated with lower mortality (LoE II-1). These data demonstrate that, despite several randomized clinical trials in ARDS, we do not yet know which ventilation strategy is optimal for the individual patient.

The general concept arising from these reanalyses is that not the highest PEEP, but the lowest driving pressure, should be the ventilation target. In summary, the driving pressures should be kept below 15 cm H₂O and the plateau ventilation pressures below a 30 cm H₂O (LoE III).

Oxygen and Fractional Inspired Oxygen

In the earlier ARDS trials, the fractional inspired oxygen (F_iO_2) was arbitrarily coupled to the amount of PEEP. The higher the PEEP, the higher the F_iO_2 . However, several observational studies have shown that higher levels of PaO_2 were associated with higher mortality (LoE II-2) [177]. Many of these studies may not have appropriately corrected for confounders, and thus controversies remain regarding these issues. Indeed, other studies were unable to confirm these findings [178, 179]. Still, the pragmatic advice is to lower the FiO_2 as long as the arterial oxygen saturation (S_aO_2) remains 88–92% (LoE III).

Rationale for Lung-Protective Ventilation

In patients with toxic pulmonary damage, the levels of pro-inflammatory cytokines, such as IL-1 β , TNF- α , IL-6, and IL-8, are elevated (LoE II-2) [180]. However, mechanical ventilation itself may cause pro-inflammatory signals [173], especially if the ventilation cannot be kept protective. ARDS is distributed unevenly throughout the lungs, which means that certain areas of the lung will not be ventilated while other parts might get hyperinflated. Even protective ventilation with tidal volumes that do not exceed 6 ml/kg of ideal body weight might result in hyperinflation of the more compliant lung areas. Patients that did have such hyperinflated areas comprising greater than 60% of the total lung had higher levels of pro-inflammatory cytokines in their bronchoalveolar lavage fluid, such as IL-6, IL-1 β , IL-1, IL-8, and TNF- α [181]. This is suggestive that less protective ventilation might lead to “ventilator-induced lung injury.” Repeated overstretching of alveoli, continuous recruitment and derecruitment, and shear stress can lead to cytokine production and subsequent multi-organ failure (LoE II-2) [165]. Obviously, lower tidal volumes are preferred but might be challenging due to insufficient ventilation, leading to hypoxia and hypercapnia. This

might be overcome by extracorporeal removal of carbon dioxide and/or extracorporeal membrane oxygenation, a concept that has been coined “lung rest” (see further section on “[Extracorporeal Membrane Oxygenation \(ECMO\)](#)”).

Prone Positioning of the Patient

In a normal healthy lung, blood flow is distributed evenly. However, when lungs are inflamed and become heavier, some parts of the lung get less blood flow, especially the gravitationally compressed dorsal parts. Putting a patient in a prone position reverses this, and the volumetrically larger dorsal parts get better perfused and ventilated [182]. Obviously, this does not apply to all patients as ARDS is not homogeneously distributed and varies considerably between patients. However, in a recent randomized controlled trial in patients with severe ARDS (defined as a $\text{PaO}_2/\text{FiO}_2$ ratio < 150), prone positioning led to significantly lower mortality after 90 days (hazard ratio for mortality after correction for severity of illness was 0.48 with confidence intervals (0.32–0.72, $p < 0.001$)) (LoE I) [169]. This was confirmed in a meta-analysis of 9 studies evaluating the effect of prone positioning (LoE I) [183]. Once the lungs are recruited in prone position, the lungs should remain recruited by applying sufficient PEEP. However, the appropriate amount of PEEP is still being debated. Obviously, enough PEEP should be applied to prevent derecruitment, but, as explained previously, higher levels of PEEP are not always beneficial. A pragmatic approach would be to choose the level of PEEP at which the highest total respiratory system compliance occurs by descending PEEP titration (LoE III) [175]. This corresponds to the lowest driving pressure for appropriately sized ventilation tidal volumes. However, overdistention and regional collapse may still occur, and repeated CT scans and/or potentially electrical impedance tomography may be needed to follow up proper ventilation dynamics (LoE II-3) [184–188].

Corticosteroids

Corticosteroids have been used and advocated for in numerous toxic inhalational injuries. There are many, at least theoretical, reasons why corticosteroid treatment might be beneficial [189]. Corticosteroids exert strong anti-inflammatory properties by means of switching off pro-inflammatory genes and transcription factors (LoE II-2) [190, 191]. These anti-inflammatory effects could be beneficial in patients who are suffering from toxic inhalational ARDS. This hypothesis has been tested in various animal and human volunteer studies [1]. Unfortunately, interpretation of many of these studies is seriously hampered by the difficulty in translating animal data to the humans. In addition, positive effects of corticosteroids were mostly seen on intermediate endpoints, such as respiratory resistance in the acute phase of intoxication. Longer-term outcomes were most often not assessed. Yet, corticosteroids did not seem to have any beneficial effect at the alveolar level and might even have had a detrimental effect on alveolar repair mechanisms (LoE II-3) [192–194]. This might be explained by the inhibitory effect on the division of corticosteroids on type II alveolar cells. These cells are essential for the reepithelialization of the alveolus [195, 196]. Understandably, there are no human intervention trials to ascertain the efficacy of corticosteroid treatment following deliberate severe exposure to lung-damaging agents.

Human data on acute, high level exposure to lung-damaging agents are limited to anecdotal reports describing accidental exposure. Most of this circumstantial evidence from “natural experiments” lacks important information, such as duration of exposure, ambient gas concentrations, environmental conditions, presence of other toxins, and breathing pattern. These case reports are therefore limited in their ability to establish a cause–effect relationship for the treatments involved [1]. A few randomized studies exposed subjects to a low inhalational dose of a lung-damaging agent. These studies showed that even pretreatment with an inhalational corticosteroid did not prevent a decline in pulmonary function (LoE I).

Again, long-term outcome was not assessed [197, 198]. A systematic review on the use of corticosteroids for lung-damaging agents concluded that, at present, there is no convincing evidence that corticosteroids have a beneficial influence on the outcome of animals or humans who are exposed to inhalational toxins (LoE III). On the other hand, adverse side effects of corticosteroid treatment are well established (e.g., prolonged neuromuscular weakness, deregulation of glucose metabolism, superinfection, and sepsis) [1].

Circumstantial evidence might be derived from corticosteroid treatment in patients with other nontoxic causes of ARDS. Unfortunately, meta-analyses of corticosteroid treatment in such patients have yielded contradictory results. One meta-analysis [199] found a significantly reduced mortality, while three other studies found a nonstatistically significantly reduced mortality for corticosteroids (LoE I) [199–202]. The meta-analyses [199] showed that corticosteroids decreased the length of stay in the intensive care unit (ICU) and decreased the length of mechanical ventilation. Yet, corticosteroids that were started in the late fibroproliferative phase (≥ 14 days after the onset of ARDS) were associated with a worse outcome (LoE I). The optimal timing of corticosteroids, if existing at all, remains undetermined. Therefore, at present, the use of corticosteroids in inhalational toxic ARDS is not advocated (LoE III) [1].

Sedation and Paralysis to Improve Ventilation

Patients with ARDS have extreme “air hunger” and high minute ventilation. It has been suggested that neuromuscular blockade will benefit these patients. This will eliminate asynchrony with the ventilator and might increase chest wall compliance leading to lower driving pressure for the protective, small tidal volumes that need to be applied. One randomized clinical trial showed a better outcome if neuromuscular blockade was used in the first 48 h of mechanical ventilation (LoE I) [203, 204]. However, prolonged application of sedation and neuromuscular blockade is

opposing the currently held belief that sedation should be kept at minimal levels. Overuse of sedative–analgesic medication has been associated with prolonged mechanical ventilation and might even increase mortality (LoE I) [205, 206]. Obviously, this is evidence that has been derived from critically ill patients that are mechanically ventilated and whether this holds true for the subgroup of patients with toxic ARDS, although common sense dictates so, needs to be determined.

Antibiotic Prophylaxis in Toxic ARDS

Another commonly applied treatment for which there is hardly any empirical support is the prophylactic treatment of patients with inhalational injury with antibiotics. A study on medications given to patients with ARDS reported that 19% of ARDS patients had a noninfectious etiology, yet all received antibiotics [207]. Another small study showed that 18 (30%) of 30 patients with severe ARDS developed nosocomial pneumonia [208]. These studies illustrate that it is very difficult to discern infection from an already inflamed lung parenchyma and many physicians treat such patients prophylactically or empirically. An invasive approach to diagnosis ventilator-associated pneumonia in patients with ARDS by means of bronchoalveolar lavage with quantitative cultures of pathogens reduces the length of antibiotic treatment, the total amount of antibiotics that are being prescribed and might even reduce mortality (from ventilator-associated pneumonia) (LoE I) [209].

Extracorporeal Membrane Oxygenation (ECMO)

Hypoxia resulting from toxin-induced ARDS needs to be reversed immediately in order to prevent multi-organ failure. Since the 1970s, extracorporeal membrane oxygenation (ECMO) has been used to treat severe ARDS [210]. In the beginning, ECMO was a cumbersome treatment

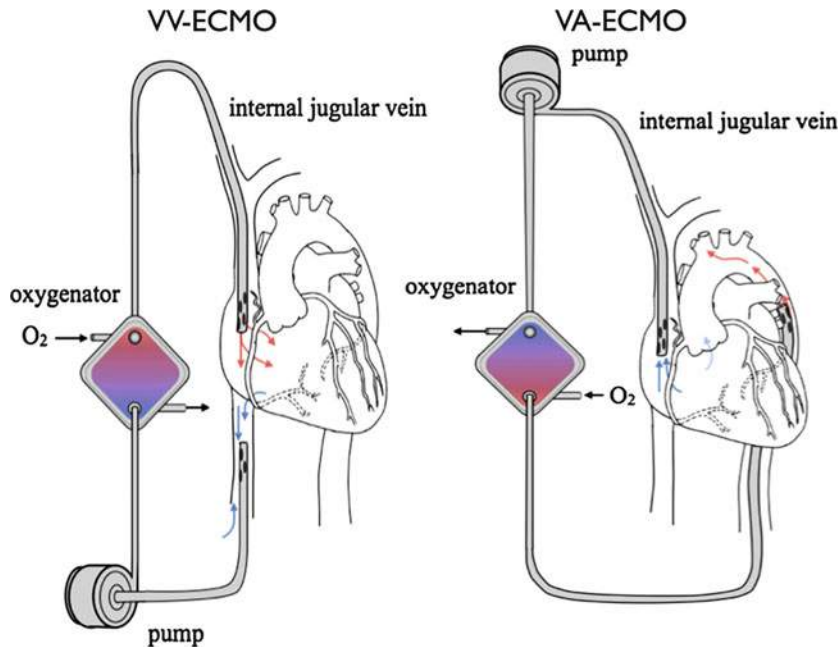


Fig. 4 VV-ECMO and VA-ECMO: In veno-venous extracorporeal membrane oxygenation (VV-ECMO), blood is withdrawn from a large vein (e.g., femoral vein or inferior vena cava), led through a pump and oxygenator. Oxygenated blood is returned to a large vein in proximity to the heart (e.g., *right* jugular vein or in the inferior vena cava). In venoarterial ECMO (VA-ACMO or ECLS),

blood is drawn from a large vessel and after oxygenation returned to the descending aortic arc. VV-ECMO is used for oxygenation of blood whenever circulation is sufficient. VA-ECMO is used to support a failing circulation (This figure was copied from De Lange et al. Ref. [2], copyrights © (2013), Informa Healthcare. Reproduced with permission of Informa Healthcare)

with many adverse effects. Therefore, it was abandoned in most hospitals treating adult patients. In critically ill children and neonates, however, ECMO remained a salvage treatment for severe respiratory failure. However, in 2009, the influenza A/H1N1 pandemic caused severe and refractory ARDS in many patients, requiring ECMO as a salvage therapy. The mortality rate for ECMO-treated patients was surprisingly low (~25%), despite them being severely hypoxic patients (LoE II-2) [211]. At that time, ECMO was increasingly applied as an assist device for cardiothoracic patients needing oxygenation as well as circulatory support. Moreover, the equipment was more biocompatible and better constructed than prior devices [212, 213]. These encouraging results ignited new interest in ECMO for severe ARDS, and many hospitals around the world have now adopted ECMO as a salvage therapy for ARDS.

ECMO Techniques

Several high-quality reviews have been published that eloquently describe how ECMO works (see Fig. 4) [2, 214–216]. Basically, there are two ECMO modalities. In veno-venous ECMO (VV-ECMO), hypoxic blood is withdrawn from a large-bore peripheral vein, often the femoral vein. This vein can be accessed percutaneously, which makes it easily accessible in emergency settings. The blood is then oxygenated and pumped back to the right atrium through a percutaneously placed catheter in the upper or lower vena cava. This technique preserves pulmonary blood flow, pulsatile systemic flow, and the oxygenated blood in the left ventricle and aortic root [214]. An additional advantage of this technique is that the lungs function as a natural filter for emboli that might be caused by the artificial

ECMO materials. Acute right ventricle failure due to ARDS, in itself, is not a contraindication for VV-ECMO. Oxygenation of the pulmonary artery blood will decrease the hypoxia-induced vasoconstriction and ameliorate pulmonary resistance (LoE II-2) [214]. Additionally, mechanical ventilation pressures can be reduced, because the gas exchange can occur by way of VV-ECMO. By lowering mechanical ventilation pressures, intrathoracic pressures will decrease. This will reduce pulmonary vascular resistance and thus the workload of the right ventricle.

VV-ECMO may not be adequate when ARDS is accompanied by severe circulatory shock. In that case, venoarterial ECMO (VA-ECMO; Fig. 4) is more appropriate. In VA-ECMO (also called “extracorporeal life support,” ECLS), hypoxic blood is drawn from the vicinity of the right ventricle through a large-bore cannula. This cannula will usually be placed percutaneously through the right jugular vein. However, the right atrium can also be accessed through the femoral vein. The latter is especially useful in emergency settings, for example, when cardiopulmonary resuscitation is performed and chest compressions prevent proper and hygienic placement of the catheter through the right jugular vein. The blood is then pumped through the oxygenator and returned to the patient via another catheter into the aorta. If the latter cannula is placed percutaneously, then the blood is pumped back into the descending aorta.

Although VA-ECMO is useful in emergency settings, it harbors some dangers. First, the large-bore catheter in the femoral artery might compromise perfusion of the lower extremity and result in ischemia in up to 21% of patients (LoE II-2) [217]. Second, because of considerable reduced blood flow through the pulmonary circulation, thrombus formation is possible. Third, the blood supply to the systemic circulation is dual; hypoxic blood is pumped through the lungs and mixed with oxygenated blood from the ECMO circuit in the descending aorta. As a consequence, the more cephalad organs, such as the brain and the heart, receive less oxygenated blood compared to the caudal organs (LoE II-2) [218]. This can easily be checked by measuring O_2 saturation at the earlobe or nostril. If decreased oxygenation

occurs, and circulatory shock is not reversed within an acceptable time, a more central cannulation needs to be performed. In this case, a cardiothoracic surgeon should place the afferent cannula in the ascending aortic arc or in the apex of the left ventricle. However, doing so requires a sternotomy. This emphasizes that VA-ECMO should be reserved only for patients with accompanying refractory circulatory shock and is best avoided if only ARDS is present.

Despite the fact that, at present, more and more hospitals are using ECMO as salvage therapy, evidence for its efficacy is lacking. A recently published trial conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory (CESAR) failure compared ECMO with conventional mechanical ventilation in patients with ARDS [219]. This trial included adult patients up to 65 years of age with a Murray score of 3.0 and higher, or uncompensated, hypercapnia with a pH less than 7.20, despite “optimum conventional treatment.” However, patients were excluded if they had received high ventilation pressures (peak inspiratory pressures 30 cmH₂O or F_iO_2 of 80% for more than 7 days). Eligible patients were then randomized to continuing of conventional mechanical ventilation ($n = 90$) or referral to an ECMO center ($n = 90$). Unfortunately, some patients died before transfer or during transit and 16 patients did not receive ECMO. Eventually 68 patients were treated with VV-ECMO. Six months after randomization, the composite endpoint of death or severe disability was seen in 33/90 ECMO patients and 46/90 patients in the conventional group ($p = 0.03$) (LoE I).

However, the results of the CESAR trial have been criticized. Opponents argue that the patients in the conventional arm trial did not get standardized treatment, and the “center experience” in the ECMO arm led to an improved outcome in patients randomized to the ECMO arm. However, despite methodological issues, VV-ECMO emerges from this trial as a salvage therapy with lifesaving abilities. At present, trials, like the French EOLIA trial, are currently underway, and early VV-ECMO in ARDS is being compared with optimal protective mechanical ventilation in the control group.

The degree of physiological decline, or expected decline, may be more important than the absolute extent of ventilatory support, and it is important that ECMO referrals are made in sufficient time to allow patient assessment, cannulation, and, in some instances, transfer to another institution (LoE III) [220]. Generally, if transport to another institution is required, a specialized ECMO retrieval team should travel to the referring institution and cannulate the patient on location before transportation. After the cannulation, the patient can then be transported to a hospital with ECMO experience. Outcome can be improved by keeping to these principles (LoE II-3) [214, 219, 221].

Cost Effectiveness

The goal of ECMO is to keep patients alive who would otherwise die despite maximum conventional treatment. Preferentially, ECMO is used as a “bridge to recovery.” Sometimes, the damage to organs is irreversible and then ECMO can be used as a “bridge to transplant” [2, 98, 101]. However, ECMO is a complex, resource-consuming expensive therapy. Although research has been scarce, there is ample evidence that ECMO is able to save many life years and the quality of life adjusted life years saved compare favorably to many other currently available treatments, such as hemodialysis, implantation of cardiac assist devices, or implantable cardioverter defibrillators (LoE II-3) [222–227].

The use of ECMO in poisoned patients is described in greater detail in the chapter on that topic.

Long-Term Outcome

The ultimate goal of critical care treatment is not merely “hospital survival.” The toxicological literature and especially case reports often focus on hospital discharge as the primary outcome measure. However, for several reasons, subsequent mortality may still be higher than expected for many months after discharge. First, patients may

have an increased mortality risk due to critical illness-related disorders, such as weakness, immunological insufficiency, or other comorbidities. Second, patients may still be moribundly ill at hospital discharge, i.e., if they are discharged from one hospital to another or to a palliative care facility. Third, the critical illness and ICU admission may accelerate the underlying diseases (LoE II-2) [228, 229]. If the patient is discharged alive but dies within weeks after discharge, this can hardly be considered “a good outcome,” and, in retrospect, the entire treatment could be considered futile [229, 230]. In a large Dutch observational cohort of intoxicated patients ($n = 7,331$), the average mortality rate 2 years after ICU discharge was 9.3%. This was substantially higher than could be expected based on their age and gender (LoE II-2) [231]. The reasons for this higher mortality are currently unknown [232]. Hypothetically, organ failure caused by the lung-damaging agent or multi-organ failure due to, or in spite of, mechanical ventilation might lead to premature aging of organs. This is especially true for the more seriously ill intoxicated patients with ARDS. Unfortunately, research in this area is lacking. Extrapolating research from ARDS patients due to infections shows that the mortality at 1 year is substantially higher than the in-hospital mortality (41% vs. 21%, respectively, $p < 0.0001$) (LoE II-2) [233, 234].

Another important outcome for those who survive beyond the initial first months of ICU discharge is quality of life. Patients who survive severe ARDS or an inhalational intoxication have a lower than average quality of life and more post-traumatic stress disorder (LoE II-2) [235–238]. However, which components or variables attribute to this lower quality of life is unclear and requires further research.

Conclusions and Recommendations to Overcome Areas of Uncertainty

ARDS is a clinical syndrome that can arise from many insults: infectious, inflammatory, and toxic. The true mechanism of toxin-induced ARDS is

unknown, but evidence extrapolated from other sources of ARDS can be extrapolated to toxic ARDS. Such knowledge from, predominantly, infectious ARDS is currently the best evidence to guide toxic ARDS. In general, patients should be treated in order to prevent secondary (multiple) organ damage. If patients need mechanical ventilation, further damage through ventilation itself should be avoided. The best strategy currently available is “protective ventilation,” which consists of low tidal volumes (~6 ml/kg ideal body weight or even less), PEEP titration to such a level that the driving pressure for tidal volumes is as low as possible (or, vice versa, total compliance of the lung is largest), decreasing driving pressures to ≤ 15 cm H₂O, and oxygen supplementation kept as low as possible while maintaining appropriate arterial oxygen saturations (88–92%). If, with the abovementioned strategy, plateau pressures cannot be kept below 30 cm H₂O, salvage therapies, such as ECMO, should be considered. Treatments with corticosteroids or antibiotics solely for toxic ARDS are not based upon sufficient evidence and should be discouraged. Long-term outcome of victims of toxic ARDS (both long-term survival and quality of life) is yet to be incorporated in future research. Clinical toxicology is in desperate need for more, preferably randomized, trials evaluating our current treatment options. Additionally, (inter)national registries for patients with intoxications, such as the Toxicology Investigators Consortium, are needed to improve the evidence we currently have and on which we base all our treatments.

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The sudden failure of a previously healthy and functioning liver is a dramatic and devastating event. Acute liver failure is the common final pathway of a multitude of conditions and insults, all of which result in massive hepatic necrosis or loss of normal hepatic function. The ensuing multiorgan system failure frequently has a fatal outcome, with mortality rates in most series ranging from approximately 55% to 95% [1]. Acute liver failure (ALF, previously often referred to as fulminant hepatic failure (FHF)) knows no age boundaries, with many cases occurring in those younger than 30 years. Short of excellent intensive care unit (ICU) support and liver transplantation in selected cases, few viable treatment options are available. Over the past few decades, however, survival has been improved by anticipation, recognition, and early treatment of associated complications, as well as the application of prognostic criteria for early identification of patients requiring liver transplantation (along with improvement in the techniques and science of transplantation itself). The etiology of ALF varies from country to country and the incidence change over time. Paracetamol (acetaminophen) has now replaced viral hepatitis as the leading cause of ALF [2]. In a study from London including 310 patients with ALF in the period 1994–2004, 42% of the cases were caused by paracetamol [3], whereas this was only the cause in 2% of 267 patients in Spain from 1992 to 2000 [4]. However, less than 10% of all liver transplants are performed in patients with ALF [5, 6].

The aim of this chapter is to help clinicians recognize the presentation and clinical features of drug- or chemical-induced ALF or liver injury, anticipate and appropriately manage the complications of ALF, and recognize the indications for timely referral for orthotopic liver transplantation (OLT). The pathophysiology, differential diagnosis, appropriate laboratory testing in the evaluation and treatment of ALF, and specific therapies available for certain etiologies of ALF will also be discussed. Current and future trends in liver transplantation will be described.

Definitions

In 1986, Bernuau and colleagues [7] suggested that the term “fulminant hepatic failure” (FHF) should be applied to patients in whom encephalopathy developed within 2 weeks of the onset of jaundice and that subfulminant hepatic failure be applied to those in whom this interval was 2–12 weeks. In 1993, O’Grady and associates [8] proposed the terms hyperacute, acute, and subacute liver failure based on whether the interval between the appearance of encephalopathy and jaundice was 0–7 days, 8–28 days, or 29 days to 12 weeks, respectively. Both Bernuau and O’Grady included cases of preexisting asymptomatic chronic liver conditions. In Japan, patients with fulminant hepatitis are classified into two types according to the onset of encephalopathy (before or after 10 days). Encephalopathy occurring after 8 weeks is defined as late-onset hepatic failure (LOHF) [9].

These classification systems reflect important differences in the clinical course and prognosis observed between patient subgroups, thus facilitating earlier diagnosis and timely referral for OLT. For example, both the hyperacute and acute liver failure groups have a high incidence of cerebral edema. However, whereas patients in the hyperacute group are more likely to survive with medical management, patients in the acute liver failure group tend to die without liver transplantation [8]. The subacute failure group has a lower incidence of cerebral edema and a higher incidence of portal hypertension manifestations, including ascites and renal failure [8]. Mortality in this group remains high. O’Grady and colleagues found that the hyperacute failure group had a 36% survival rate, as opposed to 7% and 14% in the acute and subacute failure cohorts, respectively [8]. Bernuau and coworkers also noted that those with the most rapid onset of encephalopathy had the best chance of survival [7]. Similar observations have been made in Japan [9]. However, it is important to note that although the interval between the onset of encephalopathy and jaundice

Table 1 Definitions of liver failure

Bernuau [7]	Fulminant hepatic failure: encephalopathy within 2 weeks of onset of jaundice
	Fulminant hepatic failure: encephalopathy within 2–12 weeks of onset of jaundice
O’Grady [8]	Hyperacute liver failure: encephalopathy within 7 days of onset of jaundice
	Acute liver failure: encephalopathy within 8–28 days of onset of jaundice
Tandon [12]	Subacute liver failure: encephalopathy within 5–12 weeks of onset of jaundice
Mochida [9]	ALF defined as liver disease ≤ 26 weeks in duration, $\text{INR} \geq 1.5$, and any degree of encephalopathy
	Fulminant hepatic failure: encephalopathy within 8 weeks of onset of jaundice
	Subclass acute: encephalopathy within 10 days of onset of jaundice
	Subclass subacute: encephalopathy within 10 days to 8 weeks of onset of jaundice

was of prognostic significance in O’Grady’s cohort [1], it was not an independent prognostic factor in Bernuau’s cohort [10], thus raising doubts about its universal applicability. Application of the O’Grady classification to 423 prospectively studied patients from a tertiary care referral center in northern India failed to yield any prognostic differences between the groups [11].

Although these classifications may be useful in highlighting differences in clinical course and prognosis among patient subgroups, the contribution of other independent prognostic indicators (etiology of ALF, patient age, prothrombin time, factor V level, renal function, mental status) should not be overlooked. Table 1 provides a summary of the various definitions of liver failure.

Pathogenesis

Measuring about 1500 mL in volume, the liver is the second largest organ in the body and plays a critical role in its homeostasis. At no time is this role more apparent than during an episode of acute injury. Derangements in synthetic function

(hypoalbuminemia, decreased levels of clotting factors), gluconeogenesis (hypoglycemia), drug and toxicant metabolism (sensitivity to narcotics and benzodiazepines, hyperammonemia), excretory function (hyperbilirubinemia), temperature regulation (hypothermia), and central nervous system function (encephalopathy) are the result of liver failure. Some of these parameters are used as prognostic factors and markers of severity of injury.

The exact mechanisms of injury and impairment in hepatocellular function that lead to ALF are poorly understood. Loss of integrity of the hepatocyte plasma membrane secondary to chemical, immunologic, or a wide variety of other insults is thought to represent the final common pathway that leads to cell necrosis and ALF [13, 14]. Damage to the cell membrane permits leakage of enzymes, coenzymes, and electrolytes from the cytosol, followed by an influx of calcium ions, which eventually results in cell death. The importance of calcium is underscored by the finding that normally vulnerable hepatocytes in vitro do not succumb to the cytotoxic effects of membrane-active toxins when calcium ions are not included in the culture medium [15].

New information is emerging on the role of growth factors and the inflammatory cascade in ALF. Transforming growth factor- β_1 (TGF- β_1) has been identified as exerting an inhibitory effect on hepatic regeneration, with its effects being counteracted by hepatocyte growth factor (HGF). ALF patients with viral hepatitis have demonstrated an increase in total TGF- β_1 with a less elevated HGF level, thus suggesting an imbalance in growth factor interplay as a cause of impaired hepatic regeneration [16]. This mechanism has also been suggested by research performed in posttransplant patients [17]. Studies suggest that activation of the cytokine network may represent the common final pathway for the development of ALF [18]. Although multiple inflammatory cascades come into play, interleukin-1, interleukin-6, and tumor necrosis factor- α have been identified as the more important

mediators, along with endotoxin and nitric oxide. In response to the initial hepatic insult, interplay among these mediators sets into motion a vicious self-perpetuating cycle resulting in continued hepatic injury and multiorgan failure. Furthermore, higher levels of circulating interleukin-8 and interferon- γ have been demonstrated in patients with ALF than in healthy volunteers and those with chronic liver disease, thus suggesting a pathogenic role in acute hepatic injury. Although no relationship was found between the levels of these two markers and the clinical course, elevated levels of interleukin-10 were found to be predictive of improved outcome [19].

Etiology and Differential Diagnosis

Careful diagnostic evaluation is important because the etiology can have prognostic implications (e.g., the prognosis is worse with Wilson's disease and idiosyncratic drug reactions, better with viral- and acetaminophen-induced ALF), influence treatment options (e.g., *N*-acetylcysteine [NAC] for ALF induced by acetaminophen [acetyl-*para*-aminophenol or paracetamol]), and indicate the need for genetic testing of family members (e.g., Wilson's disease) [20]. Etiologies of ALF can be divided into toxic and nontoxic. Toxic causes include pharmaceuticals, drugs of abuse, chemicals, and biologic agents. Nontoxic causes include, but are not limited to, infections, ischemia, metabolic derangements, malignancy, autoimmune problems, and primary graft failure after liver transplantation. Because ALF represents the common final pathway of injury, it is difficult to differentiate between the aforementioned causes based solely on clinical presentation and disease progression. A detailed patient history is invaluable, and a multitude of helpful diagnostic testing tools are available to help uncover the etiology of ALF in the majority of cases (Table 2).

Frequency of Causes

Although the frequency varies geographically, the most common causes of ALF remain viral and

drug-induced hepatitis. In the USA, drug-induced liver injury is responsible for almost 50% of ALF [21, 22] most often caused by APAP. In London, UK, APAP poisoning was responsible for 57% of ALF cases seen at King's College Hospital between 1973 and 1991, whereas in France, APAP was identified as the etiology in only 2% of ALF cases between 1972 and 1990 [23, 24]. A multicenter study from the USA of 295 patients in whom ALF was diagnosed between 1994 and 1996 found that the most common etiologies were APAP (20%), viral hepatitis (10% hepatitis B, 7% hepatitis A), cryptogenic (15%), and drug reactions (12%) [25]. Outside of the USA and Europe, drugs are less likely to cause ALF. In a Japanese study [26], the percentage of drug allergy-induced ALF in 432 patients collected in the period 1998–2006 was 2% in contrast to viral infection which was diagnosed as the cause in 16% of the patients (13% with hepatitis B). Even though APAP overdose was found to represent one-sixth of all causes of ALF leading to registration for liver transplantation in Europe, there was a 50-fold difference in the relative risk of ALF leading to registration for liver transplantation between countries with a low incident rate (e.g., Italy with 0.03 ALF per million inhabitants per year) and high incident rate (e.g., Ireland with 7.13 ALF per million inhabitants per year). The reasons for these differences remain unclear, but may be related to national differences in pack size restriction of APAP or antidote treatment regimens [27].

Toxic Causes

Pharmaceuticals

Hepatotoxicity can result from therapeutic or toxic doses of many medications by a multitude of mechanisms. It can be manifested as asymptomatic elevations of liver enzymes, but some cases can progress to ALF. Hepatocyte injury can occur directly from disruption of intracellular function or membrane integrity or indirectly from immune-mediated membrane disruption. Drugs can also cause cholestasis, steatosis, idiosyncratic reactions, fibrosis, veno-occlusive disease,

Table 2 Etiology of acute liver failure

Infections	Toxins/chemicals	Vascular	Metabolic/ others
Viral hepatitis	Cyclopeptide mushrooms	Budd–Chiari syndrome	Wilson’s disease
Hepatitis A virus	<i>Amanita phalloides</i>	Veno-occlusive disease	Fatty liver of pregnancy
HBV	<i>A. verna</i>	Heatstroke	Reye’s syndrome
HCV (rare, coinfection)	<i>A. virosa</i>	Chronic heart failure	Galactosemia
HDV (coinfection)	<i>A. tenuifolia</i>	Ischemia	Hereditary fructose intolerance
HEV (rare in the USA) Herpesviruses (herpes simplex virus/cytomegalovirus/varicella zoster virus/Epstein–Barr virus in immunosuppressed)	<i>A. brunnescens</i> <i>A. bisporigera</i> <i>Galerina autumnalis</i>	Myocardial infarction, pulmonary embolism, tamponade, sepsis, intraoperative hypotension, etc. Malignant infiltration	Hereditary tyrosinemia Jejunoileal bypass Autoimmune hepatitis
Yellow fever	<i>G. venenata</i>		Primary graft failure
<i>Coxiella burnetii</i>	<i>G. marginata</i>		
<i>Plasmodium falciparum</i>	<i>Lepiota josserandii</i>		
Amebic abscesses	<i>L. helveola</i>		
Tuberculosis (disseminated)	Herbals		
<i>Bacillus cereus</i>	Kava		
	Chaparral		
	Gentian		
	<i>Scutellaria</i>		
	Germander		
	<i>Alchemilla</i>		
	Senna		
	Shark cartilage		
	Sea anemone sting		
	Carbon tetrachloride		
	Aflatoxin		
	Halogenated hydrocarbons		
	Toluene		
	Trichloroethylene		
	Tetrachloroethane		
	Chloroform		
	Phosphorus		
	Ethanol Cocaine MDMA (3,4-methylenedioxy-N-methylamphetamine or Ecstasy)		
	Drugs (see Table 3)		

A, *Amanita*; CHF, congestive heart failure; CMV, cytomegalovirus; EBV, Epstein–Barr virus; G, *Galerina*; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; HEV, hepatitis E virus; HSV, herpes simplex virus; L, *Lepiota*; MI, myocardial infarction; PE, pulmonary embolism; VOD, vascular occlusive disease; VZV, varicella zoster virus

vasculitis, and granulomatous reactions. Categorization of these toxic reactions suggests the type and duration of exposure.

Acute APAP overdose (both deliberate and unintentional/supratherapeutic ingestion) remains one of the most common causes of ALF in the USA and UK (see ► Chap. 59, “Acetaminophen/Paracetamol”). The maximum daily approved dose may vary depending on the country, but is generally in the range of 80 mg/kg APAP for children and 3–4 g for adults. The minimum dose for toxicity from a single ingestion is generally 150 mg/kg for children and 7.5–10 g for adults [28]. Doses greater than 350 mg/kg almost always result in severe hepatotoxicity without antidotal treatment [23]. However, APAP toxicity is increasingly being recognized as a cause of ALF even when used in supratherapeutic doses, and such “therapeutic misadventures” may represent the most common cause of ALF in the USA [29]. These cases usually occur when APAP is misused in the setting of chronic pain and alcohol use or less commonly with medications that induce the cytochrome P-450 system (e.g., isoniazid [INH], rifampin, phenytoin) or in the setting of starvation (depleted glutathione [GSH] stores) [30, 31]. High aminotransferase levels are typical of such cases, with values usually peaking above 4000 U/L and sometimes above 10,000 U/L.

The metabolic activation of certain drugs by the liver into hepatotoxic intermediates is an important phenomenon in drug-induced ALF. The resultant toxic metabolites covalently bind to important macromolecular constituents of the cell and prevent normal functioning or cause necrosis of the cell. Acetaminophen metabolism (Fig. 1) serves as a pertinent example. Most of the ingested APAP is conjugated with glucuronide or sulfate and excreted as a harmless metabolite [32, 33]. In therapeutic doses, approximately 5% of APAP is oxidized by the P-450 system to *N*-acetyl-*p*-benzoquinoneimine (NAPQI), a toxic intermediate that is readily detoxified by reaction with GSH [32, 33]. An APAP overdose overwhelms the sulfation and glucuronidation pathways and drives the formation of NAPQI, detoxification of which depletes GSH stores [32, 33]. Once the binding capacity of GSH is exceeded, NAPQI

covalently binds to key hepatocyte membrane and cellular proteins and causes necrosis [22, 23].

Concurrent use of certain medications can further amplify the production of hepatotoxic intermediates by induction of the cytochrome family responsible for metabolism of the parent drug. For example, alcohol [34], INH [35], and possibly phenytoin [36] cause induction of the P-450 system, which enhances the conversion of APAP to NAPQI. In addition, alcohol inhibits the synthesis of GSH, thereby decreasing clearance of NAPQI [37]. Chronic alcohol abusers are also more likely to be malnourished and have an antecedent fasting period, which also depletes GSH stores. Thus, supratherapeutic doses of APAP in conjunction with regular alcohol use can result in elevated NAPQI levels and subsequent hepatic injury – the so-called therapeutic misadventure [38]. It is important to note that starvation, a GSH-depleted state, is an independent risk factor for a therapeutic misadventure with APAP, regardless of concurrent alcohol use. Another example of synergistic toxicity is noted in patients treated with INH and rifampin, where rifampin-induced cytochrome induction can potentiate INH hepatotoxicity [39].

Whereas APAP-induced injury is predictable and dose dependent, other drugs (e.g., valproic acid, troglitazone, amiodarone) can cause rare idiosyncratic and unpredictable hepatotoxic effects. Hypersensitivity reactions can occur with the use of phenytoin, *para*-aminosalicylate, chlorpromazine, and sulfonamides, with catastrophic results. Idiosyncratic reactions do not exhibit dose-related toxicity, and some can result in ALF with a single dose. They occur in a small fraction of susceptible individuals and are unpredictable. Patients with chronic liver disease may be at increased risk for such reactions. The formation of immunologically stimulating drug-protein complexes (neoantigens) with a resultant “innocent bystander” effect is thought to be one of the pathogenic mechanisms of injury [40].

The halogenated anesthetics enflurane, methoxyflurane, and isoflurane have uncommonly been associated with the development of toxic hepatitis, but hepatic failure is rare. They usually develop after multiple exposures to these

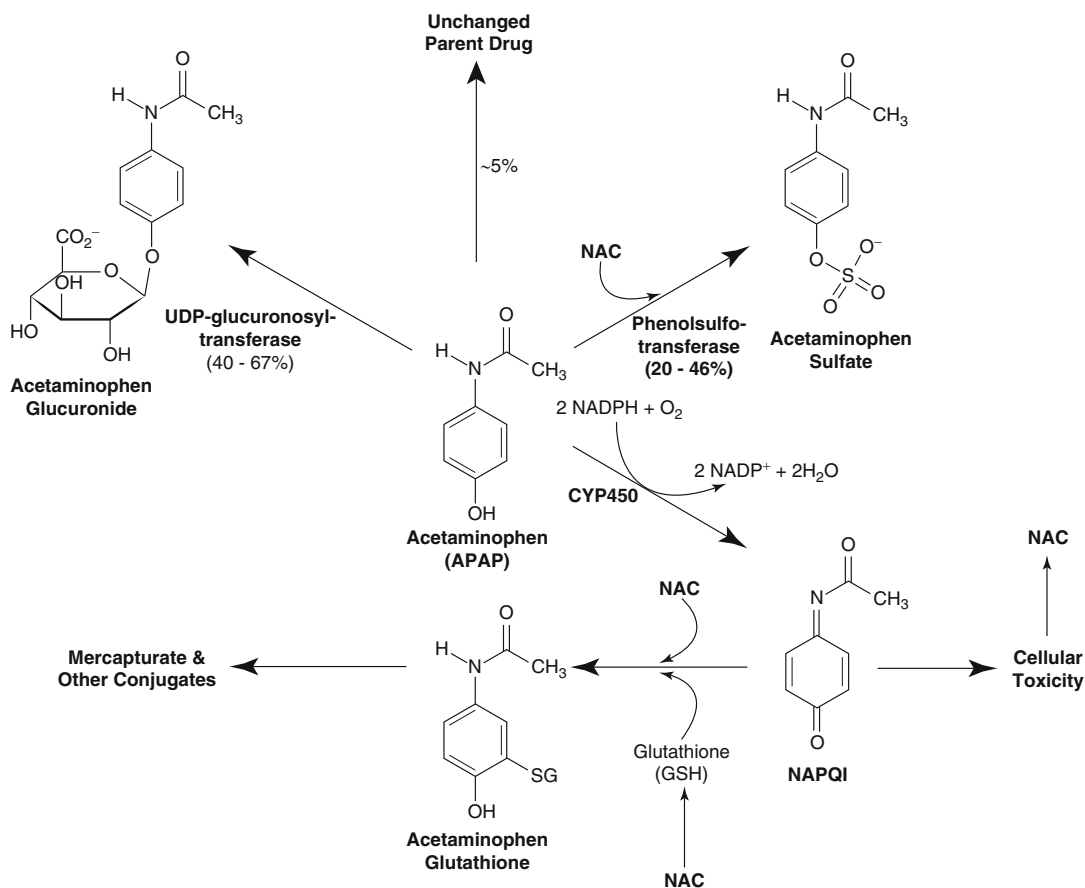


Fig. 1 Acetaminophen (paracetamol) metabolism

agents and are thought to be of combined toxic and allergic origin. Nonsteroidal anti-inflammatory drugs, especially sulindac and diclofenac, have also been known to cause liver disease, with an incidence of 1.1–3.7 cases per 100,000 prescriptions [41]. The macrolide antibiotics erythromycin and clarithromycin are rare causes of hepatic failure that exhibit primarily cholestasis on biopsy and, uncommonly, hepatic necrosis [42].

In a nationwide prospective study [43], the incidence of drug-induced liver injury (DILI) was investigated in a population-based cohort in Iceland. The most commonly implicated agent over the 2-year study period was amoxicillin-clavulanate with a rate of 43 DILI cases per 100,000 inhabitants. The highest risk of hepatotoxicity was associated with the use of azathioprin

(752 DILI cases per 100,000 inhabitants) and infliximab (675 DILI cases per 100,000 inhabitants).

Tetracycline demonstrates yet another mechanism of hepatotoxicity. It is known to bind hepatocyte tRNA and impair apoprotein synthesis, thereby causing triglyceride buildup in the liver. It may also cause concurrent derangements in fatty acid uptake, formation, and oxidation by hepatocytes, which can culminate in the loss of hepatic function secondary to acute microvesicular fatty infiltration [44]. Aspirin, valproic acid, amiodarone, and zidovudine are also known to cause microvesicular steatosis.

Herbal Medications

Widespread use of herbal remedies in Europe and their ever-growing popularity in the USA have

Table 3 Examples of drugs commonly implicated in acute liver failure

Acetaminophen (paracetamol)
Amiodarone
Carbon tetrachloride
Gold
Halothane
Isoniazid
Ketoconazole
Methyldopa
Monoamine oxidase inhibitors
Nonsteroidal anti-inflammatory drugs
Phenytoin
Rifampin
Sulfonamides
Tetracycline
Tricyclic antidepressants
Valproic acid

brought to light many case reports of associated hepatotoxicity. Herbs and alternative medications implicated include chaparral, gentian, germander, and senna, but they rarely result in liver failure [45]. However, in 2001 and 2002 two case reports suggesting a causal relationship between kava (a herbal supplement used for the treatment of anxiety) and ALF requiring transplantation were published [46, 47]. Twenty-four other reports of kava-related hepatotoxicity have led to a ban on kava in Switzerland and Germany. The US Food and Drug Administration (FDA) currently has the supplement on so-called MedWatch alert status. Although virtually any drug can cause acute liver injury, more common examples are listed in Table 3.

Drugs of Abuse

Severe liver injury and even hepatic failure can result from recreational drug use, including abuse of cocaine, 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), and phencyclidine, or from recreational inhalation of solvents containing toluene or trichloroethylene [48]. Hepatic failure in these cases may be the result of liver ischemia, hypoxemia, severe hyperpyrexia, rhabdomyolysis, and/or direct hepatotoxic effect.

In addition to these effects, cocaine's hepatotoxicity is thought to be due primarily to ischemia from systemic arterial vasospasm and congestive

heart failure, complicated by the occurrence of disseminated intravascular coagulation (DIC) and renal failure. The histologic pattern is both centrilobular necrosis and microvesicular steatosis. MDMA causes a syndrome similar to that of cocaine: hyperthermia, DIC, and rhabdomyolysis, complicated further by dehydration and acute renal failure. Toxic hepatitis may be immediate or delayed, and the histopathology is characterized by central and midzonal necrosis or by steatosis and eosinophilic infiltration [48]. The latter suggests an immune mechanism of MDMA hepatotoxicity, and liver transplantation has been required in some cases [49].

Chemicals

Industrial exposure to cleaning solvents containing fluorinated or halogenated hydrocarbons is a well-documented cause of hepatic necrosis, fatty infiltration, and, ultimately, ALF. Carbon tetrachloride's hepatotoxic effects, noted in the 1920s–1940s, led to its abandonment as an anesthetic and anthelmintic by the FDA, but it is still used in the production of solvents, refrigerants, and aerosol propellants. The fluorinated hydrocarbon chloroform, a potent central nervous system depressant once used as an anesthetic, has also been banned by the FDA because of its hepatotoxicity, but it is still found in industrial use.

Biologic Agents

Hepatotoxicity secondary to accidental ingestion of poisonous mushrooms has been on the rise because of popular interest in gathering and eating uncultivated mushrooms [50]. An increase in the incidence of mushroom poisoning is usually seen after periods of heavy rainfall or during the fall, when the conditions for growth are optimal. Ingestion of cyclopeptide-containing mushrooms accounts for up to 90% of mushroom-related deaths worldwide [50–54]. The genus *Amanita* is the source of most of these poisonings, especially *A. phalloides* (death cap), *A. verna* (death angel), and *A. virosa* (destroying angel). *Galerina* and *Lepiota* species can also be hepatotoxic (see Table 2). *Amanita* species are found primarily in the temperate coastal regions of the west coast of the USA, but they have also adapted to the mid-Atlantic

coast and the northeast. *A. phalloides* is the predominant hepatotoxic European mushroom. The mushroom itself has no distinct taste, smell, or appearance. Ingestion is usually followed 6–12 h later by fever, nausea, vomiting, and severe diarrhea. Renal and hepatic impairment may become evident by 24–48 h while the patient appears to be recovering clinically. However, renal failure and hepatic failure progress and tend to become severe by day 3–5, with the development of jaundice, encephalopathy, and possibly death. Liver transplantation has been carried out successfully for cases of severe *Amanita* poisoning [53]. Some *Amanita* mushrooms such as *A. muscaria* and *A. pantherina* do not contain hepatotoxins.

The cyclopeptide mushrooms contain two cyclic oligopeptide hepatotoxins: phallotoxins and amatoxins. Both are heat stable and resistant to drying [52, 54]. Phallotoxins are not absorbed from the gastrointestinal (GI) tract and therefore are not thought to play a role in the symptoms associated with human poisoning [55]. α -Amanitin is a dialyzable octapeptide that inhibits RNA polymerase II, thus interfering with mRNA synthesis [56]. The cell is robbed of its ability to produce vital structural proteins and undergoes necrosis. Tissues with a high rate of protein synthesis (liver, kidneys, brain) suffer the most damage [56]. α -Amanitin is easily absorbed from the intestinal epithelium and enters the hepatocyte via bile transport carriers [57]. It demonstrates low plasma protein binding and is cleared from plasma in 36 h [56, 57]. Sixty percent is excreted into bile and undergoes enterohepatic circulation, whereas the rest is cleared renally [55, 56] (see ► Chap. 108, “Cyclopeptide-Containing Mushrooms: The Deadly *Amanitas*” for a more detailed discussion).

Case reports of ALF caused by other noninfectious biologic agents include one published in 1994 describing ALF secondary to a sea anemone sting [58].

Nontoxic Causes

Infections

Viral hepatitis remains one of the most common causes of ALF worldwide. The majority of cases

are related to hepatitis A and E infections globally with death rates of more than 50% reported from the developing world [59, 60]. Also hepatitis B infection may lead to ALF [61]. It is unclear why ALF develops in a select proportion of the infected population, but historical review of previous epidemics reveals that this number remains surprisingly constant at approximately 0.4% [62]. The hepatocellular necrosis seen in cases of ALF caused by hepatitis A and B is thought to be due in part to a direct cytopathic effect of the virus. This mechanism is supported by the relative lack of inflammation seen in the livers of patients with viral ALF. However, the normal humoral and cell-mediated response to a massively infected liver also plays a role. One study found that the amount of hepatitis A virus (HAV) isolated from the livers of patients with HAV-associated ALF was higher than titers from patients with nonfulminant HAV hepatitis [63]. In addition, CD8⁺ T lymphocytes isolated from the livers of two patients with acute HAV infection demonstrated the ability to kill HAV-infected fibroblasts in culture, thus implying that the liver damage seen in virally induced ALF is in part cell mediated [64].

ALF secondary to HAV infection is a rare event: 0.35% of HAV infections will progress to ALF [58]. Patients have a comparatively low mortality rate (<40%) and usually recover without liver transplantation. Acute hepatitis B infection progresses to ALF in approximately 1% of infected patients, thus making hepatitis B virus (HBV) the most common viral cause of ALF [58]. Its role may be underestimated when the impact of infection with a pre-core mutant (HBV viral infection that does not produce the surface [HBsAg] or e antigen) is taken into account, as demonstrated by a study in which it was found that 35% of patients who underwent transplantation for non-A, non-B hepatitis had evidence of HBV infection by polymerase chain reaction [65]. One half to one third of patients with ALF secondary to HBV will clear HBsAg within a few days [66]; such rapid clearance is thought to be the result of a substantial immunologic response to HBV-laden hepatocytes. Interestingly, those who clear HBsAg rapidly have a more favorable prognosis (47% survival rate) than those with

continued HBsAg positivity (17% survival rate) [13]. Despite being an increasingly common cause of chronic liver disease, isolated infection with hepatitis C virus has yet to be definitively implicated in ALF [10]. Though rarely encountered in the USA, infection with hepatitis E virus in pregnant women carries a 40% mortality rate [67]. Infection with hepatitis delta virus has been implicated in about 30% of HBV-related ALF cases. In fact, the risk of ALF increases dramatically with any hepatitis virus coinfection [68, 69].

Infection with the viruses herpes simplex, Epstein–Barr, varicella zoster, cytomegalovirus, or parvoviruses occasionally causes ALF, though usually in an immunocompromised setting. Pediatric ALF in association with parvovirus B19 infection has been noted.

Case reports detailing other (rare) infectious causes of ALF have implicated *Coxiella burnetii*, *Plasmodium falciparum*, amebic abscesses, disseminated tuberculosis, and *Bacillus cereus* emetic toxin as causative agents.

Vascular Events

The liver has a unique blood supply, with the portal vein supplying 70% of total blood flow and the hepatic artery making up the remaining 30%. Disruption of either the inflow or outflow of blood can lead to ischemia, hypoxia, and ultimately ALF. Examples include prolonged hypotension (intraoperative circulatory collapse, acute myocardial infarction, acute pulmonary embolism), gram-negative sepsis and shock, congestive heart failure, veno-occlusive disease (chemotherapy- or bone marrow transplant related), Budd–Chiari syndrome, and hepatic artery thrombosis after OLT. Prolonged hypotension after an overdose of opiates or cardioactive drugs (e.g., β -receptor or calcium channel antagonists) or cardiac arrest from any agent may also produce hepatic failure. It is important to note that almost all cases of hepatic ischemia secondary to systemic hypotension are associated with very high aminotransferase levels and accompanying renal dysfunction. In contrast, patients with Budd–Chiari syndrome have aminotransferase levels between 100 and 600 U/L, although higher values are possible. Serum alkaline phosphatase is

around 300–400 U/L, whereas bilirubin is usually less than 7 mg/dL (120 μ mol/L) at onset. The disease commonly affects women and causes severe right upper quadrant pain and hepatomegaly.

Exertional heatstroke is also an important cause of ischemic ALF and is usually seen in young unconditioned patients pursuing a new exercise program in high ambient temperature and humidity. Classic (nonexertional) heatstroke occurs in patients with multiple chronic medical problems or those taking anticholinergic medications, which leaves them susceptible to disruption of temperature regulatory mechanisms or incapable of escaping the heat. Heatstroke is usually manifested by hyperthermia (core body temperature $>40.5^{\circ}\text{C}$ [104.9°F]), mental status changes (including seizures), peripheral vasodilation, and a host of metabolic derangements. Leukocytosis may also be a prominent initial feature. Acute mortality was 21% in one series [70]. Adverse drug effects (e.g., neuroleptic malignant syndrome, veno-occlusive disease) can play a role in ischemic ALF. Disruption of sinusoidal blood flow by metastatic cancer has also been described as a cause of ALF. Gastric, breast, and oat cell carcinomas have been implicated, as have leukemia, carcinoid syndrome, and amyloidosis.

Metabolic and Other Causes

ALF can occur even without large-scale hepatic necrosis, as demonstrated by patients who suffer from liver failure secondary to acute fatty liver of pregnancy (AFLP), Reye's syndrome, or a fulminant manifestation of Wilson's disease. ALF as an initial feature of Wilson's disease is rare but carries a very high mortality rate without liver transplantation. A relatively low serum alkaline phosphatase level and a disproportionately elevated bilirubin level (up to 30 mg/dL [$513\ \mu\text{mol/L}$]) characterize such a manifestation. The serum copper level is usually elevated.

Whereas loss of hepatocyte function in Wilson's disease is secondary to hepatic copper overload, AFLP results in ALF from an inherited defect in mitochondrial beta oxidation of long-chain fatty acids [71]. AFLP usually occurs in the third trimester and may be associated with

preeclampsia. Serum aminotransferase levels usually stay below 1000 U/L unless the HELLP syndrome (hemolytic anemia, elevated liver function tests [LFTs], and low platelet count) is present. Infant mortality is high in either case.

Reye's syndrome has a similar pathogenesis and can be seen in pediatric cases with an antecedent viral illness treated with aspirin. Other rare metabolic anomalies that can cause ALF are listed in Table 2. Rarely, autoimmune hepatitis and primary graft failure after liver transplantation will be manifested as ALF.

Diagnosis and Complications

ALF is the common final pathway of a variety of insults, and thus the features remain remarkably similar regardless of the etiology. Nonspecific flu-like symptoms, including fatigue, nausea, loss of appetite, and malaise, are the initial symptoms in previously healthy patients. These symptoms are followed by jaundice and then alteration of mental status with rapid progression to coma. Other helpful signs on physical examination include decreased or absent dullness to percussion in the right upper quadrant, indicative of reduced hepatic mass secondary to necrosis. Feter hepaticus is usually present, but recognition of this condition is somewhat subjective. Ascites is more common with subfulminant hepatic failure. Stigmata of chronic liver disease do not support a diagnosis of ALF as per the classic definition. Low blood pressure (decreased systemic vascular resistance) and hypothermia may also be evident. Laboratory derangements include high serum aminotransferase levels, low blood glucose levels, and a prolonged prothrombin time. Metabolic acidosis with respiratory compensation may be evident on arterial blood gas measurement. Complications seen in the course of the illness include cerebral edema; renal failure; cardiovascular, pulmonary, and metabolic derangements; and problems with infection, GI bleeding, and malnutrition. Multiorgan failure is commonly encountered. There is an inverse relationship between the presence and number of complications and patient survival. The diagnosis is often

delayed without an appropriate index of suspicion, and such delay can have catastrophic implications in as much as early diagnosis and appropriate management are important to preserve the ability of these patients to receive a transplant should it become necessary. Overall, the presence of coagulopathy in a jaundiced patient with an altered mental status remains the hallmark of ALF.

Coagulopathy

Coagulopathy is universally present and can be the first sign of impending liver failure. It is due mainly to decreased hepatic synthesis of clotting factors [72]. Therefore, serial measurements of prothrombin time and factor V levels have prognostic significance and provide the best measure of whether hepatic function is improving or deteriorating. DIC and local fibrinolysis do occur in ALF, and though not usually severe, they can be exacerbated by infection or by the infusion of activated clotting factors [73]. Administration of fresh frozen plasma *in the absence of bleeding* is not recommended because it has not been shown to be of value [72] and will alter the prothrombin time, thus hindering patient assessment. Platelet function is altered (prolonged capillary bleeding time), and thrombocytopenia secondary to bone marrow suppression, hypersplenism, and intravascular consumption is present in up to two thirds of patients [74]. If invasive procedures are necessary, correction of coagulation abnormalities may be relevant and needed.

Encephalopathy

Unlike the conditions observed in chronic hepatic disease, the encephalopathy associated with ALF can be manifested as agitated delirium, paranoid behavior, or even a psychotic state. Seizures may occur. The initial stages of encephalopathy are secondary to bilateral forebrain dysfunction, with the latter being secondary to brainstem impairment. Table 4 delineates the grading system used for acute hepatic encephalopathy; the

Table 4 Progressive stages of hepatic encephalopathy

Stage	Level of consciousness	Neuromuscular changes	Behavioral/intellectual changes
I	Reversal of sleep pattern	Mild asterixis	Euphoria/depression
	Mild confusion	Impaired handwriting	Short-term memory lapses
II	Slow responses	Asterixis/ataxia	Inappropriate behavior
	Increasing drowsiness	Slurred speech	Loss of time/amnesia
III	Disorientation	Rigidity/spasticity	Stuporous/incoherent
	Somnolence	Loss of continence	Marked confusion/paranoia
IV A/B	Comatose	Decorticate/decerebrate	Comatose
	A: responds to pain	Hyperreflexic	
	B: no response to pain		

presence of stupor or coma portends a poorer prognosis. Although the exact pathogenesis remains elusive, the encephalopathy is reversible and thought to be metabolic. Structural changes such as those seen with Alzheimer's disease are not part of the syndrome. It is postulated that elevated levels of neuroactive humoral substances secondary to decreased hepatic clearance cause the observed mental status changes. It is important to note that the blood–brain barrier is disrupted in ALF, and this increased permeability makes it unnecessary for a substance to be present in greater than normal concentration in plasma to affect cerebral function. In addition, with the blood–brain barrier demonstrating marked regional differences in permeability, the concentration of potentially encephalopathic agents at critical subcellular sites may be more important than their concentration in cerebrospinal fluid or plasma [75]. Studies have implicated increased GABAergic (transmitting or secreting γ -aminobutyric acid) tone, mediated by an endogenous benzodiazepine-like ligand, as a cause of the hepatic encephalopathy seen in ALF [76]. Treatment with flumazenil (a benzodiazepine receptor antagonist) has been shown to temporarily improve the coma grade of patients suffering from this syndrome.

Cerebral Edema

Cerebral edema with resultant increased intracranial pressure (ICP) is a common complication of ALF, with up to 81% of patients demonstrating signs of increased ICP during the course of the

illness [77]. Although it is a distinct entity, its signs and symptoms may be missed because of the presence of concurrent encephalopathy – often with deadly consequences. Herniation of the cerebellar tonsils or the uncinat process of the temporal lobe is a significant cause of death, and evidence of herniation is present in up to 25–30% of patients with cerebral edema [78].

The causative metabolic and pathophysiologic derangements that lead to cerebral edema have yet to be fully elucidated. Research indicates a complex interplay among vasogenic (alterations in blood flow), cytotoxic (loss of osmoregulation), and hydrocephalic (extracellular expansion) factors. Even though earlier histologic studies of the brain revealed no abnormalities [79], more recent data have found alterations in cell membrane integrity and blood–brain barrier permeability [80, 81], changes probably responsible for the increased water content and weight of the brain. Although patients with cirrhosis rarely have cerebral edema, a marked decrease in intracranial blood flow has been noted in those with acute or chronic encephalopathy [82]. This decreased blood flow, along with the systemic hypotension commonly found in ALF (see the next section) and the increased ICP secondary to cerebral edema, predisposes the brain to ischemic injury. Cerebral perfusion pressure (CPP = mean arterial pressure [MAP] – ICP) below 40–50 mmHg is associated with ischemic brain injury and can have permanent consequences, even if the liver recovers fully. A persistent and refractory perfusion pressure of less than 40 mmHg precludes transplantation [83]. Signs of increased ICP are noted in Table 5. Because they are manifested

Table 5 Signs of increased intracranial pressure in fulminant hepatic failure

Brainstem respiratory pattern, apnea
Decerebrate posturing/rigidity
Focal seizures
Increased muscle tone
Loss of oculovestibular reflex
Myoclonus
Unequal, fixed, or abnormally reacting pupils

only late in the course of events (i.e., only if ICP is greater than 30 mmHg), these signs cannot be used to gauge the need for therapeutic intervention.

Although computed tomography (CT) scans are often used to exclude intracerebral hemorrhage as a cause of a sudden change in mental state, their static nature in this rapidly evolving syndrome makes them unsuitable as a management guide. ICP monitoring provides reliable data on which treatment decisions can be made, and placement of a subdural or epidural transducer is indicated in patients being considered for transplantation. Patients should be transferred to a transplant center early in the course of the disease; transportation after the onset of cerebral edema and coma is fraught with danger because even positional changes can raise ICP with disastrous consequences. Factors that tend to increase ICP are noted in Table 6. Even without herniation, cerebral edema remains the most common cause of death in ALF.

Cardiovascular Derangements

Systemic hypotension occurs in most patients with ALF and is mediated in part by decreased systemic vascular resistance (resembling septic shock), bacteremia, hemorrhage, hypovolemia, and increased interstitial edema (increased capillary permeability) and ICP. An etiology is not found in up to 60% of cases [84]. Nearly all patients with stage IV encephalopathy suffer from arrhythmias. Although sinus tachycardia is most common, the spectrum includes heart block and cardiac arrest. ST segment and T wave

Table 6 Factors that increase intracranial pressure

Arterial hypotension
Coughing
Fever
Head and body movement
Hypercapnia
Isometric muscle contraction
Neck vein compression
Noxious stimuli
Positive end-expiratory pressure
Psychomotor agitation
Respiratory suction
Seizures
Severe hypoxemia
Shivering
Sneezing
Trendelenburg position
Valsalva maneuver
Vasodilatory agents
Vomiting

changes may occur. Exacerbating factors include hypoxemia, acidosis, hyperkalemia, and cerebral edema [85].

Renal Failure

Renal impairment is present in up to 75% of patients with ALF [86] more frequent in the elderly and in patients with APAP-induced ALF [87] and includes prerenal azotemia, hepatorenal syndrome, and acute tubular necrosis. Hepatorenal syndrome is a diagnosis of exclusion and is characterized by a serum creatinine concentration greater than 1.5 mg/dL (133 μmol/L), a urinary sodium concentration less than 10 mEq/L (without taking diuretics), lack of improvement with volume expansion, and a bland urinary sediment [88]. Systemic hypotension and splanchnic vasodilation (probably nitric oxide driven) activate the renin-angiotensin axis, with resultant renal vasoconstriction. Renal vasoconstriction leads to a drop in renal perfusion pressure, which is reflected by a decreased glomerular filtration rate and increased sodium retention (causing ascites and edema). The presence of oliguric renal failure portends a poorer prognosis [89]. Renal

impairment may also occur secondary to the toxic effects of substances that caused the ALF, such as APAP, hepatotoxic mushrooms, hydrocarbons, and MDMA.

Pulmonary and Ventilatory Derangements

Up to 30% of patients will have evidence of pulmonary edema during the course of their illness, especially those with cerebral edema [90, 91]. Accurate determination of volume status by pulmonary artery pressure monitoring has been shown to improve survival [92]. Intrapulmonary arteriovenous shunting, peripheral capillary blockage with cellular debris from necrotic hepatocytes, or low-grade DIC, interstitial edema, and increased vasomotor tone ultimately lead to lactic acidosis secondary to anaerobic metabolism, which can exacerbate cerebral ischemia [93, 94]. The use of NAC and proctacyclin to improve tissue oxygenation remains experimental and controversial [94–96].

Infection

Metabolic inhibition of polymorphonuclear leukocytes, decreased opsonization, and impaired cell-mediated and humoral immunity greatly predispose patients with ALF to bacteremia and fungemia [58, 97]. Patients have increased risk of infection secondary to multiple indwelling catheters, antacid therapy, artificial ventilation, coma, and treatment with broad-spectrum antibiotics. Skin flora organisms (*Staphylococcus* and *Streptococcus* spp.) are most commonly isolated in patients with ALF [98]. In a prospective study of 50 patients with acute liver failure, infection was suspected in 45 patients and proved by positive cultures in 40 [99]. However, prophylactic antibiotic treatment has not been shown to improve survival [100].

Gastrointestinal Bleeding

The severe coagulopathy seen with ALF predisposes patients to hemorrhage from the GI tract,

with the upper GI tract being the most frequent site of bleeding [101]. Diffusely hemorrhagic gastritis, esophagitis, and nasogastric tube trauma are common etiologies. Exacerbating factors include tissue hypoxia from hypotension, microcirculatory disruption, and hypoxemia, along with DIC, bacteremia, and ventilator-associated platelet dysfunction. Large episodes of bleeding lead to further hypotension and tissue (including cerebral) hypoxia and can cause worsening renal failure as a result of prerenal azotemia, as well as exacerbating hepatic encephalopathy. Despite the numerous risk factors for hemorrhage, infusion of fresh frozen plasma or platelets for correction of coagulopathy or thrombocytopenia is not indicated in the absence of bleeding.

Metabolic Derangements

Electrolyte and acid–base disturbances are common in ALF and can exacerbate encephalopathy and cause arrhythmias. Despite renal retention of sodium, hyponatremia occurs frequently and is due to impaired renal free water excretion. Hypokalemia is present and can be profound; etiologies are multiple and include renal losses (secondary to hyperaldosteronism and sodium retention, as well as secondary to hydrogen ion resorption to compensate for respiratory alkalosis), GI losses (decreased intake, vomiting), and iatrogenic causes (e.g., diuretics, nasogastric tube suctioning, lactulose use). Hypophosphatemia, hypomagnesemia, and hypocalcemia can also occur. Complex acid–base disturbances with multiple processes at play are seen – respiratory alkalosis as a result of spontaneous hyperventilation is commonly present early in the course of the disease. However, with disease progression and depression of the central respiratory drive secondary to edema or circulating toxins, respiratory acidosis can develop. Hypokalemia is associated with metabolic alkalosis, whereas tissue hypoxia and massive hepatic necrosis give rise to metabolic acidosis with elevated levels of lactic acid, free fatty acid, and other organic acids. The presence of lactic acidosis is a poor prognostic indicator. Impaired glucose release, loss of glycogen

reserves, and decreased gluconeogenesis are in combination responsible for severe hypoglycemia (blood glucose <40 mg/dL [2.2 mmol/L]) in up to 40% of patients. Decreased hepatic metabolism of insulin resulting in inappropriately elevated plasma insulin levels also plays a pathogenic role. If unrecognized and untreated, the fall in blood glucose can be rapid and may lead to irreversible brain injury.

Diagnostic Studies

Laboratory and radiographic testing should be performed to confirm the diagnosis, elucidate the etiology of ALF, evaluate for the presence of complications, and obtain data necessary for management, prognostication, and preparation of the patient for possible liver transplantation. See Table 7 for a list of recommended initial diagnostic tests for ALF. Serum glucose should be monitored frequently (every 2 h), and other parameters such as electrolytes, hematocrit, and arterial blood gas should be monitored at least three times daily. Coagulation parameters and LFTs are usually checked twice a day. Further testing, such as tomographic studies of the head to rule out intracerebral hemorrhage or cerebral edema as a cause of acute worsening of mental status, is performed as clinically indicated.

Treatment

Because of the unpredictable nature of the disease, the risk of acute decompensation, and the severity of the illness/complications, patients with ALF should be managed in an ICU setting, preferably at a liver transplant center. Hospitals without liver transplant programs should transfer patients with ALF to such transplant centers as soon as possible because increased ICP and severe coagulopathy make transfer later in the course of the disease much more hazardous. Uncompromised ICU support is necessary to give these patients the best chance for survival. Specific treatment strategies for commonly encountered complications are discussed in the following sections.

Table 7 Initial diagnostic testing in fulminant hepatic failure

Parameter	Rationale
Electrolytes and minerals	Imbalances are common; can cause arrhythmias, worsen encephalopathy. Hypophosphatemia is common in acetaminophen overdose
BUN/creatinine	Renal failure is typical; affects management and prognosis. Etiology (e.g., toxic effect of ingested substances) may alter therapy (e.g., hemodialysis)
Glucose	Hypoglycemia is common; can have permanent neurologic sequelae
CBC with platelets	Assess for sepsis (leukocytosis), GI bleeding (anemia), and risk of hemorrhage (thrombocytopenia)
Liver profile	Assess degree of damage, follow course of illness
Coagulation profile	Prognostic indicators (PT, factor V level), assess risk of hemorrhage
Arterial blood gases	Prognostic significance (lactic acidosis), derangements common
Blood group	Preparation for transplantation; type and crossmatch in anticipation of bleeding
Toxicology, virology, autoimmune panel, ceruloplasmin, medication history	Etiology affects management (e.g., NAC for acetaminophen, charcoal for <i>Amanita</i>) and prognosis. Refer to Table 2 for various etiologies of ALF
Blood and urine cultures	Surveillance for sepsis; aggressive treatment warranted if positive
ECG	May affect management, preparation for transplantation
Chest radiograph	Sepsis surveillance; evaluate for ARDS, pulmonary edema
Abdominal ultrasound	Evaluate for vascular thrombosis, preparation for transplantation

(continued)

Table 7 (continued)

Parameter	Rationale
Pulmonary wedge pressure	Assess volume status if hypotension present
Intracranial pressure	Assess ICP if stage III–IV encephalopathy present. Cerebral edema is the most common cause of death

ARDS, adult respiratory distress syndrome; BUN, blood urea nitrogen; CBC, complete blood count; ECG, electrocardiogram; ALF, fulminant hepatic failure; GI, gastrointestinal; ICP, intracranial pressure; NAC, N-acetyl-L-cysteine; PT, prothrombin time

Coagulopathy

Decreased synthesis of coagulation factors is a direct reflection of hepatic dysfunction and can be used as a prognostic indicator. Therefore, prophylactic correction of coagulopathy in a non-bleeding patient is not recommended because it does not influence mortality, can interfere with assessment of disease severity, and may predispose the patient to volume overload and worsening cerebral edema [24, 102]. Blood products (fresh frozen plasma or, rarely, recombinant human factor VIIa) may be used to correct coagulopathy in cases of active hemorrhage/GI bleeding and for invasive procedures [103].

Encephalopathy

Encephalopathy is part of the definition of ALF and as such plays a major role in the patient’s clinical findings and course. Patients with grade 4 encephalopathy should be intubated for airway protection. Standard treatment with lactulose enemas or lactulose via a nasogastric tube, 30 mL three to four times a day, is instituted in an attempt to decrease the amount of nitrogenous waste (in the form of ammonia) absorbed from the gut lumen. However, new evidence suggest that the use of polyethylene glycol (PEG) may be superior to lactulose in the treatment of encephalopathy in cirrhotic patients [104] (Grade I recommendation). Oral neomycin has traditionally been added if the encephalopathy is difficult to control, but it has possible nephrotoxic and ototoxic side effects. Modern drugs of choice instead are

metronidazole, 250–500 mg two to three times a day, aminopenicillins, 2–4 g/day, or vancomycin, 1–2 g/day. More recently it has been shown that the minimally absorbed oral antibiotic rifaximin maintains remission from hepatic encephalopathy more effectively than placebo [105] (Grade I recommendation).

Cerebral Edema

Cerebral edema (leading to elevated ICP, ischemic/hypoxic brain injury, and brainstem herniation) is the most common cause of death in ALF and is present in up to 80% of patients with grade 4 encephalopathy [106]. Given the deadly consequences of unrecognized cerebral edema and the difficulty in diagnosing it clinically, an epidural ICP monitor should be placed in all patients with grade 4 encephalopathy. This procedure has a 4% morbidity (infection, bleeding) rate and a 1% mortality rate and is thus safer than placement of a subdural, parenchymal, or intraventricular catheter [107]. Coagulopathy should be addressed before placement of an ICP monitor, and head CT should be considered to rule out other causes of acute mental status changes such as intracranial hemorrhage. The aim is to keep ICP lower than 20 mmHg and CPP ($\text{MAP} - \text{ICP} = \text{CPP}$) higher than 50 mmHg [2] (Grade III recommendation).

Elevated ICP can be treated with mannitol boluses (0.5–1 g/kg to achieve a plasma osmolality between 310 and 325 mOsm/kg) [108]. Clinicians should be vigilant for signs of volume overload with mannitol use; concurrent ultrafiltration or other dialysis methods may be needed to avoid hypervolemia. In addition, patients should be stimulated as little as possible because agitation can increase ICP. Sedatives should be used in the lowest dose possible so that the degree of encephalopathy can continue to be monitored. Short-acting drugs such as propofol should be used [109]. Elevating the head of the bed can decrease ICP, but it also causes CPP to fall and leads to paradoxical increases in ICP when elevation is above 30° [102]. In the absence of ICP monitoring, the head of the bed should be elevated 10–20° (Grade III recommendation). The use of positive

end-expiratory pressure during ventilation can also worsen cerebral edema [110]. Dexamethasone has been proved to be ineffective as treatment of cerebral edema and should therefore not be used [111]. Hyperventilation to lower PCO₂ has not been shown to be beneficial [102].

Renal Failure

Most patients with ALF have evidence of acute kidney injury (AKI), the presence of which carries a grave prognosis. Treatment is centered on prevention: the use of nephrotoxic drugs (e.g., aminoglycosides) is avoided, intravascular volume is optimized with judicious use of colloid supplementation in the form of packed red cells or salt-poor albumin, and MAP is maintained as close to normal as possible. A high index of suspicion should be entertained for AKI secondary to the direct toxic effects of substances such as APAP or hepatotoxic mushrooms. Although urinary sodium values can be used to guide therapy, the blood urea nitrogen concentration may underestimate the renal dysfunction because of decreased hepatic urea production.

Infection

A decline in renal function or worsening/recalcitrant encephalopathy may be the first clues to an untreated infection in patients with ALF. Thus, a high index of suspicion must be maintained, with a low threshold for diagnostic testing (including blood, urine, and sputum cultures, chest x-ray, paracentesis) and empirical broad-spectrum antibiotic/antifungal coverage. The most common sites of infection include the respiratory system, the urinary tract, and blood [112]. Although prophylactic antibiotic use has not been shown to be helpful, a surveillance culture regimen with aggressive directed therapy if an infection is suspected is recommended.

Gastrointestinal Bleeding

All ALF patients deserve stress ulcer prophylaxis with oral/IV proton pump inhibitors. Sucralfate

may also be used. Coagulopathy and thrombocytopenia should be corrected in patients with bleeding from the GI tract, but not prophylactically. Large GI bleeds are investigated and treated endoscopically. If variceal bleeding is suspected, treatment with an octreotide IV drip should be initiated without delay for endoscopic confirmation.

Metabolic Derangements

The various metabolic derangements seen in ALF have been detailed earlier. As part of supportive ICU care, electrolytes should be checked and corrected at least twice a day. Hypoglycemia is common in ALF and needs closer attention. Hypertonic glucose solutions should be administered as an IV drip to keep blood glucose levels above 65 mg/dL (3.6 mmol/L). Restriction of free water may be needed to treat hyponatremia, but hypertonic saline is rarely required. Acetaminophen-induced ALF without renal impairment is commonly associated with hypophosphatemia, which may require therapy [113].

Nutrition

A diet low in protein is advocated for patients with ALF who are able to tolerate oral intake (grade 1–2 encephalopathy). Enteral low-protein tube feeding should be considered early in the course of the disease for the rest of the patients to prevent unnecessary catabolism to preserve muscle bulk and immune function [114] and to optimize management before possible liver transplantation. Tube feeding should be administered into the distal duodenum/jejunum if possible to decrease the risk of aspiration.

Specific Antidotes

Two of the most common conditions for which specific treatment of ALF is available are APAP overdose and *Amanita* mushroom poisoning. Other rare treatable etiologies include AFLP (treated by delivery), shock liver (treated by

optimizing hemodynamic status), acute Budd–Chiari syndrome (treatment considerations include transjugular intrahepatic portosystemic shunt versus surgical decompression versus thrombolysis), herpesvirus infection (treated with acyclovir), and autoimmune hepatitis (treated with steroids).

► [Chapter 59, “Acetaminophen/Paracetamol”](#) provides detailed discussion on the treatment of APAP overdose, but in general, if severe acetaminophen toxicity is suspected, intravenous NAC should be administered without delay. Activated charcoal (1 g/kg) may decrease APAP absorption if administered within 1 or 2 h of ingestion. In most countries, the plasma APAP concentrations are determined in all suspected cases and values plotted against the established nomogram to determine whether NAC administration is indicated. However, in Denmark the use of a nomogram is not recommended. All patients suspected of APAP poisoning are treated with NAC immediately after hospital admission. Information from patients with suicidal behavior about time of ingestion are often unreliable which may lead to a wrong decision about NAC treatment if a nomogram is used [115]. However, those with liver injury and suspected acetaminophen toxicity, even in the absence of detectable APAP, should receive NAC treatment.

Mushroom poisoning can be established by isolating α -amanitin in serum or urine by radioimmunoassay. Its enterohepatic circulation can be interrupted by using repeated doses of activated charcoal, and possibly forced diuresis can increase the rate of renal clearance of the toxin (see ► [Chap. 108, “Cyclopeptide-Containing Mushrooms: The Deadly *Amanitas*”](#)). Silibinin and IV penicillin G have been used as specific therapies for *Amanita* poisoning. Silibinin is thought to impede the uptake of α -amanitin by hepatocytes and may be efficacious up to 48 h after the ingestion of toxin [57].

Prognosis

Patients with ALF can be broadly divided into two categories – those who have enough hepatic reserve left to survive and recover with optimal

medical care and those who have sustained an irreversible hepatic insult and will die despite supportive care. OLT is the best available option for the second cohort; it is not appropriate therapy for the first group. The difficulty lies in accurately categorizing patients into one of these two groups and doing so in a timely manner, before the complications associated with ALF preclude OLT as a therapeutic option. Overall, current estimates reveal that only about 10% of patients with ALF receive a transplant [106]. Posttransplant survival rates have been estimated at 55% to 75% [116], although rates may improve to over 90% with stringent selection criteria [108]. As noted earlier, ALF without OLT is associated with very high mortality rates, and survival remains dismal for those who are listed for transplantation but do not receive an organ in time. In general, transplantation is recommended if the patient’s survival rate is estimated to be below 20%.

**A number of prognostic indicators have been identified to help clinicians predict the severity of ALF and identify patients who would benefit from transplantation. It is well known that the etiology and the presence/number of associated complications can influence the survival rate. Time from the onset of jaundice/symptoms to the development of hepatic encephalopathy can also predict a survival difference in certain cohorts, as mentioned in the discussion in the [“Definitions”](#) section of this chapter. The severity of encephalopathy at admission is inversely related to survival in patients with acetaminophen toxicity and acute liver failure [25]. Although age younger than 10 or older than 40 years has been shown to be a poor prognostic indicator in older studies, it did not play a role in survival rates from a more recent US series [25]. Liver histology is not routinely used because it has not been proved to accurately predict outcome [117].

The aforementioned variables (age, etiology, degree of encephalopathy, time to onset of symptoms, etc.), though identifying survival trends, do not allow for an accurate prediction of the need for transplantation. To better identify high-risk patients who would require liver transplantation

Table 8 King’s College Criteria (indications for transplantation)

Acetaminophen toxicity	Non-acetaminophen toxicity
pH <7.3 (irrespective of other factors)	PT >35 s (US units) or INR >7.7 (irrespective of degree of encephalopathy)
<i>Or all three of the following:</i>	<i>Or any three of the following:</i>
Grade III–IV encephalopathy	Age <10 or >40 year
PT >100 s	Unfavorable etiology (non-A non-B hepatitis, idiosyncratic drug reaction, halothane hepatitis, Wilson’s disease)
Serum creatinine >3.4 mg/dL (300 μmol/L)	Serum bilirubin >17 mg/dL (300 μmol/L)
	Time from jaundice to encephalopathy >7 days
	INR >4

INR, international normalized ratio; PT, prothrombin time

for survival, a statistical model was developed by investigators at King’s College in London. From a cohort of 588 patients managed medically between 1973 and 1985, a multivariate analysis was performed on a number of biochemical and clinical variables and their relationship to mortality, and recommendations for transplantation were based on the results. The negative prognostic indicators (also known as King’s College Criteria) for which transplantation is recommended are noted in Table 8 [1].

The King’s College Criteria have been validated at other centers and in a prospective manner. Patients with ALF but without APAP toxicity demonstrated a mortality rate of 80% with the presence of any one of the negative prognostic indicators; mortality rose to 95% with the association of three negative prognostic factors. Severe acidosis (pH <7.3) in patients with APAP toxicity was associated with a mortality rate of 95%. Excluding acidosis, the presence of any other adverse characteristic in this population resulted in a mortality rate of at least 55%. These mortality rates are much higher than those associated with liver transplantation; thus, patients with even one negative prognostic indicator should be considered for listing [1]. A subsequent meta-analysis confirmed that the King’s College Criteria have

clinically acceptable specificity but more limited sensitivity [118].

Other predictive models have been developed to assess the degree of liver injury and identify patients who need liver transplantation for survival. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were similar to the King’s College Criteria in identifying those needing transplantation, but patients were recognized earlier in a few cases [119]. Serum Gc-globulin and plasma factor V levels have been used independently to predict outcome; however, they are specialized laboratory tests that may not always be available and have not been shown to be any better than the King’s College Criteria [120]. Factor V levels vary by age; transplantation is recommended for a factor V level less than 20% in ALF patients younger than 30 years or for a factor V level less than 30% for those older than 30 years [121]. However, patients have recovered without transplantation with factor V levels less than 10%, in our experience. Also measurement of arterial blood lactate may improve the speed and accuracy of selection of appropriate candidates for OLT. In a single-center study, the prediction of non-surviving APAP-induced ALF patients using lactate was similar to KCH criteria but identified them earlier [122]. Although early recognition of patients most likely to benefit from transplantation is important, it is equally important to recognize those in whom liver transplantation is contraindicated (Table 9).

Future Trends

The scarcity of donor livers has led to investigation of alternatives to transplantation not only for patients who need temporary support while their native liver recovers from the acute insult but also for those who need a “bridge” to transplantation. A number of novel and promising approaches have been tried, including auxiliary liver transplantation, liver dialysis systems, artificial hepatic assist devices, and xenotransplantation. All are in the research phase and need further study with controlled clinical trials to delineate their safety

Table 9 Absolute contraindications to liver transplantation

Severe cardiac or pulmonary disease
Severe pulmonary hypertension (PA systolic pressure ≥ 60 mmHg)
Adult respiratory distress syndrome ($\text{FiO}_2 > 0.6$)
Uncontrolled intracranial hypertension/irreversible brain damage
HIV infection/AIDS
Systemic sepsis
Extrahepatic malignancy
Portal and mesenteric vein thrombosis
Active alcohol or drug use
Severe psychological disorders
Inability to understand/commit to the procedure and the lifetime of responsibility it entails

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; PA, pulmonary artery

and efficacy. Liver dialysis systems have not met with great success. Hemodialysis, charcoal hemoperfusion, and blood and plasma exchange have been tried without any demonstrated alteration in outcome [102].

Auxiliary liver transplantation involves placement of a partial liver graft in either a heterotopic location or a space provided by partial hepatectomy. Although the graft is not large enough to sustain the patient independently, it provides enough support to allow the native liver to recover. No indications for auxiliary transplantation have been established, and it still requires a donor source in the presence of the current organ shortage. However, a number of patients have recovered when auxiliary grafting is used as a bridge, thus obviating the need for whole-organ transplantation and lifelong immunosuppression [123].

Early experiments of extracorporeal perfusion with animal organs led to the idea of hybrid artificial devices that would combine the efficacy and compatibility of a human liver with the ease of hemodialysis. These hybrids, known as extracorporeal liver assist devices (ELADs) and bioartificial livers, incorporate living human hepatocytes embedded around a nest of hollow fiber capillaries housed in a cartridge through which the patient's blood is transfused [124]. The device functions as an extracorporeal

artificial liver, with the living hepatocytes performing all the functions of the native liver across the semipermeable capillary membrane. Recent research has focused on trying to reproduce the hepatic architecture in the ELAD cartridge, identifying the optimal hepatocyte mass needed to provide the best results, and determining the ideal perfusion time necessary for a favorable outcome. The most extensively studied nonbiological device is the molecular adsorbent recirculating system which has shown some evidence in case series to improve biochemical parameters [125].

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The kidney carries out a number of crucial roles in the regulation of homeostasis. In addition to maintaining normal body volume, electrolyte concentration, and excretion of waste substances, kidneys regulate blood pressure and red cell carrying capacity and carry out a host of other functions. It is therefore not surprising that even small acute deteriorations in renal function lead to significant morbidity and mortality [1–3]. Acute kidney injury (AKI) is a common finding in hospitalized patients, with an incidence of 3–20% depending on the population studied; the incidence of AKI increases to 16–67% in intensive care units and appears to be growing [2, 3].

One of the most important roles of the kidney is organic solute excretion, including the excretion of many drugs, toxins, and their metabolites. As these solutes are excreted by the kidneys, they may reach high concentrations within the renal tubules; thus, any adverse effect these compounds exert upon cellular tissue may be magnified in the kidneys compared to other organs [4]. Drugs and toxins are frequently implicated as contributing to development of AKI – they may play a primary role or a synergistic role with other processes [5–9]. Because the kidney plays a central role in the elimination of many solutes, development of AKI from any cause may conversely worsen the severity of a multitude of poisonings through decreased excretion of toxins. Given the frequency and severity of AKI, as well as this unique importance of AKI to the poisoned patient, a comprehensive knowledge of mechanisms,

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complications, and management of AKI is important to the practice of medical toxicology.

Review of Renal Anatomy and Physiology

In normal physiology, the kidneys play a key role in maintaining normal homeostasis through solute excretion, electrolyte reabsorption and excretion, volume regulation, control of blood pressure, and a number of other functions. Despite a size of about 1% of total body mass, the kidneys receive about 20% of cardiac output. The kidneys have an extensive microcirculation; after originating through the renal arteries which arise from the abdominal aorta, the majority of renal blood flow (RBF) is directed to afferent arterioles, which in turn lead to capillaries in the renal cortex. These capillaries, known as glomerular capillaries, deliver high blood flow to the microarchitecture of the kidney; it is through this high-pressure system that a large portion of the cardiac output may be filtered through the kidneys, allowing for separation of waste products and excess fluid [10].

The kidneys are comprised of functional units called nephrons, each of which is capable of hormonal regulation as well as reabsorption and secretion of solutes and water. An average adult will have approximately one million nephrons, although this number may vary widely [11]. Nephrons are comprised of the glomerulus, the proximal convoluted tubule, the loop of Henle, the distal tubule, and the connecting tubule. The glomerulus is a network of capillaries enclosed by a layer of endothelial cells, which in turn is enclosed in Bowman's capsule, an epithelial layer of cells. As blood flows through the renal arteries, it is eventually diverted to small arterioles known as the afferent arterioles. From the afferent arterioles, glomerular capillaries arise, flowing through the glomerulus to arterioles known as the efferent arterioles. The afferent and efferent arterioles constrict and dilate in response to local and systemic hormonal factors such as angiotensin II, vasopressin, prostaglandins, and sympathetic innervation; this allows for tightly controlled regulation of renal blood flow (RBF) [10].

Blood flowing through glomerular capillaries is filtered through hydraulic pressure across the basement membrane of the glomerulus into an area known as Bowman's space. The pressure in the glomerular capillaries and Bowman's space, as well as the oncotic pressure of blood in the glomerular capillaries, provides the driving gradient for filtration of what will become the urine into Bowman's space. On average, adult kidneys produce around 150 l of filtrate; more than 99% of this is reabsorbed, producing about 1–2 l of urine daily [10, 12].

As filtrate flows into the glomerulus, it passes through the renal tubules and becomes known as luminal fluid. The proximal convoluted tubule acts as the "workhorse" of the nephron to reabsorb desired solutes (such as sodium, glucose, and a variety of others); the proximal tubule also secretes waste products ("uremic toxins," acid, and others) into the tubular lumen. It should be noted that the proximal tubule reabsorbs and secretes many organic solutes, including various drugs and toxins [13]. For this reason, the proximal tubule is often the most affected portion of the kidney by various toxic substances and a frequent site of kidney damage by nephrotoxins [10, 12, 13].

The loop of Henle serves to further reabsorb electrolytes and fluid and, through a mechanism known as the "countercurrent mechanism," generates a gradient which is used to concentrate the urine. The distal tubule and connecting tubule further act upon the electrolyte composition of the luminal fluid by reabsorbing and secreting various electrolytes, excreting additional acid, and determining the ultimate degree of concentration of the urine. Urine is then emptied into the renal pelvis, which is drained by the ureters into the bladder [12].

Kidney function is usually estimated by the glomerular filtration rate (GFR), the volume of urine filtered across the glomerulus per unit time. A normal GFR in children above the age of infancy and young adults is approximately 120 mL/min per 1.73 m² of body surface area; this decreases over time as aging progresses [10, 14]. GFR is directly proportional to RBF; the regulation (known as renal autoregulation) of

GFR, therefore, is carried out in large part by varying RBF through constriction and dilation of the afferent and efferent arterioles. Mechanistically, this regulation is carried out through responses to tubular fluid flow and composition (known as tubuloglomerular feedback) as well as arteriolar smooth muscle stretch receptors causing vasoconstriction and vasodilation of renal blood flow in order to maintain near-constant glomerular capillary pressure (known as the myogenic mechanism) [10]. In the setting of acute kidney injury, GFR cannot be estimated well from static values alone; functional measures, such as urinary output, are of more utility [3].

AKI: Definitions and Clinical Importance

AKI is characterized by reduced renal function over a period of hours to days with retention of organic waste solutes. As a consequence of reduced kidney function, fluid, electrolyte, and acid–base derangements may arise, as well as reduced excretion of a large number of drugs and toxins [3, 9]. Multiple definitions of AKI have been proposed. Most recently, the Kidney Disease Improving Global Outcomes (KDIGO) workgroup proposed criteria for a single definition of AKI to be used in research and clinical practice which incorporates multiple studies [3]. The severity of AKI is graded based upon either changes in solute excretion (as measured by increases in serum creatinine) or by the duration and severity of oliguria. The initiation of renal replacement therapy (RRT) such as hemodialysis (HD) for a renal failure-related indication is also defined as AKI (Table 1).

Among hospitalized adults worldwide, the incidence of AKI is approximately 21.6% [15]. Drug toxicity accounts for a very large number of cases of AKI; in the largest meta-analysis performed to date, medications and radiocontrast media account for a combined 27% of the principle cause of AKI. The overall mortality of hospitalized patients was 19%; patients with higher degrees of AKI, unsurprisingly, had mortality rates which were higher yet [15]. The incidence

Table 1 KDIGO AKI staging

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥ 0.3 mg/dl increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥ 12 h
3	≥ 3.0 times baseline or increase in serum creatinine to ≥ 4.0 mg/dl or initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m ²	<0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

eGFR estimated glomerular filtration rate

of AKI is increasing among hospitalized patients in the United States, as is the incidence of AKI requiring renal replacement therapy [15, 16].

Traditionally, AKI is classified into three overarching subgroups based on underlying pathophysiology. *Prerenal failure* or *prerenal azotemia* describes AKI from reduced renal perfusion or any cause. *Intrinsic renal failure* encompasses a large group of disorders of renal parenchyma causing AKI; the most common cause of intrinsic renal failure is acute tubular necrosis (ATN) [9]. *Postrenal failure* refers to AKI from obstructive uropathy at any point along the urinary tract from the renal calyces to the outlet of the urethra. While prerenal azotemia accounts for the majority of all-cause AKI, the majority of AKI in critically ill patients is due to intrinsic renal failure [2, 3]. Postrenal failure generally accounts for less than 5% of significant AKI [2, 3]. While each cause of AKI is discussed separately, it should be noted that renal failure often occurs in the context of “multiple hits” that each cause worsening of kidney function, particularly where ischemic ATN is concerned.

Prerenal Acute Kidney Injury

Prerenal failure is a condition which arises due to hypoperfusion of the kidneys and is the most common type of AKI [17]. While hypovolemia is the most frequent cause of prerenal AKI, any condition that lowers renal blood flow may result

in a prerenal state: heart failure, cardiogenic shock, cirrhosis, and others [9]. Prolonged or severe prerenal azotemia may lead to renal hypoperfusion and produce ATN [9]. Any cause of hypovolemia may lead to prerenal azotemia, encompassing not only inadequate volume intake and fluid losses but processes resulting in vascular leakage (“third spacing”) such as sepsis [9]. Poisonings that result in volume depletion – such as those causing diarrhea, increased insensible losses, reduced enteral intake due to altered mental status, bleeding, and a host of causes – may cause prerenal azotemia. In these cases, prerenal failure due to hypovolemia may be distinguished from other causes of renal failure by administering intravenous fluids and observing the response.

A number of drugs may affect renal blood flow. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen inhibit prostaglandin synthesis, resulting in reduced vasodilation of the afferent and efferent arterioles. The subsequent disruption to renal autoregulation decreases RBF, which causes prerenal azotemia [18]. Settings which lead to hypovolemia in patients taking NSAIDs further worsen renal blood flow and further increase risk for AKI [9]. The use of NSAIDs leads to a 50–100% increase in the risk of AKI compared to nonusers; this risk has not been demonstrated to be greater for one type of NSAID compared to others [19]. Acute NSAID overdose usually causes prerenal failure which is readily reversible with intravenous fluids, although intrinsic AKI requiring RRT has been described [20]. Multiple other classes of drugs may cause renal vasoconstriction, such as angiotensin-converting enzyme inhibitors, iodinated radiocontrast, and calcineurin inhibitors such as tacrolimus [9].

Poisoning causing cardiogenic shock may result in acute cardiorenal syndrome, a condition where heart failure leads to reduced renal perfusion [21]. While blood volume may be normal (and is often elevated), decreased cardiac output results in reduced renal perfusion, leading to dysfunctional autoregulation of GFR [21, 22]. Poisonings that result in acute heart failure and/or cardiogenic shock, such as cardiac sodium channel blocker, calcium channel blocker, and beta-

Table 2 Major causes of prerenal acute kidney injury

Intravascular volume depletion
Burns and skin breakdown (e.g., Stevens-Johnson syndrome)
Diuretics
Fever and hyperthermia
GI losses (diarrhea, vomiting)
Hemorrhage
Reduced enteral fluid intake
Vascular leak (“third spacing”)
Cardiorenal syndrome
Cardiogenic shock
Pulmonary hypertension
Cardiac tamponade
Decreased renal perfusion with normal or high cardiac output
Cirrhosis and hepatorenal syndrome
Sepsis
Vasodilator poisoning
Renal vasoconstriction
Angiotensin-converting enzyme inhibitors/angiotensin II inhibitors
Antimicrobials (amphotericin B, foscarnet, others)
NSAIDs
Cyclosporine and tacrolimus
Radiocontrast agents

blocker toxicity among many others, may result in AKI due to cardiorenal syndrome (Table 2).

Intrinsic Acute Kidney Injury

Intrinsic AKI refers to a broad swath of disease processes which cause renal failure due to damage to renal architecture. This class encompasses diseases affecting the renal tubules, such as acute tubular necrosis or intratubular crystalluria; the renal interstitium, such as acute interstitial nephritis; the renal microvasculature, such as thrombotic microangiopathy or vasculitis; and/or the glomeruli, such as glomerulonephritis. Table 3 lists many toxic causes of various forms of intrinsic AKI.

Acute tubular necrosis (ATN) and tubular injury is generally thought to account for the majority of cases of intrinsic AKI [3, 9, 15]. The renal tubules are vulnerable to injury from hypoperfusion; if the tubules, and particularly the proximal tubule, have reduced blood flow or

Table 3 Selected toxic causes of intrinsic acute kidney injury

Glomerulonephritis and vasculitis
Captopril
Gold salts
Heroin
Levamisole
Mercury compounds
Pentazocine
Nephrotoxic acute tubular necrosis
Acetaminophen
Aminoglycosides
Amphotericin B
Aristolochic acid
Boric acid
Chemotherapeutic agents (many)
Colchicine
Diethylene glycol
Diquat and paraquat
Foscarnet
Iron
Lead
Myoglobinuria (rhabdomyolysis)
Orellanine
Pennyroyal oil
Radiocontrast agents
Rattlesnake venom
Salicylates
Sympathomimetic agents
Synthetic cannabinoids
Vancomycin
Acute interstitial nephritis
Allopurinol
Antibiotics (many)
Carbamazepine
Cimetidine
Clofibrate
Diuretics
Isoniazid
Methyldopa
NSAIDs
Phenobarbital
Phenytoin
Propranolol
Proton pump inhibitors
Synthetic cannabinoids
Thrombotic microangiopathy
Cocaine
Cyclosporine
Gemcitabine

(continued)

Table 3 (continued)

Interferon alpha and beta
Mitomycin
Oxymorphone ER
Quinine
Sunitinib
Tacrolimus
Rhabdomyolysis
Antipsychotics (neuroleptic malignant syndrome)
Crotalid envenomation
HMG-CoA inhibitors (“statins”)
Opioids
Scorpion envenomation
Serotonin syndrome
Sympathomimetic agents
Hemoglobinuria
Arsine
Benzene
Hydralazine
<i>Loxosceles</i> envenomation
Phenol

hypoxic injury to a point where oxygen delivery to tissues is impaired and ischemia occurs, tubular injury and necrosis may result [9, 23]. In addition, as the renal tubules are involved in reabsorption and secretion of many organic compounds, toxins and drugs frequently reach very high concentrations relative to other tissues and may exert an adverse effect on renal tissue. The S3 (most distal) segment of the proximal tubule has limited ability to carry out anaerobic glycolysis and is at higher risk for ischemic injury than other parts of the nephron [23]. Because of the role of the proximal tubule in carrying out the majority of drug reabsorption through endocytosis, most ATN due directly to tubular toxicity occurs in the proximal tubule, particularly affecting the S1 and S2 (more proximal) segments of the proximal tubule [24]. Pathologically, tubular injury is visible on kidney biopsy samples [24].

Acute tubular injury and necrosis from ischemic injury may result from any cause of reduced renal perfusion; in the poisoned patient, this usually results from shock or hypoxic injury. Severe prerenal azotemia from hypovolemia, cardiorenal syndrome, or medications affecting renal blood flow may also progress to ATN [23]. In patients

with preexisting chronic kidney disease, renal autoregulation is impaired; this may lead to earlier development of ATN and reduced likelihood of renal recovery [9].

A host of nephrotoxins may cause damage to the renal tubules in both therapeutic use and poisoning. Many antimicrobial agents, such as aminoglycosides, amphotericin B, and vancomycin, can be nephrotoxic in short-term use. Natural products such as aristolochic acid (found in Chinese traditional medicine) may cause both AKI as well as chronic kidney damage with repeated use [25]. Aristolochic acid may also cause kidney tumor formation; an outbreak of grain contaminated with *Aristolochia* species leads to endemic chronic kidney disease and kidney tumors in Eastern Europe termed Balkan chronic nephropathy [26]. Toxins causing oxidative renal injury, such as diquat, paraquat, and orellanine, may lead to tubular damage [27, 28]. Refer to Table 3 for a partial list of nephrotoxic compounds that may produce ATN.

Most cases of acute interstitial nephritis (AIN) are thought to be caused by idiosyncratic allergic reactions to various drugs [29]. Kidney biopsy findings in patients with AIN reveal an inflammatory infiltrate within the renal interstitium most often comprised of eosinophils (although neutrophilic or other infiltrates may occur). Often, other phenomena suggesting systemic allergic or inflammatory reactions may be present, such as fever or rash. Eosinophils are also found in the urine, although this is often not a sensitive finding due to their fragility [24, 29]. Common drugs implicated in the cause of AIN include antibiotics, proton pump inhibitors, and NSAIDs [30]. Medications that may cause other systemic allergic reactions, such as vancomycin, allopurinol, or phenytoin, may produce AIN as a manifestation of systemic disease [30, 31]. AIN may also result from autoimmune disease such as sarcoidosis [24]. Recently, synthetic cannabinoids have been implicated as a cause of AIN during outbreaks of synthetic cannabinoid-induced AKI; ATN was also commonly found [32]. It is not clear if this is allergic in nature or represents a different mechanism of interstitial inflammation such as apoptosis [33].

Glomerulonephritis and vasculitis are rarely caused primarily by poisoning, although cases do exist. Typically, these diseases are autoimmune in nature; this may still be the underlying pathophysiology in cases induced by poisoning, although no evidence exists to confirm or deny this. More likely, a variety of types of pathophysiology are present; however, clear models to describe the cause of drug-induced variants of most of these rare conditions do not exist, and pathophysiologic mechanisms remain speculative. Methamphetamines have been associated with C3 glomerulopathy, a form of membranoproliferative glomerulonephritis [34]. Necrotizing vasculitis (anti-neutrophil cytoplasmic antibody negative) has been associated with methylenedioxymethamphetamine [35, 36]. Levamisole, an antihelminthic drug which is commonly found as a contaminant in cocaine, has been associated with small vessel vasculitis similar to granulomatosis with polyangiitis; this may cause rapidly progressive glomerulonephritis with crescents [37]. Heroin has been associated with collapsing focal segmental glomerulosclerosis [38].

Thrombotic microangiopathies (TMAs) refer to a wide category of conditions which result in microangiopathic hemolytic anemia, the presence of microthrombi in a systemic or local distribution, and a constellation of clinical findings as a result. The kidneys are frequently involved in TMAs; the nature of the extensive network of renal arterioles and capillaries is often a nidus for clot formation [39]. Thrombotic thrombocytopenic purpura (TTP) is a prototypical TMA; it may produce multiple, often very severe, manifestations such as severe thrombocytopenia, renal failure, anemia, stroke, myocardial infarction, and seizures [39]. Hemolytic-uremic syndrome (HUS), in contrast, is a predominantly renal-limited TMA which usually causes significant AKI but has extremely varied systemic symptoms [39]. While most TMAs were previously categorized under the umbrella of either TTP or HUS, a more nuanced pathophysiologic approach is often taken nowadays, with drug-induced TMA simply being referred to as such.

Multiple drugs and agents have been associated with TMA; a partial list is found in Table 3.

Notably, while many drugs have been associated with TMA, only about one-quarter have clear evidence to establish a causal relationship [40]. In a series of cases of note, intravenous use of extended-release preparations of oxymorphone (Oxymorphone ER) was associated with a rash of cases of TTP-like thrombotic microangiopathy [41, 42]. The extended-release preparation of oxymorphone involved was formulated with a tamper-resistant matrix which forms a gel-like substance when heated; it is unclear whether the nature of TMA in this case is due to the drug itself or the tamper-resistant compounds.

Rhabdomyolysis leads to development of AKI through high concentrations of heme breakdown products and myoglobin in renal tubules; these lead to intratubular cast formation, direct tubulotoxicity, and renal vasoconstriction [43]. Many poisonings may produce rhabdomyolysis from direct muscle injury and/or systemic hypoperfusion; a partial list is mentioned in Table 3. Sympathomimetic toxins are particularly likely to cause drug-induced rhabdomyolysis; among these agents, synthetic cathinones may lead to greater degrees of rhabdomyolysis than cocaine and amphetamines [44]. The risk of AKI is directly correlated with the elevation in creatinine kinase – patients with creatine kinase elevations above 20–25,000 units/L have a risk for AKI which is an order of magnitude greater than lower elevations [45, 46]. While much less common than rhabdomyolysis, significant hemoglobinuria may also produce heme pigment nephropathy; toxins causing massive hemolysis, such as benzene or arsine gas, and *Loxosceles* venom may produce AKI in this manner [24, 47].

Crystalluria may be caused by a number of drugs in acute poisoning or chronic use; however, not all are equally likely to cause AKI. Drugs that form sharp, needlelike crystals such as acyclovir or indinavir are more likely to cause AKI than others [48]. Mechanisms by which crystalluria may induce AKI through blockage of renal tubules, damage to renal tubular epithelium, or both [49]. Not all drugs that cause crystalluria are likely to induce AKI; e.g., primidone may cause massive crystalluria but is less likely to cause AKI, and beta-lactams may cause microscopic crystalluria

Table 4 Major drugs and toxins known to cause crystalluria-induced AKI

Acyclovir
Atazanavir
Ciprofloxacin
Ethylene glycol
Foscarnet
Indinavir
Methotrexate
Primidone
Sulfamethoxazole and other sulfa antibiotics
Triamterene

but have not been reported to cause AKI through this mechanism [24, 49].

Factors which increase the risk of crystalluria-induced AKI largely result in the production of low urine volumes; this leads to a higher drug concentration to form inside renal tubules, increasing the likelihood of crystalluria. Examples of risk factors include hypovolemia, preexisting AKI or CKD, high doses of drugs, and concurrent NSAID use. Higher doses of drugs are an important risk factor for AKI; in high-dose sulfamethoxazole use (e.g., as used in treatment of *Pneumocystis*, *Stenotrophomonas*, and other organisms), development of AKI is more likely to occur in patients with preexisting CKD [50]. Depending on the nature of the drug involved (i.e., whether it is more likely to form crystals in acidic or basic urine), either high pH or low pH may also be a risk factor [49]. Medications notorious for causing AKI through crystalluria include acyclovir, methotrexate, sulfamethoxazole, and others; a partial list is given in Table 4.

Analgesic nephropathy is mentioned mostly for historical interest, as the incidence of this condition has dropped dramatically since its recognition [51]. Rather than encompassing all analgesic-induced AKI (e.g., NSAIDs), classic analgesic nephropathy refers to a slowly progressive form of chronic kidney disease that results from chronic high-dose use of multiple over-the-counter analgesic agents including at least two antipyretic agents, one of which was usually phenacetin, plus caffeine. More patients were identified per capita in Australia than in any other country, likely related to local analgesic

availability and habits – in 1990, analgesic nephropathy accounted for nearly 10% of end-stage renal disease in Australia. The disease results in chronic interstitial nephritis, renal papillary necrosis, and characteristic “lumpy” kidney contours on renal imaging [51].

Osmotic nephrosis is an uncommon kidney injury pattern seen in response to high-osmolality medications such as sucrose-containing intravenous immunoglobulin, hydroxyethyl starch, and iodinated contrast. The pathophysiology is thought to be related to excess solute accumulation by the proximal tubules in response to a high osmotic load, leading to massive vacuolization and tubular injury [52]. Another uncommon cause of AKI, phosphate nephropathy, was first identified in the early 2000s. A series of patients who took oral phosphate salts as bowel preparation for endoscopy presented with AKI; kidney biopsy findings revealed extensive intraluminal and tubular calcium phosphate deposition, suggesting that a transient extremely high serum phosphorus level led to massive phosphate excretion with crystal formation. Many patients with phosphate nephropathy do not recover kidney function after the injury; anecdotally, phosphate crystals may be present years later on kidney biopsies [53].

Postrenal Failure

Postrenal failure, or AKI related to obstruction at any point along the urinary tract from the renal papillae to the urethral outlet, accounts for far fewer cases of AKI than prerenal or intrinsic renal causes [9, 24]. In poisoning, postrenal failure is usually related to urinary obstruction through bladder wall contraction; agents which commonly cause this include opioids, anticholinergic medications, and antidepressants. While postrenal failure is reversible in the acute setting, prolonged obstruction may be associated with surprisingly few symptoms, and irreversible renal failure can develop when obstruction is present for a long duration of time [54].

More recently, ketamine and related analogues (e.g., methoxetamine) have been associated with

lower tract urinary dysfunction. A series of 59 patients in Hong Kong who used ketamine illicitly were found to have moderate to severe symptoms of urinary urgency, dysuria, and/or hematuria. On urodynamic studies, detrusor overactivity and decreased bladder compliance were common [55]. Similar findings have been noted in surveys of ketamine abusers [56]. Animal studies have produced evidence of postrenal failure and kidney damage in mice using ketamine; despite a perception that methoxetamine is more “bladder-friendly,” murine studies found evidence of bladder and renal toxicity with chronic methoxetamine administration [57, 58].

Diagnostic Evaluation of Acute Kidney Injury

The determination that AKI is present is a clinical diagnosis; while staging guidelines may be of help, at present, biomarkers of kidney injury which are more rapidly able to identify AKI are not in widespread clinical usage, although they may be helpful in the future [8]. Close attention to history and physical examination, urinary examination, laboratory testing, and renal imaging forms the cornerstone of evaluation of the AKI patient. In less common situations, a kidney biopsy may be of utility as well.

History taking in the patient with AKI and suspected poisoning should focus on potential ingestions as well as known exposures. In the hospitalized patient with AKI, drugs and medications are a common cause of renal failure [3, 15–17]. Examination should give special attention to evaluation of volume status, any findings to suggest systemic inflammatory disorders (vasculitic-appearing rash, livedo reticularis, etc.), and the presence of identifiable toxidromes (e.g., sympathomimetic toxidrome). The bladder should be palpated, and any prolonged period of anuria should prompt urinary catheterization to exclude lower urinary tract obstruction [3, 9].

Urinary analysis – both by chemical means (i.e., urine dipstick, laboratory parameters) and by visual inspection by the clinician – still occupies a core role in the evaluation of the patient

Table 5 Common urinary diagnostic indices in prerenal versus intrinsic renal failure

Parameter	Renal failure	
	<i>Prerenal</i>	<i>Intrinsic</i>
Urinalysis	Hyaline or no casts	Abnormal, cellular, or granular casts
Specific gravity	>1.020	Around 1.010
Urine osmolality (mOsm/kg)	>500	<350
Urine sodium (mmol/L)	<20	>20
FE sodium, %	<1	>2
FE urea, %	<35	>35
BUN:creatinine ratio	>20:1	<20:1

BUN blood urea nitrogen, *FE* fractional excretion

with AKI. Chemical and visual analysis probably plays the most significant role in distinguishing between prerenal failure (bland urine) and intrinsic renal failure (presence of abnormal findings); Table 5 summarizes the most commonly evaluated urinary diagnostic indices. When distinguishing between acute tubular necrosis and prerenal azotemia, the presence of “muddy-brown” granular casts is highly suggestive of ATN, although the absence of such casts is not particularly specific [24]. Microscopic evaluation of urine also serves to allow the astute clinician to find uncommon but very helpful specific urinary features, such as white blood cell casts (suggestive of acute interstitial nephritis), red blood cell casts (suggestive of glomerulonephritis), or crystalluria [3, 9].

It should be noted that urinary analysis is not perfect by any means, and a number of pitfalls exist for the clinician who relies too heavily upon it to diagnose AKI. The most important factor to remember when evaluating fractional excretion of sodium and other solutes is that this is only validated in the oliguric patient; in patients who are non-oliguria, these parameters are not very specific. Moreover, patients with underlying heart failure or cirrhosis will often have prerenal-appearing indices even in the setting of ATN. Urine which is allowed to sit for a prolonged period of time may have findings such as casts or eosinophils degrade; ideally, urine samples

should be collected from the freshest sample available (i.e., the urine furthest up in the urinary catheter, not the urine in the collecting bag!).

Ultrasound is the initial imaging modality of choice to evaluate AKI; not only is ultrasound able to visualize the kidneys and bladder well, it is noninvasive and can be obtained rapidly in most situations. While the chief utility of ultrasound in AKI is excluding obstructive uropathy as a cause, with a sensitivity of over 90%, it often is able to identify the presence of significant CKD as well through characterization of renal parenchyma. In some settings, computed tomography or other imaging modalities may be useful to identify the site of ureteral obstruction [9].

In certain situations, obtaining a kidney biopsy may be of utility in distinguishing certain types of AKI. Most clinical scenarios in which a biopsy may be considered are those where potential treatment changes are thought to justify the risk of performing the procedure. In a group comprised of largely outpatients, kidney biopsy carried 0.9% of a risk for bleeding, and 0.6% of patients needed angiographic intervention; this risk would be expected to be higher for biopsies in AKI [59]. Thus, in scenarios where a biopsy is unlikely to yield additional information – e.g., when AKI is likely due to ATN from shock or hypoxic injury – biopsy is largely avoided. Similarly, kidney biopsy is rarely performed when patients have thrombocytopenia, as this may increase bleeding risk over tenfold from average [60, 61]. When a patient’s presentation is suggestive of glomerular disease (proteinuria, hematuria) or AKI due to an unknown cause without clear reason to consider ATN, kidney biopsy may be worth considering.

Complications of AKI

In the setting of AKI, inability to excrete fluid and electrolytes and maintain acid–base balance may lead to volume overload, dangerous electrolyte derangements such as hyperkalemia and severe acidemia. Complications of isolated AKI arise slowly, over the course of days; however, as AKI often occurs in the context of multiorgan failure, loss of kidney function may exacerbate

electrolyte, acid–base, and volume disorders that arise from poisoning or the treatment of the poisoned patient.

The most dangerous electrolyte abnormality that may arise in AKI is usually hyperkalemia. Severely elevated potassium levels may lead to decreased inotropy and chronotropy, followed by fatal arrhythmias [62]. Hyperkalemia may be more likely to occur in patients who have AKI with concomitant processes that raise potassium levels, such as rhabdomyolysis or Na–K ATPase blockade. Mineral acidosis – aka non-anion gap acidosis – leads to hyperkalemia through intracellular buffering of acid through hydrogen–potassium antiports on red blood cells and various tissues [62]. It should be noted that this process does not occur to a great extent in lactic acidosis; lactic acid crosses cell membranes directly, decreasing the activity of the hydrogen–potassium antiport [63].

Other electrolyte disorders that may arise secondary to AKI include hyponatremia, hyperphosphatemia, and hypocalcemia; unlike hyperkalemia, these rarely produce life-threatening effects in the context of AKI [9, 62].

When kidney failure occurs, normal acid excretion mechanisms are not able to excrete the amount of acid generated each day, and non-gap acidosis (from lack of acid excretion) as well as an anion gap acidosis (from uremic toxins) develop over time. In poisoning with multiorgan failure causing lactic acidosis or in poisonings with other causes of acidosis (e.g., ethylene glycol ingestion), AKI may compound acidemia by removing normal mechanisms of toxin removal. If AKI occurs over a prolonged period of time, other complications usually seen in CKD may develop to an extent, such as anemia [3, 9].

Uremia – literally “urine in the blood” – is a constellation of symptoms and clinical effects that occur in the context of inability to excrete a variety of metabolites termed “uremic toxins.” These toxins include small molecules as well as small- and medium-sized proteins. Early symptoms of uremia include poor appetite, abnormal taste in the mouth, fatigue, and difficulty concentrating. Severe symptoms, usually arising after a prolonged period of reduced renal function,

include encephalopathy, seizures, abnormal bleeding, neuropathy, and pericarditis [9]. Bleeding from uremia is related to platelet dysfunction and reduced clotting factor activity and may not respond well to administration of clotting factors [64]. Pericarditis is typically hemorrhagic and may lead to acute or chronic cardiac tamponade. Unlike hyperkalemia and acidemia, which often may be mitigated before hemodialysis can occur, severe manifestations of uremia often respond less well to medical therapy other than urgent hemodialysis [3, 9].

A number of poisonings are treated by rapid intravenous fluid administration; in these cases, AKI may lead to volume overload, complicating patient management. This may lead to particularly difficult problems in the setting of toxin-induced cardiogenic shock, where development of pulmonary edema may be accelerated due to decreased inotropy. Volume overload in the setting of AKI usually necessitates dialysis; as some patients may respond to diuretic therapy, this is a reasonable intervention to attempt as long as hemodialysis is not delayed when clinically necessary [3].

When the kidneys are a major route through which a toxin or drug is excreted, AKI may worsen toxicity through greater periods of high toxin concentration; prominent examples of this include methotrexate, salicylate, and lithium poisoning, among others [65–67]. In cases of crystalluria-induced AKI, this may lead to a vicious circle where AKI leads to prolonged drug retention in renal tubules, leading to increased drug precipitation and worsened AKI [48].

Management of Acute Kidney Injury

Supportive care is the cornerstone of management of AKI. In general, the goals of AKI management are to identify and reverse any underlying cause (s), mitigate further deterioration of renal function, treat complications such as electrolyte disorders and volume overload (including consideration of renal replacement therapy), and provide general supportive care to the patient [3].

Hypovolemic prerenal failure should be treated with adequate volume resuscitation. There is little benefit to colloid over crystalloid solutions in most clinical scenarios, although intravenous albumin has a clear role in managing AKI in patients with substantial liver failure [3]. Discontinuing or minimizing drugs likely to cause renal vasoconstriction is recommended, although not always feasible (e.g., discontinuation of tacrolimus in a new heart transplant patient). Prerenal failure due to poisonings which affect renal hemodynamics, such as NSAIDs, usually responds to intravenous fluid resuscitation alone. In settings where renal hemodynamics were profoundly affected and ischemic ATN is present, however, care should be taken to avoid excess volume resuscitation, as this may lead to poorer outcomes [3, 68]. In overdose settings where prerenal failure is due to cardiorenal syndrome, hemodynamics should be optimized; this may require the use of inotropes and/or invasive monitoring [21, 22].

When ischemic or toxic ATN is present, the kidney will have reduced metabolic capacity to deal with further injury, and care should focus upon avoiding further events which could compound AKI. Whenever possible, nephrotoxic drugs should be withheld or minimized. Even if ischemic ATN was not the cause of renal failure, in the setting of AKI, the kidney's ability to carry out normal autoregulation is compromised; adequate mean arterial pressures (usually 65 mmHg, sometimes higher) should be maintained as necessary [3, 9, 24].

Development of AKI from pigment nephropathy in rhabdomyolysis is best avoided through administration of aggressive isotonic fluids to increase urinary output and thus heme breakdown product formation [9]. While risk-scoring systems have been developed to estimate the risk of need for dialysis, there is little evidence to suggest that other therapies besides intravenous fluids are of utility. A single review of rhabdomyolysis in patients with trauma ICU admissions found a statistically nonsignificant ($p < 0.09$) trend toward benefit in administration of sodium bicarbonate and mannitol in patients with creatine kinase levels greater than 30,000 units/L; no

randomized trials for bicarbonate versus isotonic saline exist [45].

Drug-induced vasculitic disease, glomerulonephritis, and thrombotic microangiopathies are often treated in much the same way as their counterparts not caused by drugs. Few studies exist to guide the clinician with a rare case of drug or toxin-induced vasculitis; in addition to discontinuing the suspected agent, immunosuppression is often worth considering as the pathophysiology of such diseases is not well understood. While plasma exchange is a consideration for drug-induced thrombotic microangiopathies, most of the available data suggests against the use of this modality due to lack of evidence of efficacy [69].

The major goals of treatment of crystal-induced AKI are to flush out any existing crystals and reduce the likelihood of further crystal formation. Often, AKI from crystalluria may be avoided or mitigated by providing high urinary flow through extensive intravenous fluid administration along with drug usage. After AKI has occurred, this approach may still be of utility, although careful monitoring to avoid volume overload is often necessary. Depending on the drug or toxin (e.g., methotrexate), urinary alkalinization may be of utility [48].

Acute interstitial nephritis is primarily treated by removing the drug thought to be causative. There is evidence both for and against the use of corticosteroids to decrease the inflammatory process, with mixed results from studies; the best available data seems to suggest that if steroids are initiated, they should be initiated as soon as possible and tapered over at least 2 weeks (if not 4–6 weeks) [9, 70, 71].

Postrenal failure is treated by relief of the obstruction; depending on the nature and location of the urinary obstruction, this may involve the use of a urinary catheter, suprapubic catheter, ureteral stent, and/or nephrostomy tube [3, 9, 24]. For short-lived bladder obstructions as caused by anticholinergic medications or opioids, a temporary urinary catheter is usually sufficient.

Complications of AKI, such as volume overload and electrolyte imbalances, may be dealt with either medically or via the use of renal

replacement therapy. Diuretic therapy has been demonstrated to not greatly affect the outcome of AKI, although a patient's response to diuretic therapy may predict whether RRT will ultimately be needed [72]. Indications for renal replacement therapy are abbreviated by the acronym "AEIOU" – acidosis, electrolyte imbalance, intoxication, volume overload, and uremia refractory to medical management. Methods of renal replacement therapy available for the patient with AKI include hemodialysis (HD), continuous renal replacement therapy (CRRT), and in some locations (largely outside of the United States) peritoneal dialysis (PD). All three therapies act through the processes of diffusion (movement of solutes from high to low concentration), convection (passive "solvent drag" of solutes along with movement of water), and ultrafiltration (movement of fluid driven by a pressure gradient) to remove toxins, restore electrolyte balance, and remove excessive fluid volume. Acute peritoneal dialysis is generally not chosen for management of AKI except in special circumstances (e.g., developing countries where hemodialysis is unavailable, infants and children too small to undergo CRRT) [3, 9].

No clinical trial has ever evaluated the utility of acute hemodialysis for life-threatening complications of AKI; however, hemodialysis is widely used for patients who have or are reasonably expected to develop if untreated with dialysis, severe complications of AKI. While hemodialysis is commonly employed for noncritically ill patients with AKI, either HD or CRRT may be employed for patients with shock or other critical illness [3].

The literature concerning choice of HD versus CRRT in critically ill patients with AKI does not show benefit for one therapy versus another; however, this literature is generally derived from treatment of patients with postsurgical or septic shock rather than acutely poisoned patients. In many settings where both therapies are available, CRRT is commonly chosen for management of patients with shock due to the ability to perform slow volume removal, which is often better tolerated by patients due to reduced hypotension [3]. Similarly, patients treated with CRRT for AKI in the setting of shock generally have a reduced need for vasopressors [3, 9, 73].

For patients without shock due to poisoning who do not require extracorporeal toxin removal, CRRT and SLED (slow low-efficiency dialysis, which is performed using an HD machine) are both appropriate therapies [74]. When patients have AKI without shock, hemodialysis and CRRT are appropriate therapies; in this setting, hemodialysis is commonly performed [3].

In settings where extracorporeal removal of toxins is needed in addition to renal replacement therapy, strong consideration of HD should be given (even in the setting of shock) due to its greater ability to remove toxins quickly. At maximal settings, the ability of HD to remove toxins is several times greater than CRRT for most toxins [66, 67]. Similarly, renal replacement therapy should be instituted in a timely manner when appropriate to limit the risk of patient decompensation [66]. Often, from time of initial contact of the nephrologist to the start of hemodialysis takes several hours even in emergent situations; in settings where this speed can be reduced due to systems in place that allow for rapid catheter placement and immediate preparation of the dialysis machine, it is very likely that this process will still take over an hour. Thus, early consultation of a nephrologist in situations where extracorporeal therapy may be required for supportive care and/or drug removal is of paramount importance.

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The central nervous system (CNS), with its large lipid content and extensive blood supply, is often the target organ of drugs or toxins (toxicants). Signs resulting from chemical effects on the CNS frequently include mental status changes often progressing to coma. Coma may be due to direct toxic effects, metabolic abnormalities, or anoxia. A review of the final diagnosis of 500 patients hospitalized with “coma of unknown etiology” found that 149 (30%) were due to the adverse effects of drugs, with metabolic disorders accounting for 35% of cases [1].

Pathophysiology

Alterations in consciousness can be classified into several categories. *Lethargy* (or somnolence) denotes an inability to maintain the wakeful state without external stimulation, whereas *stupor* is defined as arousability only in response to a vigorous or noxious stimulus. Arousal usually does not outlast the stimulus application. *Obtundation* implies a patient who is aroused by loud speech or gentle shaking but appears to be confused upon arousal. *Delirium*, or acute cortical–subcortical neuronal encephalopathy, is a fluctuating condition characterized by confusion, irritability, and disorientation that develop over a short period. The mental status end point of impaired consciousness is *coma* (unresponsiveness that is not arousable by any stimulus). Seizures may occur at any point. Substance intoxication and withdrawal

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are common causes of delirium and can cause seizures or coma. Mental status changes due to drugs or toxins usually are characterized by three tenets: (1) a strong dose–response relationship, (2) occurrence either at the time of exposure or after a short latent period, and (3) neurological improvement after cessation of exposure, unless a secondary process, such as the effect of prolonged hypoxia or seizures, supervenes [2].

Disturbances in consciousness leading to coma directly due to drugs or toxins usually are due to the suppression of activity in the neurons located in the reticular activating system of the upper brainstem and throughout the cerebral cortex. The reticular activating system is interspersed through paramedian regions of the rostral pontine and midbrain tegmentum, in the thalamus and the midbrain [3]. Although damage to the dominant (language-producing) cerebral hemisphere can produce temporary coma, prolonged coma due to a toxic insult implies bilateral (global) hemispheric or midbrain (through the reticular activating system) involvement. Alteration in consciousness may result from direct effect of the toxicant on the neuronal membranes of the reticular activating system or cerebral cortex (e.g., ethanol and general anesthetics).

Drugs or toxins (e.g., organophosphate agents, nicotine, or barbiturates) may also interact with neuroreceptors and neurotransmitters [3]. Examples include the enhancement of γ -aminobutyric acid (GABA) inhibitory influences on presynaptic and postsynaptic receptors, resulting in the opening of neuronal chloride channels. The resulting influx of chloride ions increases the negative resting potential, causing hyperpolarization, which stabilizes the nerve membrane and reduces neuronal firing rate [4–6]. Other drugs (e.g., benzodiazepines) increase the intracellular flux of chloride ions by enhancing GABA binding to other (GABA_A receptors) neuroreceptor sites and by unmasking high-affinity GABA receptors [6]. Table 1 and Fig. 1 present neurotoxic agents and their targets for disruption of neurosynaptic transmission. Metabolic neuronal disturbances (due to factors such as concomitant hypoxia, hyperkalemia, hypokalemia, acidosis, or vitamin deficiencies) are an additional mechanism for

Table 1 Cellular targets and potentially neurotoxic agents

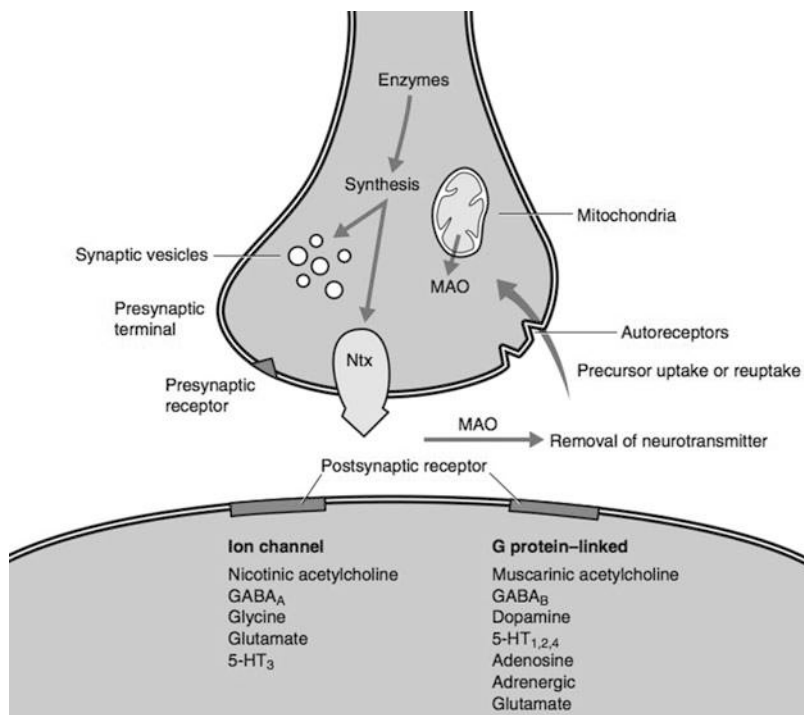
Acetylcholine	Aminopyridines, Black widow spider venom, botulinum toxin, crotoalid and elapid venom
Acetylcholinesterase	Physostigmine, edrophonium, carbamate insecticides, organophosphates
Adenosine receptors	Adenosine, caffeine, carbamazepine, TCAs, indomethacin
α -Adrenergic receptors	Dobutamine, phenylephrine, clozapine, ergot alkaloids, terazosin, olanzapine, clonidine, guanfacine, dexmedetomidine
β -Adrenergic receptors	Epinephrine, norepinephrine, albuterol, ritodrine, beta-blockers
Calcium ion channel	Calcium channel blockers, calciseptine (black mamba snake) conotoxins (cone snails), agatoxin (North American funnel web spider), octanol, flunarizine
Cannabinoid receptor	Marijuana, JWH-018
Dopamine receptors	Apomorphine, bromocriptine, antipsychotic drugs
GABA receptors	Benzodiazepines, zopiclone, zolpidem, zaleplon, vigabatrin, barbiturates, ethanol, penicillin, muscimol (<i>Amanita muscaria</i>), bicuculline, neuroactive steroids (alphaxalone), flumazenil, baclofen

GABA γ -aminobutyric acid, *LSD* lysergic acid diethylamide, *MAO* monoamine oxidase, *NDMA* *N*-methyl-D-aspartate, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

impaired consciousness. Hypoglycemia (serum glucose <40 mg/dL [2.2 mmol/L]) can result in cerebral cortex or brainstem dysfunction or both, occasionally also causing focal neurologic deficits.

An additional mechanism for coma production involves cerebral nitric oxide production through the enzyme nitric oxide synthase, which is involved in *N*-methyl-D-aspartate receptor activation. Neurodegeneration attributable to nitric oxide production is due to a peroxynitrite-induced oxidant stress, leading to endothelial damage in cerebral blood vessels, reversal of platelet aggregation, and cerebellar synaptic depression. This

Fig. 1 Schematic representation of a synapse showing the principal structures and sites of drug action. This synapse is a hybrid for the purpose of visualization; as outlined in the text, a neuron is typically highly specialized for a specific neurotransmitter system. *GABA* γ -aminobutyric acid, *5-HT* 5-hydroxytryptamine, *MAO* monoamine oxidase, *Ntx* neurotransmitter (From Burkhart and Akhtar [7])



mechanism is probably involved in the mediation of carbon monoxide, glutamate, sodium nitrite, and paraquat toxicity. Other toxins involved in *N*-methyl-D-aspartate receptor activity include domoic acid and acute ethanol withdrawal.

Delirium can be caused by virtually any drug, but it is especially noted with anticholinergic drugs (Table 2). It can be considered as a disorder of neurotransmission in the cortical and subcortical regions of the brain involving acetylcholine, dopamine, GABA, and serotonin [8–10].

Clinical Characteristics

Delirium may be hypoactive, with inattention and decreased activity, or hyperactive, characterized by agitation and combativeness. It is a disorder of attention and arousal and can be detected easily using the confusion assessment method. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [11], criteria specify three aspects of the clinical characteristics of delirium: (1) onset within hours or days, with fluctuation

during the course of the day and usually worse at night, (2) cognition change (disorientation, memory deficit, or language disturbance), and (3) disturbance of consciousness with a reduction of ability to focus, sustain, or shift attention. After recovery, the patient usually is amnesic about the delirium episode.

The general clinical characteristics of coma due to an acute toxic cause are an absence of meningeal irritation and a lack of focal neurologic signs (unless hypoglycemia is involved). Usually no discrete morphologic causative lesion can be detected on neuroimaging. In the absence of seizures, the patient often progresses to coma through varying stages of lethargy, confusion, and stupor with these stages often noted on reemergence from the comatose state. Deep tendon reflexes and oculocephalic and oculovestibular reactions are also usually preserved except in intoxications involving sedative-hypnotics and anticonvulsant agents. Agents causing prolonged coma (possibly lasting for >100 h) with intermittent periods of arousal are usually drugs that undergo enterohepatic or

Table 2 Toxic causes of delirium

Medicinal agents
Acyclovir
Aldesleukin
Alfentanil
Alprazolam
Aminophylline
Amiodarone
Amitriptyline
Amoxapine
Amphotericin B
Atropine
Belladonna
Benztropine
Buprenorphine
Bupropion
Butorphanol
Butriptyline
Caffeine
Camphor
Cantharidin
Carbamazepine
Chloral hydrate
Chlorpheniramine
Chlorpromazine
Choline magnesium trisalicylate
Cimetidine
Ciprofloxacin
Clomipramine
Clonidine
Clozapine
Cocaine
Codeine
Colchicine
Cortisone acetate
Cyclobenzaprine
Cycloserine
Cyclosporine
Desipramine
Dextroamphetamine
Dibenzepin
Dicyclomine
Digitoxin
Digoxin
Diphenhydramine
Doxepin
Drug withdrawal
Ergotamine
Estazolam
Ethchlorvynol

*(continued)***Table 2** (continued)

Ethyl alcohol
Famotidine
Fentanyl
Flumazenil
Fluorouracil
Fluoxetine
Fluphenazine
Glutethimide
Heroin
Hydrocodone
Hydrocortisone
Hydromorphone
Hydroquinone
Hydroxyzine
Hyoscyamine
Imipramine
Interferon alfa-2a
Interferon alfa-2b
Interferon alfa-n3
Interferon beta-1b
Interferon gamma-1b
Ipratropium
Isocarboxazid
Ketamine
Levodopa
Levomethadyl acetate HCl
Levorphanol
Lidocaine
Lithium
Loperamide
Maprotiline
Mefloquine
Meperidine
Mephentermine
Mesoridazine
Methadone
Methamphetamine
Methohexital
Methotrexate
Methyl salicylate
Methyldopa
Metoclopramide
Mianserin
Midazolam
Morphine sulfate
Nalbuphine
Niacin
Nitroprusside
Nizatidine

(continued)

Table 2 (continued)

Nortriptyline
Opium alkaloids
Opium tincture
Oxycodone
Oxymorphone
Para-aminosalicylate
Paraldehyde
Paregoric
Paroxetine
Pentazocine
Pentobarbital
Perphenazine
Phencyclidine
Phenelzine
Phenobarbital
Phenylephrine
Phenytoin
Prazepam
Prednisolone
Procarbazine
Prochlorperazine
Promazine
Promethazine
Propoxyphene
Protriptyline
Quinidine
Ranitidine hydrochloride
Rifampin
Salicylate
Salsalate
Scopolamine
Secobarbital
Serotonin syndrome
Sertraline
Sodium fluoride
Sparfloxacin
Stanozolol
Sufentanil
Tacrolimus
Theophylline
Thioridazine
Thiothixene
Tocainide
Tramadol
Tranylcypromine
Trazodone
Triamcinolone
Trifluoperazine
Triflupromazine

(continued)

Table 2 (continued)

Trimethaphan camsylate
Trimipramine
Valacyclovir
Venlafaxine
Vigabatrin
Vinorelbine
Vitamin A
Zolpidem
Nonmedicinal agents
2-Propanol
Arsenic
Benzene
Bromates
Carbon dioxide
Carbon tetrachloride
Dichlorodiphenyltrichloroethane (DDT)
Diethyltoluamide (DEET)
Ethylene dichloride
Gasoline
Lead
Lysergic acid diethylamide (LSD)
Mercury
Nerve gases
Nickel carbonyl
Nitrous oxide
Tetrachloroethane
Thallium sulfate
Toluene
Triethyltin
Biologic agents
Angel's trumpet
Black nightshade
Boxthorn
Cathinone
Chicken soup
Christmas cherry
<i>Claviceps purpurea</i>
Daphne
Deadly nightshade
Foxglove
Jimsonweed
Lantana
Marijuana (cannabis)
Morning glory
Mushrooms (monomethylhydrazines, cholinergic, anticholinergic, psychedelic)
Oleander
Pennyroyal oil
Potato (leaves, stems, tubercles)

(continued)

Table 2 (continued)

Sand brier
Scorpion fish
Stonefish
Turkey fish
Woody nightshade
Wormwood

Table 3 Drugs that can cause cyclic coma

Barbiturates	Glutethimide
Carbamazepine	Meprobamate
Clonazepam	Olanzapine
Ethchlorvynol	Quetiapine

enteroenteric recirculation of their active metabolites, resulting in cyclic coma (Table 3).

Ancillary clinical signs are essential in determination of the toxic etiology. An adequate ocular examination is crucial [12]. The salient feature of the ocular examination can be divided into three categories: pupillary size, pupillary reactivity, and assessment of the presence of nystagmus.

The pupillary size represents a constant balance between the autonomically innervated sphincter pupillae and the radially arranged dilator muscle of the iris. In toxic cases, the pupillary size is generally symmetrical, although 20% of normal individuals exhibit up to 0.5 mm of asymmetry [3]. Tables 4 and 5 list agents that may cause miosis (pupils <2 mm) and mydriasis (pupils >4 mm) [13]. Pupil size can be variable in drug toxicity, however, due to multiple conflicting neurotransmitter responses in critical illness, and also polydrug ingestion of drugs with competing pupillary activity is not a consistently reliable diagnostic finding [14].

The pupillary light reflex is usually spared in coma of toxic origin; however, there are some exceptions. High-dose barbiturate poisoning and opiates can result in fixed miosis, whereas anticholinergic agents can cause fixed mydriasis that may not be reversible with physostigmine. Other causes of midrange-to-large, fixed pupils include methanol toxicity, hypothermia, and hypoxia [3].

Drug-induced nystagmus (involuntary rhythmic eye movement) commonly results in “jerk nystagmus.” In jerk nystagmus, the eye movements alternate between the slow component of initial (or induced) movement and the fast corrective component (jerk) in the opposite direction. Common causes for horizontal nystagmus include alcohol, anticonvulsants, sedative–hypnotics, solvents, and quinine. Lithium may cause downbeat nystagmus [15]. Phencyclidine, dextromethorphan, phenytoin, and sedative–hypnotics may cause a combination of vertical, horizontal, and rotary nystagmus. Sedative–hypnotics may cause disconjugate gaze. Opsoclonus (rapid, conjugate eye oscillations worsened by voluntary movement) may be caused by intoxication with antidepressants, anticonvulsants, organophosphates, thallium, lithium, and haloperidol. Periodic gaze disturbances (“ping-pong” gaze) have been described with monoamine oxidase inhibitor intoxication [16]. Anoxic coma causing cortical dysfunction can result in a cyclic downward dipping motion of the eyes (ocular dipping) [17].

Several agents can cause intracranial hypertension (pseudotumor cerebri) (Table 6). While most cases are limited to single case reports (i.e., phenytoin, indomethacin, danazol), the vitamin A derivatives (including topical formulations) have been particularly associated as causes [18].

Posterior reversible encephalopathy syndrome (PRES) is a recently described entity that causes cortical visual loss, visual field defects, seizures, and mental status changes. Several conditions are associated with PRES, including hypertensive crisis, hepatic encephalopathy, and eclampsia; toxic responses to medications are described in Table 7 [18].

The nature of the respiratory response is a valuable clinical clue to ascertain a toxicologic cause in the patient with altered mental status. Slow, regular breathing (usually at a rate <12 breaths/min) indicates an opiate or sedative–hypnotic toxicity. These drugs inhibit the pontine and medullary respiratory centers, resulting in diminished responsiveness of these centers to increases in carbon dioxide tension [18, 19]. Alternatively, sympathomimetic agents directly stimulate these respiratory centers, resulting in tachypnea with increased tidal

Table 4 Drugs and toxins causing miosis

Medicinal agents
Aceclidine
Alfentanil
Ambenonium
Bethanechol
Bunazosin
Bupivacaine
Buprenorphine
Buspirone
Caffeine
Chloral hydrate
Chlorpromazine
Clonidine
Codeine
Dextromethorphan
Dezocine
Dihydroergotamine
Distigmine
Edrophonium
Fentanyl
Fluroxamine
Guanabenz
Guanidine
Heroin
Hydromorphone
Hydrocodone
Levomethadyl acetate HClide
Levorphanol
Lidocaine
Loperamide
Melperone
Meperidine
Meprobamate
Meptazinol
Methadone
Methyprylon
Morphine sulfate
Nalbuphine
Neostigmine
Nicotine
Nilutamide
Opium alkaloids (ides)
Opium tincture
Oxycodone
Oxymorphone
Paregoric
Pentazocine
Phencyclidine
Phenobarbital

(continued)

Table 4 (continued)

Phenylephrine
Phenoxybenzamine
Physostigmine
Pilocarpine
Piritramide
Procaine
Propoxyphene
Pyridostigmine
<i>Rauwolfia serpentina</i>
Reserpine
Risperidone
Tetracaine
Tilidine
Tramadol
Valproic acid s
Xylazine
Zolpidem
Nonmedicinal agents
2,4-Dichlorophenoxyacetic acid
2-Methyl-4-chlorophenoxyacetic acid
Aldicarb
Amitraz
Bromoform
Bromophos
Carbamates
Carbaryl
<i>Chenopodium oils</i>
Chlorfenvinphos
Chlorpyrifos
Coumaphos
Diazinon
Dichlorvos
Dicrotophos
Dioxathion
Disulfoton
Endosulfan
Ethion
Fensulfothion
Fenthion
Isofenphos
Malathion
Methidathion
Methiocarb
Methomyl
Mevinphos
Nerve gases
Organophosphates
Parthion
Profenofos

(continued)

Table 4 (continued)

Propoxur
Terbufos
Tetraethyl pyrophosphate
Biologic agents
Betel nut
Castor bean
Eucalyptus oil
Fire-bellied toad
Mushrooms, cholinergic
Nutmeg
Poison hemlock
Poison lily
Tetrodotoxin

volume [3]. Kussmaul respirations (rapid, regular respirations with large tidal volumes) are usually related to metabolic acidosis. Another typical respiratory pattern due to acute intoxication is Cheyne–Stokes respiration. This pattern is characterized by periods of hyperpnea that regularly alternate with a shorter period of apnea. This abnormal pattern is due to neuronal metabolic disturbances, which isolate the respiratory center in the brainstem from the cerebral cortex. Pulmonary complications, such as acute respiratory distress syndrome (e.g., caused by salicylates, opioids, cyclic antidepressants, sedative–hypnotics) and aspiration pneumonitis, are indirect consequences of toxin-induced coma. Aspiration pneumonitis occurs in approximately 10% of patients hospitalized after a drug overdose and more frequently when mental status is depressed [20].

Cranial nerve dysfunction may be observed in patients with toxin-induced impaired consciousness (Table 8). Examples include trichloroethylene causing trigeminal nerve sensory neuropathy and organophosphate exposure involving multiple cranial nerves. These cranial neuropathies are usually bilateral. Nonspecific neurologic signs, such as asterixis, fasciculation, and myoclonus, are associated with toxic delirium and are not caused by psychiatric conditions mimicking delirium (see Table 2) [21–23]. Motor response to noxious stimuli is symmetric and nonfocal. Anticholinergic medications are associated specifically with an increase in delirium incidence and severity in elderly patients [24]. This

increase is thought to be due to the frequency of anticholinergic drug prescribing in the elderly, age-related decrease in cholinergic neurotransmission, pharmacodynamic changes in cholinergic receptor sensitivity, and deficient drug metabolism and elimination [25]. Antibiotics reported to cause a toxic encephalopathy and/or toxic psychosis include the beta-lactams, cephalosporins (which can cause triphasic waves on the electroencephalogram), trimethoprim–sulfamethoxazole, quinolones, and linezolid [26].

Laboratory Studies

Diagnostic modalities used to determine the cause of altered mental status usually are focused on serum analysis rather than on acute neuroimaging studies. Any toxic cause of high anion gap metabolic acidosis requires investigation. The presence of a decreased anion gap suggests lithium or bromide exposure. The presence of an osmolar gap usually indicates ethanol, isopropanol, methanol, or ethylene glycol poisoning, diabetic ketoacidosis, sepsis, or alcoholic ketoacidosis. Pure respiratory acidosis is consistent with hypoventilation, a clue to possible intoxication with sedative–hypnotics or opioids. Although urinary immunoassay results may provide a clue to the cause of altered consciousness, they often yield misleading false-positive and false-negative results. Serum concentrations of specific drugs can be diagnostic and are more useful if available (Table 9). Tricyclic antidepressant intoxication can lead to electrocardiographic abnormalities, dysrhythmias, and seizures (described in chapter on tricyclic antidepressants). Patients with QRS interval prolongation greater than 0.1 s with QRS axis shifted to the right (as is the axis in the terminal 40 ms of the QRS interval) may be at risk for neurologic complications [27]. This is seen most easily as a terminal R wave in lead AVR. For this reason, a screening electrocardiogram often is used in the initial assessment of patients with coma or seizures. Hair testing for the presence of drugs provides only qualitative interpretation, is fraught with technical

Table 5 Toxicants typically causing mydriasis

Medicinal agents
Acetaminophen
Acetophenazine
Amisulpride
Amitriptyline
Anisotropine
Apraclonidine
Atropine
Azatadine
Belladonna
Benztropine
Biperiden
Botulinum toxin type A
Bretylum
Bromides
Brompheniramine
Bucizine
Budipine
Buflomedil
Bupropion
Butriptyline
Butylscopolamine
Camphor
Carbamazepine
Carbinoxamine
Chlormezanone
Chlorprocaine
Chlorpheniramine
Chlorphenoxamine
Chlorpromazine
Chlorprothixene
Cimetidine
Clidinium
Clozapine
Cocaine
Cyclizine
Cyclobenzaprine
Cyproheptadine
Desipramine
Diazepam
Dibenzepin
Dicyclomine
Diethylpropion
Dimenhydrinate
Diphenhydramine
Disopyramide
Disulfiram
Dopamine
Doxapram

(continued)

Table 5 (continued)

Doxepin
Doxylamine
Ephedrine
Estazolam
Ethchlorvynol
Ethyl alcohol
Fenfluramine
Fluoxetine
Flurazepam
Fosphenytoin
Glutethimide
Glycopyrrolate
Homatropine
Hyoscyamine
Imipramine
Ipratropium
Isocarboxazid
Isopropamide
Ivermectin
Lidocaine
Mecamylamine
Meclizine
Melperone
Meperidine
Meprobamate
Methamphetamine
Methantheline
Methscopolamine
Midazolam
Naphazoline
Nicotine
Nortriptyline
Opiate withdrawal
Otilonium
Oxybutynin
Papaverine
Paroxetine
Pemoline
Pentoxifylline
Phencyclidine
Phenelzine
Pheniramine
Phentermine
Phenylephrine
Phenylpropanolamine
Phenytoin
Pizotylline
Pralidoxime
Procaine

(continued)

Table 5 (continued)

Procyclidine
Promethazine
Proparacaine
Propranolol
Protriptyline
Pseudoephedrine
Quinidine
Quinine
Reserpine
Scopolamine
Sertraline
Sodium fluoride
Tetrahydrozoline
Thioridazine
Thyroid
Tolazoline
Tridihexethyl chloride
Trimeprazine
Trimethaphan camsylate
Trimipramine
Tripelennamine
Trospium
Yohimbine
Zotepine
Nonmedicinal agents
1,2-Dibromoethane
2-Butoxyethanol
3,4-Methylenedioxymeth-amphetamine
Aldcarb
Barium
Benzene
Bromophos
Carbaryl
Carbon monoxide
Chenopodium oils
Chlorfenvinphos
Chloroform
Chloromethane
Chlorpyrifos
Coumaphos
Cyanide
Diazinon
Dichlorvos
Dicrotophos
Dioxathion
Disulfoton
Ethion
Ethylene glycol
Fanthion

(continued)

Table 5 (continued)

Fensulfothion
Heptachlor
Hydrazine
Lysergic acid diethylamide (LSD)
Malathion
Methaldehyde
Methidathion
Methiocarb
Methomyl
Methyl bromide
Methyl ethyl ketone
Mevinphos
Parathion
Pentachlorophenol
Phosdin
Profenofos
Propoxur
Sodium azide
Sodium monofluoroacetate
Terbufos
Tetraethyl pyrophosphate
Thallium
Toluene
Trichloroethylene
Turpentine oil
Biologic agents
Black henbane
Boxthorn
Burdock root
Cathinone
<i>Clostridium botulinum</i>
Corn lily (<i>Veratrum</i>)
English ivy
Ephedra
Golden chain tree
Goldenseal
Horse chestnuts
Jimsonweed
Khat
Lantana
Lupine
Marijuana (cannabis)
Mate
Mescaline
Morning glory
Mushrooms, anticholinergic
Mushrooms, psychedelic
Neurotoxic shellfish poisoning
Nutmeg

(continued)

Table 5 (continued)

Peyote
Sassafras oil
Scotch broom
Tetrodotoxin food poisoning
Tyramine hydrochloride food poisoning
Valerian
Water hemlock
Wild cucumber
Woody nightshade
Yew

Table 6 Drugs and chemicals that can cause intracranial hypertension (pseudotumor cerebri)

Medications
Cycline antibiotic (tetracycline, doxycycline, minocycline)
Corticosteroids
Danazol
Indomethacin
Phenytoin
Somatotropin (human growth hormone)
Vitamin A derivatives (isotretinoin, retinoids)
Nonmedicinal
1, 4-Dioxane
Bromethalin
Cresols
Diethyltoluamide
Ethyl glycol
Lead
Nitrous oxide
Pentaborane
Thallium sulfate
White phosphorus
Biologicals
Cone shells
Margosa oil

difficulties, and offers no utility in the acute investigative causes of coma [28].

The electroencephalogram is useful in assessing cerebral cortical dysfunction and identifying seizure activity. Normal alpha with theta-delta (grade I) activity is compatible with a good prognosis, as is paradoxical monomorphic delta activity, whereas low-voltage delta activity (with alpha coma), alternating patterns, or isoelectric

Table 7 Drugs that can cause posterior reversible encephalopathy syndrome (PRES)

Anti-disialoganglioside (anti-GD2)
Bevacizumab
Carbamazepine
Carboplatin
Ciprofloxacin
Cisplatin
Corticosteroids
Cyclosporin A
Cytarabine
Erythropoietin
Gemcitabine
Granulocyte colony-stimulating factor
Infliximab
Interferon alpha
L-Asparaginase
Linezolid
Methotrexate
Monoclonal antibody immunotherapy
Oxaliplatin/5-fluorouracil/leucovorin
Pazopanib
Sirolimus
Sorafenib
Sunitinib
Tiazofurin
Vincristine

tracing (grades IV or V) is indicative of a poor prognosis [29, 30]. Brainstem auditory evoked potentials correspond with brainstem dysfunction during coma and may be modified by anesthetics and barbiturates [31–35].

Treatment of Patients with Altered Mentation

Respiratory compromise is the primary life threat in most toxic exposures causing alterations of consciousness. Maintenance of airway patency and respiration must be prioritized. Endotracheal intubation may be required, particularly if the patient does not rapidly respond to reversal maneuvers (such as naloxone) [36]. A complete set of vital signs including temperature is mandatory. Supplemental oxygen should be administered if there is a suspicion of hypoxia or carbon

Table 8 Agents causing cranial nerve palsies

Aldicarb
Arizona bark scorpion
Botulinum toxin type A
Bromophos
Carbaryl
Carbon disulfide
Chlorfenvinphos
Diazinon
Demeton-S-methyl
1,1,-Dichloroethane
Dichlorvos
Dicrotophos
Didanosine
Dioxathion
Disulfoton
Ethion
Ethylene glycol
Fensulfothion
Fenthion
Ketoprofen
King cobra venom
Lead
Linezolid
Malathion
Mercury
Methidathion
Methiocarb
Methomyl
Methotrexate
Mevinphos
Parathion
Phosdrin
Pravastatin
Profenofos
Propoxur
Rabies virus
Terbufos
Tetracycline
Tetraethyl pyrophosphate
Toluene
<i>Trichinella spiralis</i> food poisoning
Trichloroethylene
Vincristine

monoxide poisoning. Rapid determination of blood glucose should be performed [37]. If the patient is determined to be hypoglycemic, or if rapid measurement is unavailable, dextrose should be administered [38].

Gastrointestinal decontamination with activated charcoal is of possible benefit in some toxic ingestions, especially if given early after ingestion. Activated charcoal should be administered cautiously, if at all, in non-intubated patients who may have ingested an agent that may cause a decline in the level of consciousness. Multiple dosing of activated charcoal can enhance the elimination of the few drugs listed in Table 3 (except for clonazepam and olazepine). Whole-bowel irrigation with polyethylene glycol may be warranted in ingestions of drug packets or medications not found to bind to activated charcoal, such as lithium or iron tablets [39]. All of these techniques have possible morbidity, however, and none have been shown to alter outcome in poisoned patients. After initial stabilization measures and decontamination, most toxicities may be managed expectantly. If the agent is known, specific antidotal therapy may be indicated (Table 10). Use of a series of agents – a “coma cocktail” – is often employed as a diagnostic and therapeutic strategy in a patient with altered mental status of unknown etiology. Dextrose with thiamine, supplemental oxygen, and naloxone is used widely in this setting. Two other antidotal agents, flumazenil and physostigmine, at one time also were considered components of the coma cocktail. Because of concern over the safety of these agents, however, many authors have discouraged their indiscriminate use in comatose patients with an unknown ingestion [40–43]. Familiarity with these agents, including risks and benefits of their use, is essential.

Opioid Antagonists

Opioids produce alterations in consciousness via interaction with multiple opioid receptors (μ_1 , μ_2 , κ , and δ) located in the CNS. Stimulation of these receptors results in analgesia, euphoria, CNS and respiratory depression, and miosis. Although naloxone and nalmefene are structural analogues of morphine, they possess no agonist activity of their own. When administered, these agents antagonize the effect of opioids by competing for opioid receptor sites. Naloxone is the opioid antagonist

Table 9 Serum levels of specific drugs or toxins that can result in coma

Drug	Conventional units	SI units
Acebutolol	20 mg/L	77.12 μ mol/L
Acetaminophen	300 mg/mL	1984 μ mol/L
Acetone	500 mg/L	8.6 mmol/L
Amitriptyline	2 mg/L	7320 nmol/L
Amobarbital	43 mg/L	190 μ mol/L
Baclofen	1 mg/L	
Barbital	160 mg/L	
Butabital	39 mg/L	
Caffeine	100 mg/L	516 μ mol/L
Calcium	15 mg/dL	3.75 mmol/L
Carbamazepine	18 mg/L	13.77 μ mol/L
Carboxyhemoglobin	30%	
Carisoprodol	30 mg/L	115.2 μ mol/L
Cetirizine	2 mg/L	
Chloral hydrate (trichloroethanol)	20 mg/L	134 μ mol/L
Chlordiazepoxide	20 mg/L	67.2 μ mol/L
Chlormethiazole	7 mg/L	
Chlormezanone	60 mg/L	
Chloroquine	1 mg/L	3.12 μ mol/L
Chlorpromazine	0.5 mg/L	1.57 μ mol/L
Chlorprothixene	0.8 mg/L	
Cimetidine	10 mg/L	
Clonazepam	0.07 mg/L	
Clonidine	2 μ g/L	
Clozapine	2 mg/L	
Codeine	5 mg/L	
Diazepam	20 mg/L	70.24 μ mol/L
Diethyltoluamide (DEET)	50 mg/L	
Digoxin	4 ng/L	5.124 μ mol/L
Dothiepin	1 mg/L	
Doxepin	0.4 mg/L	1431.6 μ mol/L
Ethanol	300 mg/dL	65.13 mmol/L
Ethchlorvynol	50 mg/dL	345.8 μ mol/L
γ -Hydroxybutyrate	100 mg/L	
Glucose	800 mg/dL	44 mmol/L
Glutethimide	10 mg/L	46 μ mol/L
Iron	500 μ g/dL	89.6 μ mol/L
Isoniazid	20 mg/L	145.82 μ mol/L
Lead	100 μ g/mL	4.8 μ mol/L
Lidocaine	5 μ g/mL	21.3 μ mol/L
Lithium	3 mEq/L	3 μ mol/L
Lorazepam	0.3 mg/L	
Loxapine	0.7 mg/L	
Meprobamate	60 mg/L	274.9 μ mol/L
Mephobarbital	40 mg/L	
Methanol	100 mg/dL	31.2 μ mol/L
Methaqualone	8 mg/L	32 μ mol/L
Methemoglobin	20%	

(continued)

Table 9 (continued)

Drug	Conventional units	SI units
Methypyrlyon	50 mg/L	272.9 $\mu\text{mol/L}$
Nomifensine	10 mg/L	
Olanzapine	100 $\mu\text{g/L}$	
Orphenadrine	3 mg/L	
Phenobarbital	65 mg/L	27,950 $\mu\text{mol/L}$
Phenytoin	40 mg/L	160 $\mu\text{mol/L}$
Propoxyphene	1 mg/L	2.946 $\mu\text{mol/L}$
Quetiapine	13 mg/L	
Quinine	12 $\mu\text{g/mL}$	
Salicylates	100 mg/dL	7.24 $\mu\text{mol/L}$
Secobarbital	7 mg/L	
Sodium	160 mEq/dL	
Theophylline	40 mg/L	222 $\mu\text{mol/L}$
Tetrahydrocannabinol	180 $\mu\text{g/L}$	
Toluene	10 mg/L	
Tramadol	2000 $\mu\text{g/L}$	
Tranylcypromine	1 mg/L	
Triazolam	31 $\mu\text{g/L}$	
Valproic acid	500 mg/L	3500 $\mu\text{mol/L}$
Venlafaxine	6 mg/L	
Zopiclone	300 $\mu\text{g/L}$	

Table 10 Agents used to reverse coma or encephalopathy of toxic etiology

Agent	Toxin
Naloxone	Opioids
	Clonidine
	Tetrahydrozoline
	Valproic acid
	Camylofin hydrochloride
Flumazenil	Captopril
	Benzodiazepines
	Zolpidem
	Baclofen
	Carbamazepine
	Chloral hydrate
Oxygen (100% or hyperbaric)	Zopiclone
	Carbon monoxide
Physostigmine	Hydrogen sulfide
	γ -Hydroxybutyrate
	Baclofen
Pyridoxine	Anticholinergic agents
	Isoniazid
Methylene blue	Hydrazine

(continued)

Table 10 (continued)

Agent	Toxin
Dextrose	Ifosfamide
Cyanide antidote kits or hydroxocobalamin	Hypoglycemic agents
Sodium thiosulfate	Cyanide
	Nitroprusside

most frequently used in the prehospital, emergency department, or postanesthesia setting. Its administration is indicated in patients with coma of suspected toxic etiology, particularly when signs of opioid intoxication (e.g., miosis, hypoventilation) are present. The use of opioid antagonists is discussed in detail in the chapter on opioids. Their clinical pharmacology is described in ► [Chap. 157, “Opioid Receptor Antagonists.”](#)

Several clinicians have reported a clinical response to naloxone in patients with various nonopioid drug intoxications. Improvement in mental status after naloxone has been reported in the setting of ethanol, clonidine and related

imidazolines, valproate, and possibly even ibuprofen overdose [44–48]. The mechanism of this effect is unclear, but it is theorized that these agents have some degree of activity at the μ receptor. In clinical practice, however, response to naloxone with these overdoses has proved inconsistent, suggesting that in some cases the true mechanism may be one of coincidence, concomitant therapy, or nonspecific arousal.

Dosing practices for naloxone vary widely. An initial dose of 0.4–2.0 mg (0.01 mg/kg in pediatric patients) intravenously generally is recommended, although higher doses (10 mg) are needed in some cases [49, 50]. The therapeutic index of naloxone is remarkable; 4 mg/kg has been administered to volunteers without adverse effect [51]. Use of this agent is not totally without risk, however. Precipitation of withdrawal can be a significant obstacle to patient management. If opioid dependency is suspected, a lower starting dose (0.1–0.2 mg) should be used to minimize the risk of this complication [49]. Seizures also have been reported rarely [49]. Although intravenous infusion is the most common route of administration, naloxone is also effective when given subcutaneously, intramuscularly, endotracheally, or nebulized [52]. In fact, naloxone (both injectable and intranasal) is being increasingly utilized in the prehospital setting by non-health-care personnel [53]. Onset of action occurs in 1–2 min.

The elimination half-life of naloxone is 60–90 min, resulting in a duration of effect that may not extend beyond the duration of opioid toxicity. Naloxone-responsive patients must be monitored carefully because rebolus of naloxone may be required. In cases of intoxication with long-acting opioids (methadone, levomethadyl acetate), an option is to use a continuous naloxone infusion. One protocol recommends that two thirds of the response dose should be infused hourly [49]. A naloxone infusion always should be titrated to the desired clinical effect, however.

Nalmefene is a derivative of the opioid antagonist naltrexone, which differs in activity from naxolone only in its longer duration of action. The half-life of nalmefene after intravenous administration is 11 h [54]. The typically recommended dose is 0.5–1.0 mg/70 kg body

weight intravenously. In opioid-naïve patients, 0.5 mg/70 kg body weight can be given intravenously as an initial dose, followed 2–5 min later by a second dose of 1 mg/70 kg body weight, if needed. Doses over 1.5 mg/70 kg body weight are unlikely to be of further benefit. Clinical response is expected within 5 min. Although nalmefene administration may be advantageous in the setting of toxicity from a long-acting opioid, special consideration must be given to the disadvantages of routine use of this agent. Opioid withdrawal produced by nalmefene is protracted compared with naloxone [55, 56]. Additionally, emergency department discharge of substance abusers who are treated with nalmefene for opioid abuse is theoretically dangerous because the antagonist's persistent effects may compel the individual to use higher doses of illicit opioid to overcome the effect. If possible, diagnostic trials should be done with naloxone. If naloxone is unavailable, low-dose nalmefene (e.g., 1 mg) may be considered. Finally, substance abusers who receive nalmefene in the emergency department should be admitted for observation [55].

Flumazenil

The benzodiazepine receptor antagonist flumazenil may be useful for reversal of benzodiazepine-induced sedation after general anesthesia, procedural sedation, or overdose [43]. Flumazenil is a nonspecific competitive antagonist at the benzodiazepine receptor. The effectiveness of flumazenil is well documented [57–61]. Its use can confirm quickly a clinical diagnosis of benzodiazepine receptor agonist-induced decreased level of consciousness, obviating the need for time-consuming, expensive investigations and interventions in patients with altered mental status. In patients with pure benzodiazepine overdose, return to consciousness after flumazenil administration occurs within minutes. Its administration also results in faster return to baseline alertness in patients undergoing conscious sedation with benzodiazepines. It has also been used successfully in reversing coma due to newer hypnotics used for insomnia (i.e.,

zolpidem, zopiclone, and zaleplon) [62]. The intrinsic safety of flumazenil is remarkable; 100 mg intravenously has been given without significant adverse effects. Seizures and cardiac dysrhythmias have occurred after flumazenil administration, however [57, 58, 62–66]. In most cases, these effects are well tolerated and do not alter clinical outcome, but fatalities do occur [63]. Coingestion of drugs with proconvulsant properties (Table 9) is associated with an increased risk of seizure after flumazenil administration. This risk presumably is due to loss of the benzodiazepine’s protective anticonvulsant effect when the antagonist is administered. Combined overdose with tricyclic antidepressants accounts for 50% of these cases [56]. Other coingestants possessing proarrhythmic properties, such as carbamazepine and chloral hydrate, may increase the likelihood of cardiac effects by a similar mechanism [58]. Other risk factors contraindicating the use of flumazenil are summarized in Table 11. Using these criteria, stratification of patients into high-risk and low-risk categories can be done easily, but few patients are eligible for flumazenil if the criteria are strictly applied [67]. Nevertheless, flumazenil has been shown to safely reduce

the need for ventilatory support and extensive diagnostic studies in selected patients, even when coingestants were involved [66].

One common and important relative contraindication to flumazenil is regular use of benzodiazepines. Administering flumazenil to benzodiazepine-dependent patients may provoke severe benzodiazepine withdrawal, a condition that is characterized by agitation and potential seizures [68].

Although flumazenil has been shown to be effective in reversing benzodiazepine-induced sedation, it does not reverse respiratory depression consistently [69]. Because the duration of action of flumazenil is short (0.7–1.3 h), re sedation occurs in 65% of patients and requires either redosing or continuous infusion [57, 70, 71]. In patients undergoing conscious sedation, use of lower doses of benzodiazepines may reduce this risk [61]. Any patient who has reversal of CNS depression with flumazenil must be monitored closely for a minimum of 1 h for the possibility of re sedation.

The usual recommended initial adult dose of flumazenil is 0.2 mg intravenously over 30 s. A second dose of 0.3 mg may be given, followed by 0.5-mg doses at 1-min intervals, to a total dose of 3 mg. Most patients respond to less than 3 mg. In children, weight-based dosage of 0.01 mg/kg is recommended. Use of a continuous intravenous flumazenil infusion (0.25–1.0 mg/h) after a loading dose may maintain better overall consciousness but does not decrease the rate of complications arising from severe benzodiazepine toxicity [71].

Because of the aforementioned potential adverse effects, flumazenil should not be used indiscriminately in all patients with altered mental status. Flumazenil should not be used in place of standard support measures, including airway control, gastrointestinal decontamination, and hemodynamic stabilization. The clinical pharmacology of flumazenil is described in detail in ► Chap. 148, “Flumazenil.”

Table 11 Use of flumazenil

Indications
Isolated benzodiazepine overdose in a nonhabituated user
Reversal of procedural sedation
Contraindications
<i>Absolute</i>
Known or suspected coingestant that lowers seizure threshold:
Tricyclic antidepressants, cocaine, amphetamines, lithium, methylxanthines, isoniazid, tramadol, MAO inhibitors, bupropion, velafaxine, diphenhydramine, carbamazepine, GHB, PCP
Chronic (habituated) benzodiazepine user
Active sedative–hypnotic and/or alcohol withdrawal
Seizure activity or myoclonus already present
Hypersensitivity to flumazenil
Patient with neuromuscular blockade
<i>Relative</i>
Head injury
Panic attacks
Known seizure disorder
Alcoholic patients

Physostigmine

Physostigmine is a short-acting acetylcholinesterase inhibitor used to reverse toxicity from

anticholinergic agents. By competing with acetylcholine for metabolism via this enzyme, physostigmine effectively increases the concentration of acetylcholine in the synapse. The higher concentration of acetylcholine overcomes competitive postsynaptic muscarinic receptor blockade produced by anticholinergic agents. Use of physostigmine should be considered in the presence of signs and symptoms of anticholinergic toxicity, including tachycardia, fever, mydriasis, anhidrosis, gastrointestinal hypomotility, urinary retention, and altered mental status (Table 12). Other acetylcholinesterase inhibitors – pyridostigmine, neostigmine, and edrophonium – are ineffective due to an inability to penetrate the blood–brain barrier [72]. The anticholinergic syndrome is discussed in detail in ► Chap. 23, “Anticholinergic Syndrome.”

Use of physostigmine in the appropriate setting of severe anticholinergic toxicity may have advantages over supportive care alone [73]. Clearing of signs of toxicity after administration of this antidote confirms the diagnosis and may obviate the need for an intensive workup for altered mental status. Respiratory depression from severe intoxication may be reversed, avoiding the need for advanced airway management. Finally, a study suggested that physostigmine may control anticholinergic-induced agitation and delirium more adequately than benzodiazepines, which

currently are the preferred agents to manage agitation in this setting [70]. Multiple doses of physostigmine were required in 58% of the patients, with side effects occurring in 11% [70]. Nevertheless, clinicians considering the use of physostigmine must have a thorough understanding of its pharmacologic effects and risks of its use. Administration of physostigmine in the absence of actual anticholinergic toxicity may produce cholinergic effects. Seizures after physostigmine administration have been reported, especially when concomitant intoxication with substances known to lower the seizure threshold has occurred [74]. Several drugs associated with seizures in overdose, such as tricyclic antidepressants, carbamazepine, and phenothiazines, also have anticholinergic effects that may render a misleading picture of pure anticholinergic overdose. Physostigmine has a parasympathomimetic effect, increasing vagal tone, which can lead to bradydysrhythmia. Asystole has been reported after use of physostigmine in a patient with poisoning from a tricyclic antidepressant [75], although the asystole may have resulted from the tricyclic ingestion itself. Physostigmine has been shown to be safe and effective in large series and case reports when used appropriately [76–78].

The use of physostigmine also has been reported to result in arousal of a series of patients with coma due to gamma hydroxybutyrate (GHB) intoxication [79]. The proposed, although unvalidated, mechanism is nonspecific CNS arousal. Two of the three patients in this series manifested cholinergic symptoms. Physostigmine should not be used routinely in cases of suspected intoxication by GHB or its congeners because of the risks of unrealized coingestants or precipitation of cholinergic symptoms (including emesis with risk for aspiration) [79]. GHB intoxication generally resolves without sequelae after a few hours of supportive care and airway protection [80, 81]. Intoxication with GHB or its congeners is discussed in detail in ► Chap. 76, “Gamma-Hydroxybutyrate and Its Related Analogues Gamma-Butyrolactone and 1,4-Butanediol.”

The usually recommended dose of physostigmine is 2 mg in adults or 0.02 mg/kg in children. Rapid intravenous bolus administration can be dangerous; slow infusion over approximately

Table 12 Agents with anticholinergic effects

Antihistamines: diphenhydramine, doxylamine, cyproheptadine, hydroxyzine, brompheniramine
Antispasmodics: oxybutynin, hyoscyamine, atropine
Ipratropium bromide
Scopolamine
Diphenidol
Phenothiazines
Ophthalmic cycloplegics
Antiparkinsonian agents
Tricyclic antidepressants
Pirenzepine
Carbamazepine
Pizotifen hydrogen maleate
Botanicals: jimsonweed, deadly nightshade, angel’s trumpet, black henbane, Paraguay tea, <i>Amanita muscaria</i> (mushroom)

2–4 min generally is recommended. Onset of the effect may be delayed for 10–15 min. Signs and symptoms of toxicity may recur because the duration of action of physostigmine is only 20–60 min. Repeated doses are not usually necessary [74]. Some patients with otherwise hard-to-control anticholinergic delirium may benefit from repeat administration; however, it is not usually required to treat acute anticholinergic-based plant toxicity (usually related to *Datura stramonium*) [82]. The clinical pharmacology of physostigmine is discussed in detail in ► Chap. 161, “Physostigmine.”

Lipid Emulsion Therapy

Administration of intravenous lipid emulsion has been increasingly utilized in the resuscitation of local anesthetic, antidepressant, and cardiovascular drug cardiac toxicity [83]. Additionally, published case reports record reversal of toxicity from other lipophilic drugs, such as quetiapine, sertraline, lamotrigine, and olanzapine [84]. It has been demonstrated to improve Glasgow Coma Scale scores due to nonlocal anesthetic drug intoxication in young adults [85].

The dosage and administration of lipid emulsion antidotal therapy is further discussed in ► Chap. 152, “Lipid Resuscitation Therapy.”

Management of the Agitated Patient

Management of patients with violent behavior or agitation due to intoxication is often challenging to the clinician. Verbal attempts to de-escalate violent behavior in the intoxicated patient should remain the first approach, as should evaluation and treatment of any medical condition (e.g., hypoxia, pain) that may be contributing to the agitation. If these measures fail, use of restraint may be considered. Physical restraint of violent patients with intoxications causing hyperadrenergic states or seizures (e.g., cocaine, amphetamines, phencyclidine, withdrawal from ethanol or benzodiazepines) may be dangerous, particularly if inadequate sedation is given. Pharmacologic

management (i.e., “chemical restraint”) also may be employed, but the clinician must remain mindful of potential side effects or drug interactions. Antipsychotics and benzodiazepines are the two most commonly used agents in this setting.

The butyrophenones (e.g., haloperidol) have traditionally been the preferred antipsychotic agents because they manifest fewer anticholinergic and quinidine-like effects compared with the phenothiazines (e.g., chlorpromazine). Haloperidol has been shown repeatedly to be a safe and effective drug for acute control of agitation [86]. The commonly recommended dose is 5–10 mg deep intramuscularly (into the gluteal region) or intravenously every 10–30 min, titrated to the desired effect. Extrapyramidal side effects, such as dystonia or akathisia, may occur in up to 16% of patients and should be treated with either benztropine, 1–4 mg intravenously or intramuscularly, or diphenhydramine, 50 mg (0.5–1 mg/kg in pediatric patients) intravenously or intramuscularly. Although the use of haloperidol has been shown to lower seizure threshold in animals, there are no reports of seizures clearly induced by haloperidol in humans. Droperidol differs from haloperidol in its faster onset of effect, shorter half-life, more pronounced sedation, and lower incidence of extrapyramidal side effects. Transient orthostatic hypotension has been reported after its use. The commonly recommended dose of droperidol is 2.5–10 mg intramuscularly.

Ziprasidone is an atypical antipsychotic agent often used to control agitation. It is a serotonin (5-HT_{2A}) and dopamine (D₂) receptor antagonist. Weaker dopamine receptor effects result in fewer extrapyramidal effects compared with haloperidol. Prolongation of the QT/QT_c interval on ECG may occur in a dose-related manner, but clinically relevant prolongation is rare (0.06%). Its dose is 10 mg every 2 h intramuscularly (or 20 mg every 4 h) to a maximum daily dose of 40 mg [87, 88].

Benzodiazepines are the agents of choice in patients with ethanol or benzodiazepine withdrawal or in patients with hyperadrenergic states from sympathomimetic agents. Although many benzodiazepines have been shown to be effective, lorazepam has been studied most extensively. The usual recommended dose of lorazepam is 2–4 mg

intravenously. Some studies suggest that combination therapy with a benzodiazepine plus an antipsychotic may control violent behavior more effectively [86]. Intravenous dexmedetomidine (0.2 ug/kg/h initial dose followed by titration doses up to 0.7 ug/kg/h titration) or low-dose ketamine (0.2 mg/kg/h) appears to reduce benzodiazepine requirements as an adjunctive agent in treating the alcohol withdrawal syndrome [89, 90]. It should be noted that dexmedetomidine cannot be used in patients with heart block [88].

New alternatives to benzodiazepines in treating withdrawal delirium include phenobarbital, either orally or intravenously (up to 2000 mg on day 1, although at not more than 400 mg/dose), carbamazepine (approximately 800 mg per day), or oxcarbazepine (approximately 900 mg per day) [91]. Patients unresponsive to high doses of benzodiazepines usually respond to propofol after intubation (dose 0.3–1.25 mg/kg intravenously up to 4 mg/kg/h for up to 48 h) [91]. To avoid precipitating Wernicke's encephalopathy, higher doses of thiamine should be utilized (500 mg intravenously, three times daily for 5 days) along with daily parenteral multivitamins [92, 93].

The routine use of thiamine (100 mg daily orally for up to 30 days) has been recommended in combination with benzodiazepines in treating any severity of alcohol withdrawal [93].

Patients with drug-induced or toxin-induced alterations in consciousness require close monitoring. Progressively worsening intoxication may lead to profound CNS depression and airway compromise. The propensity for these conditions to occur may be increased by the use of pharmacologic agents to achieve behavior control and sedation. Seclusion should never be employed unless some method of continuous observation (e.g., video monitoring) can be arranged.

Prognosis

Generally, recovery from coma due to a toxic cause is much better than that from an anoxic cause. Mortality of coma due to a sedative drug intoxication is less than 1% [94]. Table 13 presents prognostic signs of worsening of coma and

Table 13 Poor neurologic prognostic signs for recovery from toxic coma

Loss of pupillary reflexes (up to 1 week)
Absence of corneal reflexes after day 1
Lack of oculovestibular response
Absence of eye-opening response at day 3
Absence of bilateral cortical component of somatosensory evoked potential responses
Abnormal skeletal muscle tone
Absence of spontaneous eye movement
Low-voltage delta activity (with alpha coma) or isoelectric tracing on electroencephalogram

Data from Adams et al. [3]

poor outcome [2, 95]. Although these prognostic indicators generally have been studied in patients with hepatic encephalopathy, they seem to be a reasonable guideline for patients with a toxic cause of coma. Patients taking agents described in Table 3 resulting in cyclic coma can exhibit a full recovery despite these prognostic signs [94, 96]. Full recovery from prolonged coma and loss of brainstem reflexes has been described after amitriptyline and doxepin overdose [97, 98]. Short-term memory deficits and amnesia after coma usually are due to injury of the pyramidal neurons of the hippocampus (CA 1 subfield) and are possible sequelae of an anoxic injury or carbon monoxide toxicity [99].

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Seizures are a common feature of high-dose and, in some instances, minor or therapeutic exposure to a variety of drugs, chemicals, and toxins. It is estimated that 6.1% of new-onset seizures could be drug related [1].

In a prospective study of critically ill medical patients, seizures were found to be second only to metabolic encephalopathy as the most common neurologic complication encountered [2]. In addition to exhibiting a direct, dose-dependent relationship to exposure to various substances, seizures are characteristic of withdrawal from numerous drugs and chemicals with CNS-depressant effects. Seizures may occur as a paradoxical effect of anticonvulsant medications, particularly after overdose or in seizure-prone individuals on accepted therapeutic regimens of these medications [3, 4].

Classes of agents frequently implicated in drug-induced, chemical-induced, and toxin-induced seizures (hereafter collectively referred to in this chapter as *toxicant-induced seizures* or *toxicant-induced convulsions*) include antidysrhythmics, anticonvulsants, antidepressants, antihistamines, antipsychotics, antimicrobials, antiasthmatics, antineoplastics, CNS stimulants, local anesthetics, opioid analgesics, sedative-hypnotics/alcohol (withdrawal), metals (e.g., lead, alkylmercury), pesticides (e.g., insecticides, rodenticides), and certain alcohols [5]. Table 1 provides a more complete listing, by functional class, of agents with proconvulsant potential.

This chapter is a revision of the chapter on this topic by Kevin Wallace in the first edition of this text. Much of the material herein was contained in the chapter in the first edition.

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Table 1 Proconvulsant agents: classification by source and use

Class	Example(s)
Pharmaceuticals	
Analgesics	Meperidine/normeperidine, propoxyphene, pentazocine, salicylate, tramadol
Anesthetics	Local anesthetics (lidocaine, benzocaine)
Anticonvulsants	Carbamazepine
Antidepressants	Tricyclics (amitriptyline/nortriptyline), amoxapine, bupropion, SSRIs (citalopram), venlafaxine
Antihistamines	Diphenhydramine, doxylamine, tripeleennamine
Antimicrobials	Antibacterials (selected penicillins, cephalosporins, carbapenems, and fluoroquinolones), antimalarials (chloroquine), tuberculostatics (isoniazid)
Antineoplastics	Alkylating agents (chlorambucil, busulfan)
Antipsychotics	Clozapine, loxapine
Asthma medications	Theophylline
Cardiovascular drugs	Propranolol, quinidine
Cholinergics	Pilocarpine, bethanechol
Muscle relaxants	Baclofen, orphenadrine
NSAIDs	Mefenamic acid, phenylbutazone
Psychostimulants/anorectics	Amphetamine, caffeine, cocaine, methamphetamine, MDMA, synthetic cannabinoids
Vitamins/supplements	Vitamin A, iron salts (ferrous sulfate)
Nonpharmaceuticals	
Alcohols	Methanol, ethanol (withdrawal)
Antiseptics/preservatives	Ethylene oxide, phenol
Biologic toxins	
Marine animals	Domoic acid (shellfish [blue mussels])
Mushrooms	Monomethylhydrazine (<i>Gyromitra</i> spp.)
Plants	Coniine (poison hemlock), virol A (water hemlock), camphor

(continued)

Table 1 (continued)

Class	Example(s)
Gases (naturally and/or anthropogenically occurring)	Carbon monoxide, hydrogen sulfide, hydrogen, cyanide
Metals/organometallics	Alkyl mercurials (dimethylmercury), arsenic, lead, thallium, tetraethyl lead, organotins (trimethyltin)
Metal hydrides	Pentaborane, phosphine
Pesticides	
Fungicides/herbicides	Dinitrophenol, diquat, glufosinate
Insecticides	Organochlorines (lindane, DDT), organophosphates (parathion), pyrethroids (type II), sulfuryl fluoride, alkyl halides (methyl bromide)
Molluscacides	Metaldehyde
Rodenticides	Strychnine, zinc, or aluminum phosphide

MDMA 3,4-methylenedioxymethamphetamine, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRIs* selective serotonin reuptake inhibitors

Toxicant-induced convulsions, given the typically diffuse CNS distribution of proconvulsant substances and their highly specific neurochemical mechanisms, usually are generalized. They may be prolonged, recurrent, or both; they meet clinical and mechanistic definitions for status epilepticus (SE) [6], and they may be remarkably refractory to widely recommended antiepileptic drug regimens. Definitions of SE, a condition of prolonged or recurrent seizure activity without interictal awakening, have incorporated critical time intervals for continuous seizure activity that range from 5 [2, 6] to 30 min [7]. Although there is little evidence to support these temporal cutoffs as thresholds beyond which seizure-induced CNS injury occurs, these definitions emphasize the apparent direct relationship between duration of seizure activity and clinicopathologic outcome and the paramount importance of anticonvulsant therapy in the management of sustained seizure activity.

Conservative estimates of the incidence of SE in the United States range from 60,000 to 160,000

patients per year [7, 8]. The mortality associated with SE since the 1980s has been observed to be higher in adults (15–22%) than in children (3–15%) and greater than 10% if caused by drug toxicity [9]. Extremes of age and seizure duration of greater than 1 h have been predictive of poor outcome [6]. In published case series of SE patients, the reported proportions of cases judged to be of toxic etiology (ethanol or drug related) range from 2.4% in patients younger than 16 years old [7] to 24% in older alcoholic individuals [6].

Subtle [10] and *nonconvulsive* are descriptive terms that have been used to denote less than obvious or subclinical SE (i.e., ongoing electrical seizure activity shown by electroencephalography [EEG] with or without subtle convulsive movements, such as rhythmic muscle twitches or tonic eye deviation). Nonconvulsive SE, which may occur after pharmacologic neuromuscular blockade, has been an underrecognized cause of altered consciousness or behavior [11], with coma at the time of diagnosis of SE predictive of fatal outcome [12]. In a study of 236 patients (age range 1 month to 87 years) with coma and no overt clinical seizure activity, 8% had at least 30 min of continuous electrographic seizure activity [13].

The mortality rate associated with subtle SE in a multicenter trial comparing four drug treatments for generalized convulsive SE was 65% versus 27% in patients with overt SE. Longer hospital stays also were associated with subtle SE [10]. There may be a rational basis for the concern that neuronal injury resulting from unrecognized subclinical SE is of equal or even greater severity than that occurring as a result of overt clinical SE. Understanding of the pathophysiology and prognosis of nonconvulsive SE is limited, however, by the current lack of controlled comparative data, difficulties with case definition, confounding factors (e.g., underlying neurologic disorder), and the highly anecdotal nature of available clinical data [9, 14].

The main objectives of this chapter are to provide a rational mechanistic approach to the evaluation and treatment of toxicant-induced convulsions. Emphasis is on the importance of considering nontoxic and primarily toxic causes of seizures and of employing an aggressive and

more selective approach to anticonvulsant treatment than might be indicated in seizures of nontoxic origin.

Epidemiology

The leading causes of drug-induced seizures may vary over time. It is important for the clinicians to be aware of the evolving changes in prescribing patterns to better predict which toxic substances may be responsible for serious complications. The trends of drug-related seizures may be estimated from the data reported to the poison control centers.

In 1994, Olson and colleagues [15] observed that in 191 cases of seizures associated with poisoning and drug overdose reported to a West Coast US regional poison control center, the most commonly implicated agents or class of agent were cyclic antidepressants (29%), cocaine (22%), diphenhydramine (7%), theophylline (5%), isoniazid (5%), and methamphetamine/amphetamine (3%).

In a retrospective review of all calls to the California Poison Control System in 2003, the leading causes of seizures were bupropion (23%), diphenhydramine (8.3%), tricyclic antidepressants (7.7%), amphetamines (6.9%), isoniazid (5.9%), and venlafaxine (5.9%) [16]. In comparison with a similar study performed in 1993, there was a significant increase in recent antidepressant-related seizures, but a decrease of tricyclic antidepressant- and cocaine-related seizures. In the majority of the cases, seizures were limited to a single episode, while SE remained a rare complication (3.6%). Seizures were mostly the consequence of suicide attempts and 14.8% resulted from drug abuse. Death observed in a limited number of cases was more likely to occur in patients who were exposed to stimulants.

A study conducted by the Swiss Toxicological Information Centre between January 1, 1997, and December 31, 2010, examined which pharmaceutical exposures were commonly associated with overdose-induced seizures [17]. Among 15,441 single-agent exposures, seizures occurred in 313 cases. The most prevalent pharmaceuticals

were mefenamic acid (51), citalopram (34), trimipramine (27), venlafaxine (23), tramadol (15), diphenhydramine (14), amitriptyline (12), carbamazepine (11), maprotiline (10), and quetiapine (10). The seizure potential of a pharmaceutical was calculated by dividing the number of cases with seizures by the number of all cases recorded with that pharmaceutical. Drugs with a high seizure potential were bupropion (31.6%), maprotiline (17.5%), venlafaxine (13.7%), citalopram (13.1%), and mefenamic acid (10.9%). The probability of seizures with mefenamic acid, citalopram, trimipramine, and venlafaxine increased as the ingested dose increased. Considering the different age groups, it appeared that adolescents might be more susceptible to seizures after mefenamic acid overdose than adults.

With the increasing use of tramadol as analgesic, seizures are also becoming more frequently reported, not after chronic tramadol therapy (except for co-ingestants or individual susceptibility factors), but particularly in overdose. In a series of 525 intentional tramadol exposures, 46.1% of the patients developed seizures (single episode in 88.1%, recurrent seizures in 11.9%) [18]. This is also in accordance with the results of a previous prospective observational study conducted on 401 patients, where the incidence of seizures was 30.2% [19]. The mean ingested dose was 1511 mg, and 200 mg was the lowest dose associated with seizure. Seizure activity appeared to be dose dependent, but no significant correlation was found with tramadol blood concentrations. Seizures are usually described as brief, self-limiting, and most often occur within 4–6 h post-ingestion.

More recently, special attention has been given to synthetic cannabinoid receptor agonists (which are discussed in detail in a separate chapter on these agents) due to their wide availability from the Internet, and seizures have been reported following recreational exposure [20–23].

In summary, these epidemiological data illustrate the changes of pharmaceutical and nonpharmaceutical exposures responsible for seizures, with progressive shifts within the classes of substances (antidepressants, analgesics,

recreational drugs). Recent trends have highlighted the prominent role of SSRIs, bupropion, tramadol, and synthetic cannabinoids with a progressive decline of tricyclic antidepressants and cocaine.

Pathophysiology

According to Schaumberg [24], “The nature of the discharging lesion in toxin-induced seizures presumably is different in some respects from the lesion in most epileptic patients; the toxin-induced seizure usually originates in previously normal neurons, while the patient with epilepsy frequently has a focus in an abnormal cortical area.” Other authorities on epilepsy note that the pathophysiology of posttraumatic or idiopathic seizures is characterized by the spread of electrical activity from a relatively isolated focus to neighboring cortical regions when the intensity of seizure discharge overcomes the inhibitory influence of surrounding neurons [25]. In contrast, toxicant-induced seizures involve simultaneous increases in electrical discharge from susceptible neuronal populations in response to toxicant-induced neurochemical or other functional (e.g., metabolic) derangements or both.

Proconvulsant substances exert their neurotoxic effects through a variety of postulated mechanisms, for which there are a growing abundance of supporting experimental data [26]. A common theme that applies to most of these proconvulsant mechanisms is that in some manner they give rise to an imbalance in the normal neurochemical homeostasis of the central nervous system (CNS) (i.e., they cause a disturbance in the balance between excitatory and inhibitory neurotransmission). This imbalance can result from increased excitatory tone, decreased inhibitory tone, or both, leading to a diffuse increase in neuronal excitability in typically dose-dependent fashion beyond the physiologic threshold for seizure activity. The remainder of this section focuses on the role that several major CNS neurotransmitter systems play in the genesis of toxicant-induced convulsions.

Gamma-Aminobutyric Acid (GABA) Antagonism

GABA is the principal inhibitory central neurotransmitter, present in an estimated 30% of all central synapses. Substances that antagonize GABA activity produce CNS excitation and convulsions. Paradoxically, GABA is synthesized in the brain through the actions of glutamic acid decarboxylase on glutamate (Fig. 1), the brain's main excitatory neurotransmitter.

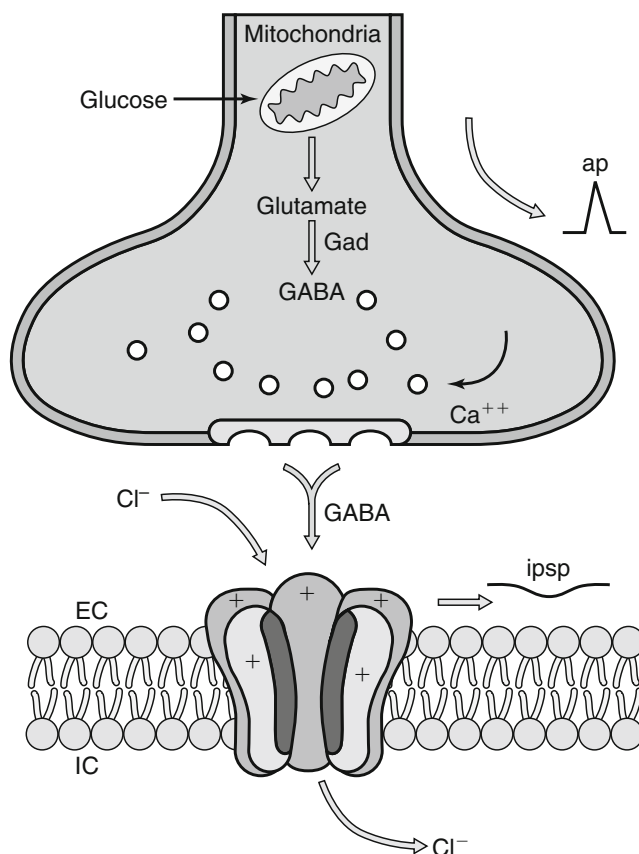
GABA is stored in vesicles in presynaptic nerve terminals and is released into synapses in the brain and spinal cord via calcium (Ca^{2+})-dependent exocytosis. There are two main subtypes of transmembrane polypeptide receptors that bind GABA, designated GABA_A and GABA_B .

Antagonism of GABA_A receptors has been implicated most frequently in the proconvulsant actions of drugs, chemicals, and toxins. The GABA_A receptor complex (Fig. 2) is a ligand-gated

chloride (Cl^-) channel that is integral to the postsynaptic neuronal membrane. When GABA binds to its receptor site on the complex, it triggers postsynaptic Cl^- influx, which results in membrane hyperpolarization and a decrease in postsynaptic neuronal excitability and impulse propagation (see Fig. 1) [31].

In addition, the $\text{GABA}_A \text{Cl}^-$ channel has multiple binding sites for exogenous and endogenous modulatory agents, including excitatory/proconvulsant drugs (e.g., penicillin, amoxapine, maprotiline [32–34]) and depressant/anticonvulsant drugs (e.g., benzodiazepines, barbiturates), which produce their actions through allosteric conformational enhancement or impairment of Cl^- influx in response to GABA binding [35]. Most of these drugs require that GABA itself bind to its receptor site on the GABA_A complex for inhibitory or excitatory effects to occur and are termed *indirect* agonists and antagonists. Substances that exert their effects on the GABA_A chloride ionophore by directly binding to

Fig. 1 Presynaptic and postsynaptic elements. *ap* action potential, *Gad* glutamic acid decarboxylase, *EC* extracellular, *IC* intracellular, *ipsp* inhibitory postsynaptic potential (From Brody et al. [27], p. 367)



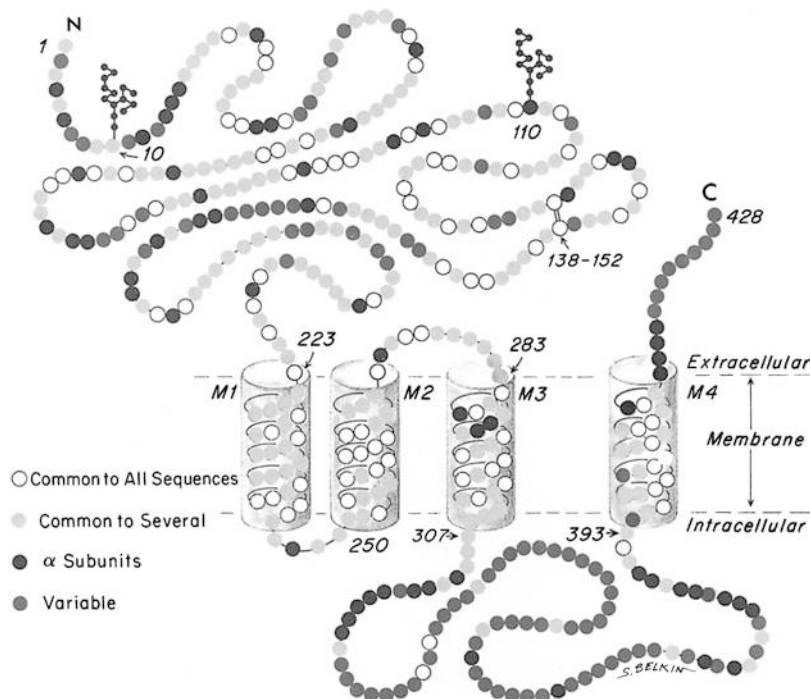


Fig. 2 Generic GABA_A receptor protein subunit sequence and putative topologic structure. The numbering follows that of the rat α_1 sequence used by Khrestchatsky and colleagues [28]. Note the NH₂ terminal (labeled N, residue 1) presumed extracellular domain, with probable sites for asparagine glycosylation (polymeric black circles at positions 10 and 110), and the cystine bridge (solid line connecting 138 and 152). Four putative membrane-spanning α -helical cylinders M1, M2, M3, and M4 are shown. The COOH-terminus (labeled C, residue 428) is

extracellular. A large intracellular cytoplasmic loop between M3 and M4 is present. The shading indicates the degree of variability within the family of rat polypeptides published to date: α_1 , α_2 , α_4 , β_1 , β_2 , β_3 , γ_2 , and δ . Amino acids that are identical in all the clones are shown in white; amino acids identical in two or more types are light gray; amino acids identical in all α but not in β , γ , and δ are black; and amino acids that vary between types are dark gray (A from Smith and Reynard [29]. B from Olsen and Tobin [30])

the GABA receptor locus are termed *direct* agonists (e.g., muscimol) and antagonists (e.g., bicuculline).

Reduction in GABAergic neuroinhibitory tone also results from inhibition of GABA synthesis, such as that produced by isoniazid and other hydrazine compounds. Isoniazid lowers CNS GABA concentrations by several mechanisms, the main one being competitive inhibition of pyridoxine kinase, which results in depressed synthesis of pyridoxal phosphate, a cofactor needed for glutamic acid decarboxylase activity and GABA synthesis (see Fig. 1). Other mechanisms include direct inhibition of glutamic acid decarboxylase and increased urinary excretion of pyridoxine [36, 37].

Human and experimental data support direct and indirect antagonistic actions at the GABA_A

complex as the basis for the epileptogenic effects of members of several classes of antibiotics (penicillins, cephalosporins, carbapenems, and fluoroquinolones) [38], organochlorine compounds such as lindane and cyclodiene insecticides (e.g., dieldrin) [39], various antidepressants [32–34], and virol A, a long-chain alcohol found in *Cicuta virosa*, a species of water hemlock [40]. Penicillin has been distinguished from other GABA antagonists on the basis of its multiple mechanisms of effect at GABA_A chloride channels, including direct actions within the chloride channel itself (i.e., independent of its direct and indirect GABA-agonist actions) [38]. In addition, cefazolin, a first-generation cephalosporin antibiotic, and pentylentetrazol, an analeptic compound

that binds to the picrotoxin-binding site on the GABA_A complex and is used widely in experimental epilepsy research, contain tetrazole moieties and are potent proconvulsants, consistent with a common structure–activity relationship.

Increases in the ratio of central neuroexcitatory to neuroinhibitory tone, resulting in convulsive activity, also can occur as a result of abrupt GABA-agonist withdrawal after a chronic exposure period of sufficient duration to produce pharmacodynamic tolerance by downregulating GABA_A functional expression (see ► Chap. 45, “Anxiolytics, Sedatives, and Hypnotics”). Agents that possess GABA_A-agonist properties include ethanol, various benzodiazepines and barbiturate sedative–hypnotics, carisoprodol, meprobamate, zolpidem, and propofol. GABA_B receptors are metabotropic transmembrane receptors for GABA that are linked via G-proteins to potassium channels. GABA_B receptors are involved in behavioral actions of ethanol, gamma-hydroxybutyric acid (GHB), and gamma-butyrolactone (GBL).

Glycine Antagonism

Another type of neuroinhibitory ligand-gated ionophore, the glycine-gated chloride channel, has a well-established role in modulating efferent motor neuron activity at the level of the lower brainstem and spinal cord. Glycine functions as a postsynaptic inhibitory neurotransmitter in a manner that is analogous to GABA at GABA_A chloride channels and prevents excessive lower motor neuronal electrical impulse propagation and reflex arc activation in response to afferent excitatory input. Strychnine antagonizes glycine’s actions at these postsynaptic inhibitory chloride channels in the spinal cord and brainstem, resulting in polysynaptic motor neuronal disinhibition and subsequent increase in motor tone and convulsive activity (“spinal convulsions”) (see ► Chap. 95, “Rodenticides”) [41].

Glutamate Agonism

As previously noted, glutamate is the main CNS excitatory neurotransmitter. It is synthesized in

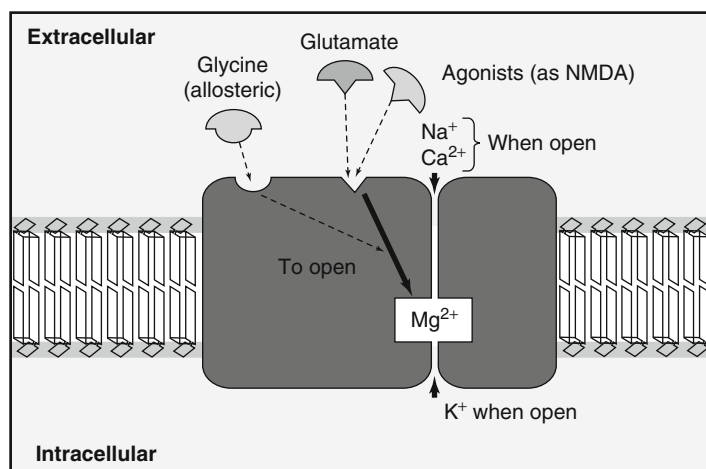
presynaptic nerve terminals from α -ketoglutarate or glutamine and released from storage vesicles as a result of the influx of calcium through voltage-gated presynaptic calcium channels in response to propagated electrical impulses. Its postsynaptic actions are mediated through receptor sites on ligand-gated Ca²⁺ channels that also have binding sites for other ligands, including glycine and *N*-methyl-D-aspartate (NMDA). When open, these NMDA-glutamate Ca²⁺ channels also permit sodium (Na⁺) influx and, in some cases, potassium (K⁺) efflux (Fig. 3). The pathophysiologic consequences of these transmembrane ion fluxes are postsynaptic neuronal membrane depolarization and enhanced electrical excitability and neuronal cytotoxicity as a result of increases in intracellular Ca²⁺ concentration. The clinical effects are agitation/seizures and persistent neurologic functional impairment [42, 43].

Proconvulsant substances that have direct agonist and neuroexcitatory actions at NMDA-glutamate receptors include the marine toxins, domoic acid and kainic acid [44, 45], and glufosinate, a broad-spectrum herbicide [46]. Chronic administration of NMDA-glutamate receptor antagonists (e.g., ethanol, meprobamate), which exert more potent anticonvulsant effects than GABA_A agonists in some experimental models, results in upregulation of glutamatergic neurotransmission and pharmacodynamic tolerance to the sedative effects [47, 48]. Abrupt discontinuation of these agents is thought to result in increased NMDA-glutamate receptor complex-mediated ion flux, enhanced neuronal excitability, and increased risk of convulsions [43, 49]. This is combined with evidence supporting ethanol’s actions at GABA_A chloride channels, strongly suggesting a dual and concordant effect of ethanol on the balance between excitatory and inhibitory neurotransmission.

Acetylcholine (Muscarinic) Agonism

Although their clinical importance is uncertain, other excitatory neurotransmitter systems are postulated to play a role in the proconvulsant actions of a variety of toxicants. The proconvulsant

Fig. 3 Suggested components of glutamate receptors in the central nervous system. Channel shown in resting stage. Depolarization by agonist binding or voltage gating releases blockade by magnesium ions and lets potassium ions pass outward and Na^+ and Ca^{2+} pass into the nerve cell. Glycine acts to augment agonist effect (From Brody et al. [27], p. 18)



effects of the muscarinic agonist pilocarpine, used in experimental models of human epilepsy [50, 51], and the observation that stimulation of brain muscarinic receptors causes persistent tonic-clonic convulsions [52] suggest enhancement of muscarinic neurotransmission as a mechanism of induction of seizure activity by agents that inhibit neural acetylcholinesterase (e.g., organophosphate insecticides). It also has been suggested, however, that secondary GABAergic and glutamatergic mechanisms may be involved more directly in seizure production by these agents [53].

Adenosine Antagonism

A third major mechanism of proconvulsant action involves interference with the normal modulation of presynaptic excitatory neurotransmitter (e.g., glutamate) release. Substantial evidence implicates adenosine as an endogenous anticonvulsant substance that is “released during seizure activity, exerts stabilizing effects on the epileptogenic focus and surrounding neural tissues and the accumulation of which terminates seizure activity while increasing the threshold for further seizure induction” [54]. Prolonged clinical and electrographic seizure activity occurs when the anticonvulsant actions of adenosine are antagonized, as occurs with excessive doses of xanthine derivatives, such as theophylline or caffeine [55].

Adenosine is released from the presynaptic nerve terminal in the brain along with other neurotransmitters, such as glutamate, then binds to G-protein-coupled receptors on the same presynaptic terminal. The effect of stimulation of these so-named A_1 subtype adenosine receptors is a decrease in voltage-gated Ca^{2+} influx and inhibition of further presynaptic excitatory neurotransmitter release. When involved in negative feedback modulation of this sort, receptors commonly are referred to as *autoreceptors* (Fig. 4).

Adenosine-mediated spontaneous arrest of seizure activity is characterized by its alternating synaptic accumulation and clearance and is reflected in the ictal–interictal cycling that occurs during SE [55]. In addition, stimulation of a second adenosine receptor subtype, A_2 , located on cerebral blood vessels, results in vasodilation and a compensatory increase in cerebral blood flow during times of increased oxygen and nutrient requirements (e.g., during seizure).

Adenosine’s anticonvulsant activity has been shown convincingly in experimental studies of its effects on seizures induced by adenosine antagonists, such as theophylline [56]. Many other drugs have been found to alter the excitatory/inhibitory neurotransmitter balance through their effects on synaptic adenosine levels or more direct actions at adenosine receptors. There is evidence that benzodiazepines enhance neuroinhibitory tone, in part, through inhibition of presynaptic adenosine

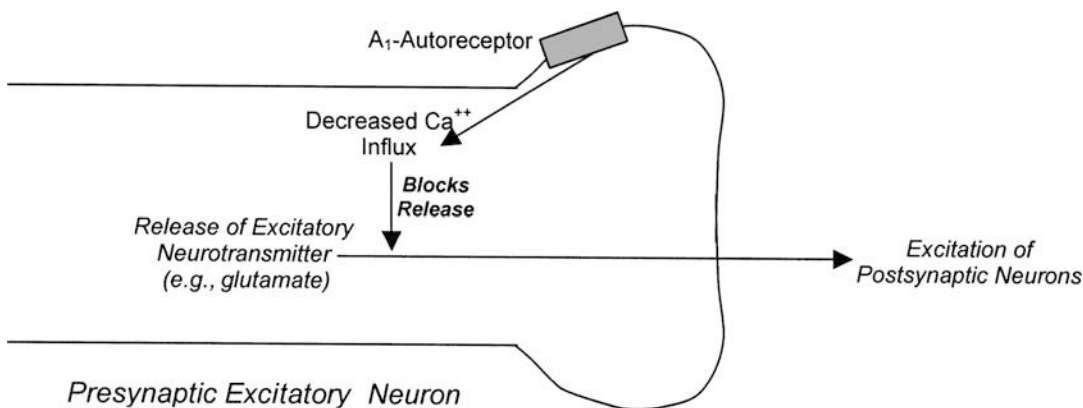


Fig. 4 Presynaptic inhibition of excitatory neurotransmitter releases by adenosine. Agonism of the presynaptic inhibitory (also known as *autacoid*) A₁ receptor by

adenosine attenuates voltage-gated Ca²⁺ release, reducing the release of excitatory neurotransmitters (e.g., glutamate)

reuptake [54], whereas carbamazepine exhibits dose-dependent agonistic and antagonistic actions on adenosinergic modulation of excitatory neurotransmitter release [54, 57–59].

Other Mechanisms

Other neurotransmitter system components and mechanisms are postulated to play a contributory role in the proconvulsant effects of various pharmacologic agents, but supporting data are limited (Table 2). These mechanisms include the following:

- Presynaptic and postsynaptic GABA_B receptors as loci of action responsible for seizures observed in the setting of baclofen overdose [60] and withdrawal [61, 62]
- Presynaptic nerve terminal potassium channel blockade (e.g., by 4-aminopyridine) [63, 64], resulting in membrane depolarization, opening of voltage-gated calcium channels, increased calcium influx, and increased release of excitatory neurotransmitters (e.g., acetylcholine)
- Central histaminergic (H₁) receptor antagonism by antihistaminergic drugs (see ► Chap. 42, “Antihistamines”) (although supporting experimental evidence for this as a proconvulsant mechanism of action of antihistamines is mixed [65])
- Neuronal sodium channel blockade-mediated inhibition of presynaptic GABA release (e.g., by local anesthetics, such as lidocaine and procaine [66]) or disinhibition of excitatory neurons [4], or both, as a basis for the paradoxical proconvulsant effects of anticonvulsants that possess sodium channel-blocking properties (e.g., phenytoin, carbamazepine) [3, 4, 67–69]

The mechanisms of seizure production of other proconvulsive agents less directly involve alterations in neurotransmitter balance and have more to do with effects on neuronal metabolism and maintenance of functional and structural integrity. These agents include the following:

- Mitochondrial poisons that impair cellular adenosine triphosphate synthesis by uncoupling oxidative phosphorylation (e.g., salicylate, dinitrophenol) or inhibiting cellular respiration (e.g., cyanide, carbon monoxide) [70–72]
- Agents that cause direct cytotoxic injury (e.g., alkylating agents, such as ethylene oxide and methyl bromide) [73]
- Agents that cause fluid/electrolyte and other metabolic disorders, including hyponatremia, as a consequence of syndrome of inappropriate antidiuretic hormone (e.g., carbamazepine), hypoglycemia (e.g., sulfonylurea compounds), hypoglycorrhachia and neuroglycopenia (e.g.,

Table 2 Mechanism of action of proconvulsant drugs and toxins

Presumptive mechanism	Examples of toxic agents ^a
Neurochemical effect	
GABAergic	
GABA _A antagonism	
Direct	Bicuculline, penicillin
Indirect	Lindane (and other organochlorines), amoxapine, maprotiline, tricyclic antidepressants, penicillin , type II pyrethroids, cephalosporins, fluoroquinolones, virol A (<i>Cicuta virosa</i> , water hemlock), avermectin analogues (ivermectin)
Depressed GABA production	Isoniazid , monomethylhydrazine, cyanide
GABA _B agonism (?)	Baclofen
Agonist tolerance/withdrawal	
GABA _A	Ethanol, benzodiazepines, barbiturates , carisoprodol, meprobamate, zolpidem
GABA _B	Baclofen, GHB, GBL
Glycinergic	
Antagonism (spinal cord)	Strychnine , picrotoxin
Agonism tolerance/withdrawal (brain NMDA-glutamate)	Ethanol
Glutamatergic agonism	Domoic acid, kainic acid , glufosinate
Adenosinergic antagonism	Theophylline, caffeine
Cholinergic agonism	
Acetylcholine release	Aminopyridines
Direct nicotinic receptor agonism	Nicotine (and other nicotinic alkaloids)
Direct muscarinic agonism	Pilocarpine, bethanechol alkaloids
Acetylcholinesterase inhibition	Organophosphates (sarin, diazinon)
Adrenergic agonism	Amphetamine, cocaine
Histaminergic antagonism	Diphenhydramine, tripeleminamine
Sodium channel blockade (membrane-stabilizing effect)	Local anesthetics, cocaine, propranolol, carbamazepine, phenytoin, diphenhydramine
Metabolic or cytotoxic effect	
Hypoglycemia	Insulin, sulfonylureas, disopyramide, pentamidine, ackee fruit
Hyponatremia (SIADH)	Carbamazepine, vinca alkaloids, chlorpropamide, phenothiazines
Direct mitochondrial dysfunction	
Uncoupling of oxidative phosphorylation	Salicylate, dinitrophenol
Cytochrome oxidase inhibition	Cyanide/cyanogens, carbon monoxide, hydrogen sulfide, iron, methanol/formate, azide (?), phosphine (?)
Krebs cycle inhibition	Arsenic, sodium monofluoroacetate
Cellular injury	
Nonspecific irritant/denaturant	Phenol
Alkylating injury	Busulfan, chlorambucil, ethylene oxide, methyl bromide, methyl chloride
Unknown	
	Bupropion, camphor, cicutoxin, chloroquine, gamma-hydroxybutyrate, pyrimethamine, quinine/quinidine, mexiletine, tocainide, lithium, mefenamic acid, phenylbutazone, normeperidine, pentazocine, propoxyphene, tramadol, nonionic radiopaque contrast agents (intravenous/intrathecal metrizamide, iopamidol, iophendylate), propylene glycol, ethylene glycol (?), metaldehyde, organotin, pentaborane

^a**Bold type** = best supported by available evidence – see text for referenced discussion

GABA γ -aminobutyric acid, *GBL* gamma-butyrolactone, *GHB* gamma-hydroxybutyrate, *NMDA* *N*-methyl-D-aspartate, *SIADH* syndrome of inappropriate diuretic hormone secretion

salicylate), and hypercalcemia (e.g., mithramycin)

- The neurotoxic mechanisms of action for a large array of proconvulsant substances, including camphor, metaldehyde, cicutoxin, organotins, pentaborane, and tramadol, are unknown. The reader is referred to Table 2 for a mechanistically based listing of various drugs, chemicals, and natural toxins that can induce seizures.

Pathophysiology of Neurologic Sequelae and Systemic Complications

The development of neurologic sequelae of toxicant-induced convulsions, particularly when seizure activity is prolonged, likely involves excessive NMDA-glutamate-mediated influx and intracellular accumulation of calcium, which triggers events (e.g., apoptosis) that result in cell death. The relative importance of this mechanism, compared with the hypoxic-ischemic injury that might occur as a result of simple asphyxiation, is supported by the experimental occurrence of neuronal injury well before cerebral demand for oxygen exceeds supply [9, 74]. Irreversible neuronal injury has been shown to occur within 1 h of the onset of seizure activity [7, 9], whereas cerebral blood flow and oxygenation increase dramatically during the initial phase of SE and do not decline significantly until after several hours of seizure activity [9].

Neuronal tissue necrosis, atrophy, and sclerosis can result from relatively prolonged seizure activity and tend to occur in areas of the hippocampus where NMDA-glutamate receptors are relatively concentrated. This tissue injury ultimately may result in the formation of an epileptic focus [9]. Cerebral edema, herniation, cerebral hypoperfusion, and brain death represent a common lethal sequence of events after severe, prolonged generalized SE.

Numerous other systemic complications may occur as a result of toxicant-induced convulsions, particularly when convulsions are prolonged [9, 75, 76]. Respiratory failure may occur as a result of central apnea, upper airway obstruction, aspiration, or noncardiogenic pulmonary edema

secondary to persistent elevation of pulmonary vascular pressure. The consequences of marked, diffuse increase in skeletal muscle contractions include hyperthermia (also may be centrally mediated); rhabdomyolysis, with attendant hyperkalemia and myoglobinuric renal injury; and metabolic acidosis from increased consumption of oxygen and energy reserves [77]. The hyperadrenergic tone of the convulsing individual is manifested clinically by hypertension, cardiac tachydysrhythmias, and initial hyperglycemia. Experimental and clinical evidence supports the notion that hyperthermia, hypoxia, hypotension, and cerebral hypoperfusion that occur during relatively prolonged convulsive activity exacerbate neuronal injury and promote continuation of seizure activity [74, 75].

Clinical Features

Toxicant-induced convulsions may occur with or without clinical “warning” symptoms (e.g., aura) or signs (e.g., altered mental status). Although seizures that occur after overdose of tricyclic antidepressant drugs commonly occur after decline in sensorium, seizures occurring as a result of acute supratherapeutic and, in some cases, therapeutic exposure to some agents (e.g., bupropion) may occur without an obvious clinical prodrome. With some extended release preparations, seizures may be delayed. In one study of bupropion XL overdoses, a seizure occurred in 32% of patients. Of the 32% of patients who experienced a seizure, the initial seizure was delayed more than 8 h after ingestion in 24% of cases [78].

Other agents for which the clinical onset of proconvulsant effect is characteristically rapid, abrupt, or without obvious warning include isoniazid [38], amoxapine, camphor, cicutoxin, cyanide, hydrogen sulfide, lidocaine, organochlorine insecticides such as lindane and toxaphene, and strychnine.

Most toxicant-induced seizures occur as generalized, tonic-clonic (“grand mal”) episodes [24], with the relatively rare exception of focal seizure activity in individuals with preexisting epileptogenic foci [25]. Myoclonus (brief

muscular contractions typically lasting <0.1 s [25] may be the most frequently documented convulsant effect of some agents, such as penicillin [79], normeperidine [80, 81], and selective serotonin reuptake inhibitors [82]. The convulsive episodes that occur as a result of strychnine's actions at inhibitory glycine-gated chloride channels in the spinal cord and lower brainstem are characterized by opisthotonos and tonic symmetric back and limb extensor spasm (spinal convulsions) without ictal or interictal change in sensorium. It is incumbent on the clinician to carefully distinguish between true seizure activity and abnormal motor activity resulting from voluntary and involuntary movement disorders, such as pseudoseizures, tremor, dystonia, akathisia, chorea, and athetosis (Table 3) [83].

As electrical seizure activity continues, the clinical features of such an episode may be more subtle or even absent [84]. The occurrence of nonconvulsive SE should be considered in an individual whose sensorium remains depressed after an overt convulsive episode. It has been estimated that at least 20% of SE episodes are nonconvulsive [2], with an estimated prevalence of nonconvulsive SE by electrographic case definition of 26% among comatose patients and those with subtle convulsive movements, such as "muscle twitches or tonic eye deviation" [10]. Nonconvulsive SE is even more likely to occur in the emergency department or intensive care unit than in other clinical settings, where pharmacologic masking of seizure activity frequently occurs owing to the use of neuromuscular blocking agents.

Seizure activity that is prolonged, recurrent, or refractory to initial treatment suggests poisoning by a member of a relatively select group of toxicants, notably theophylline, isoniazid, and certain older antidepressant drugs (e.g., amoxapine). This observation was reflected in the findings of Olson and colleagues [15], who reported in their series of nearly 200 toxicant-induced convulsive episodes the proportional occurrence of multiple or prolonged seizures (or both) after acute overdose of antidepressants (29%), theophylline (40%), and isoniazid (50%).

Few studies have looked at the specific complications of drug-induced seizures. It appears that

Table 3 Differential diagnosis of toxicant-induced seizures

Toxic neuromuscular disorders that may be mistaken for seizures
Serotonin syndrome ^a
Acute dystonia (butyrophenones)
Chorea (cocaine)
Akathisia (phenothiazines)
Strychnine ^b
Tetanus ^b
Neurotoxic scorpion envenomation (<i>Centruroides sculpturatus</i>)
Nontoxic causes of seizure disorders
Stroke (hemorrhagic, nonhemorrhagic)
Subarachnoid hemorrhage
Traumatic brain injury (contusion, hemorrhage)
Intracranial neoplasm
Intracranial infection (abscess, meningitis, encephalitis)
Metabolic/electrolyte disorder (hypoxemia, hypoglycemia, uremia, hyponatremia, hypernatremia, hypocalcemia, hypomagnesemia)
Idiopathic (epilepsy)

^aAlthough the neurologic presentation of serotonin syndrome commonly is limited to muscular rigidity and myoclonus, it also may include more clinically overt seizure activity

^bStrychnine-induced and tetanus-induced convulsions are mediated primarily by effects at the level of the spinal cord (hence the use of the term spinal convulsions to describe the seizure-like posturing and movements observed in the former) and are not considered true seizures

there is a relatively high risk of complications in patients admitted in the emergency department after drug-induced seizures in comparison with seizures from other etiologies. In a retrospective analysis dealing with 121 patients who presented seizures after toxic exposure, risk factors associated with morbidity and mortality were investigated [85]. Complications were divided in the following categories: prolonged hospital stay (>72 h), need for endotracheal intubation, status epilepticus, anoxic brain injury, or death. The impact of ten predictor variables on these outcomes was analyzed: gender, reason for exposure, substance type, primary decontamination method, initial antiepileptic medication given (after benzodiazepines), presence of initial acidosis, hyperthermia, rhabdomyolysis, hyperglycemia, or hypotension. In the multivariate analysis, three

predictors demonstrated statistically significant associations: stimulant exposure, initial acidosis, and hyperglycemia. It remains, however, difficult to affirm whether acidosis and hyperglycemia were true contributors to complications or merely a consequence of generalized seizures. The association between hyperthermia and morbidity or mortality has to be further investigated.

Olson and colleagues [15] also observed in their series of toxicant-induced convulsion cases that the most frequent complications were respiratory failure (34%), cardiac arrhythmias (22%), hypotension (16%), hyperthermia (7%), rhabdomyolysis (6%), and death (9%). Systemic complications typically are more severe and occur more commonly with prolonged seizure activity. Hyperthermia has been documented to occur in SE at case frequencies ranging from 28% to 79% [74]. Prolonged strychnine-induced convulsions in one reported case resulted in hyperthermia (peak body temperature 43 °C at 3 h postexposure), metabolic acidosis (initial arterial pH 6.55), acute rhabdomyolysis (peak serum creatine phosphokinase 359,000 mU/mL [5983 µmol/L] approximately 2 days later), and myoglobinuria with transient acute renal insufficiency (peak serum creatinine 3.7 mg/dL [327 µmol/L]) [86]. The same patient's clinical course subsequently was remarkable for diffuse weakness, severe myalgias, and transient upper and lower limb motor deficits consistent with acute, reversible compressive neuropathy. Postictal focal neurologic deficits of central origin may be transient (e.g., Todd's paralysis) or permanent in instances of irreversible cerebral insult.

Diagnosis

Patient History

Obtaining a detailed history is crucial to effective decision making in the treatment of patients who have had toxic exposure to proconvulsant agents. A search for information regarding witnessed or possible unwitnessed exposure should include currently prescribed or available medications,

nature of the occupational setting and presence of proconvulsant agents, and material evidence or history corroborating alcohol or illicit substance abuse. The presence of preexisting conditions, such as renal insufficiency, musculoskeletal disorders, epilepsy, and psychiatric illness, may lead to the early identification of a toxic convulsive etiology and prompt appropriate management decisions, including discontinuation of an offending pharmaceutical agent. Risk factors for toxicant-induced convulsions that may be discernible from a careful review of the patient's medical history include the following:

- Drug or alcohol (or both) withdrawal (e.g., benzodiazepine, meprobamate [which is rarely used], or barbiturate sedative-hypnotics) and drug overdose, with the paradoxical inclusion of some anticonvulsants (e.g., phenytoin, carbamazepine)
- Advanced age or demonstrated reduction in renal clearance (e.g., penicillins, cephalosporins [38], normeperidine [81, 87])
- Impaired drug metabolism (e.g., isoniazid and slow acetylator status)
- Drug-drug interaction (e.g., fluoroquinolone antibiotics, cyclosporine, and theophylline [88, 89])
- Preexisting or underlying seizure disorder
- Intrathecal, intraventricular, or intravenous route of administration (e.g., penicillin and other antibiotics, bethanechol) [24, 38, 90]

Bedside Evaluation

The bedside evaluation of a patient at risk for onset or recurrence of toxicant-induced convulsions and associated complications should focus on the presence of other signs that may provide clues to the nature of the toxic exposure, such as tricyclic antidepressant-induced electrocardiographic abnormalities or organophosphate-induced cholinergic manifestations. The clinical approach should emphasize continued close monitoring for evidence of seizure activity (e.g., signs of adrenergic excess, including pupillary dilation, hypertension, and tachycardia) and should

anticipate the development of complications of prolonged seizure activity, such as hypoxemia, respiratory failure, hyperthermia, hypoglycemia, and rhabdomyolysis.

Laboratory Evaluation

Appropriate laboratory evaluation includes routine monitoring of arterial blood gases, bearing in mind that arterial pH may be lower than 7.0 if measured during or immediately after a seizure episode. Other indicated studies include serum chemistries, with particular attention to bicarbonate, anion gap, glucose, sodium, calcium, and magnesium, and toxicological analysis of urine or blood or both, particularly in instances in which the results support clinical decision making and treatment (e.g., in theophylline or tricyclic antidepressant poisoning) or are of forensic importance. The rapid urine drug immunoassays that commonly are employed in clinical treatment settings are severely limited in some cases by their low sensitivity or specificity or both. Rapid tricyclic antidepressant “screens” that have been commercially available have been notably false positive for a variety of other drugs, such as phenothiazines, diphenhydramine, carbamazepine, orphenadrine, and cyclobenzaprine, and have failed to detect the presence of other cyclic antidepressant drugs, such as amoxapine [91].

Transient pleocytosis is a common, nonspecific finding in the cerebrospinal fluid obtained during the early postictal interval, with total cerebrospinal fluid white blood counts ranging from 1/ μ L to 50/ μ L in about 15% of patients after seizure episodes [25, 92]. It has been suggested that serum prolactin and adrenocorticotrophic hormone levels, which have been observed to increase and stay elevated for 10–20 min after generalized seizures [21], may help to differentiate seizure from pseudoseizure. These elevations also are recognized to be unreliable markers of seizure activity, however, because their specificity frequently is low in critically ill patients with multiple confounding disorders, and their sensitivity declines with increasing seizure frequency [2].

Electroencephalogram

The most valuable test employed during the diagnostic evaluation and management of patients with documented or suspected toxicant-induced convulsions is EEG.

The interpretation of EEG data should be made by a neurologist with an expertise in drug-induced EEG changes. This is particularly true for substances that can cause unusual EEG changes mimicking epilepsy. Toxic encephalopathy with epileptic-like changes (spikes, periodic shape waves) has been demonstrated with baclofen and 4-aminopyridine. On the other hand, electroencephalographic recordings made in patients receiving stable doses of bupropion showed that 19.8% of the population had abnormal, asymptomatic EEG findings. The incidence of sharp waves was significantly increased in women [93].

A role for continuous, rather than intermittent, EEG monitoring is supported by continued uncertainty as to the “extent to which occasional seizures produce incremental neuronal damage in refractory SE” [2]. This role is underscored further by observations that CNS injury can occur as a consequence of subclinical seizure activity within minutes of its onset and is supported by the argument that continuous EEG enhances the sensitivity and specificity of clinical seizure monitoring. Continuous EEG monitoring is especially applicable in instances in which the use of sedative-hypnotic agents or neuromuscular blockade blunts or abolishes the clinical seizure activity. Alternatively, the nonconvulsant (e.g., choreiform) effects of certain agents (e.g., cocaine) or manifestations of hypoxic-ischemic brain injury (e.g., decerebrate posturing) may be misinterpreted as seizures [2].

Further appreciation of the role of EEG in critically ill patients is based on the observation that as documented electrical seizure activity becomes recurrent or prolonged, the clinical manifestations become more subtle (e.g., facial twitching, clonic ocular movements) or may be clinically indistinguishable from coma of nonictal origin [74]. In a study of patient transfers to a neurological intensive care unit with a transfer diagnosis of SE, only 14 of 26 (54%) patients

satisfied the electrical definition for SE; of the remaining 12 patients, half were determined to be in drug-induced coma or were encephalopathic, and the other half were determined to have pseudoseizures [94].

EEG monitoring should be instituted for any patient who is managed with relatively long-acting neuromuscular blockade, who does not regain consciousness after initial anticonvulsant treatment, or who requires prolonged treatment for refractory status [74]. SE may be defined and recognized readily on EEG as “continuous spike, sharp wave, or sharp and slow wave discharges with a generalized distribution persisting for all or most of a tracing lasting 20 min or longer” [12]. Many electrographic patterns of seizure activity can occur, however, depending on the specific cause, neuroanatomy, and physiology involved, warranting formal interpretation by a qualified expert in most, if not all, instances [25]. Magnetic resonance imaging signal abnormalities in the hippocampus have been associated with SE [25]; however, the diagnostic utility of this and other imaging modalities in the evaluation and management of toxicant-induced convulsions has not been established.

Electrocardiogram

An electrocardiogram should be obtained in any patient presenting with isolated seizures or status epilepticus. Many drugs causing seizures are also cardiotoxic. The main electrocardiographic findings suggesting toxin-induced seizures are a widening of the QRS complex induced by a drug influencing the sodium channel and a prolongation of the QT interval by an agent inhibiting the outward potassium rectifier current.

Differential Diagnosis

The differential diagnosis of seizure-like activity that fails to fulfill the clinical and electrical definition of true seizure episode includes decorticate/decerebrate posturing, choreiform or athetoid movements, acute dystonic posturing, increased motor tone associated with hyperserotonergic states, pseudoseizure, posthypoxic myoclonus

[4, 94], syncope, migraine, drop attacks, panic attacks, cataplexy, and hysterical pseudoseizures [25]. Nontoxic etiologies of convulsive episodes that meet accepted case definition for true seizure activity commonly are divided into two clinical subgroups on the basis of whether the seizure activity or associated neurologic deficits they cause are predominantly focal or nonfocal.

Key Points in the Evaluation of Toxin-Induced Seizures

1. Suppression of clinical and electrical seizure activity is the main goal of therapy.
2. Phenytoin has no rational role in the treatment of toxicant-induced seizures (possible exceptions are aminopyridine antimuscarinic drugs).
3. Benzodiazepine and barbiturate anticonvulsant drugs are the mainstays of pharmacologic treatment in patients with toxicant-induced convulsive disorders.
4. Intravenous pyridoxine is the preferred first-line treatment for isoniazid-induced neurotoxicity; it should be administered on a gram-for-gram basis if the toxicant dose is known or in 5-g incremental bolus doses if isoniazid dose is unknown.
5. Administration of high-dose phenobarbital, higher-potency barbiturates (e.g., pentobarbital), midazolam, or propofol may be effective in the management of toxicant-induced convulsions that are refractory to first-line and second-line anticonvulsant pharmacotherapy.

Treatment

As generally applies to the management of ongoing or recurrent seizures of nontoxic origin, termination and suppression of further seizure activity are paramount in the management of a patient with toxicant-induced convulsions. Stopping seizure activity may play an integral role in

stabilizing the airway, ventilation, and circulatory status of the affected individual. In addition, *delay in termination of SE is associated with a marked decline in responsiveness to subsequent anticonvulsant treatment*. Lowenstein and Alldredge [74] observed an 80% response rate to first-line anticonvulsant treatment if it was initiated within 30 min of seizure onset and a decrease in response rate to less than 40% if treatment was begun 2 or more hours after onset of seizures.

The principal desired characteristics of an anticonvulsant regimen designed for use in a critical care setting are initial rapid onset of effect, subsequent prolonged duration of effect, marked enhancement in efficacy for instances when seizures prove refractory to initial treatment, and acceptably low acute and chronic adverse effect rates. Although some anticonvulsant drugs (e.g., phenytoin, fosphenytoin) are recommended widely for use in the general management of SE [2, 7, 25, 74], other choices may be more rational in the management of toxicant-induced convulsions, as discussed subsequently.

Initial Anticonvulsant Therapy

The ultimate goal of acute anticonvulsant drug treatment in the critical care setting is suppression of clinical and electrographic seizure activity or induction of a burst-suppression pattern on EEG, whichever occurs first [74]. Long-term anticonvulsant maintenance therapy usually is not indicated in patients in whom the sole cause of seizure activity is a transient metabolic or toxic disturbance (i.e., in the absence of a preexisting CNS structural disorder or seizure focus and without the development of a new and more permanent focus for recurrence) [7].

Management of seizures involves provision of supportive care and administration of an anticonvulsant to terminate the seizure promptly.

First-Line Therapy

Benzodiazepines are recommended as first-line therapy. Evidence for this is mainly from

nonpoisoned patients, as there are no randomized controlled trials or large case series that have investigated the effectiveness of benzodiazepines in poisoned patients. The level of evidence should be categorized as II-2. The choice of the benzodiazepine (diazepam, midazolam, or lorazepam) usually relies upon the physician's experience or local hospital policy on first-line benzodiazepine for seizures.

Benzodiazepines, such as diazepam and lorazepam, bind to the benzodiazepine receptor on the GABA_A chloride ionophore to increase the binding affinity of GABA to its receptor and to increase the frequency of Cl⁻ channel opening in response to GABA binding (Fig. 5). In addition, there is evidence that diazepam inhibits adenosine reuptake [96, 97], enhancing adenosinergic inhibition of excitatory neurotransmitter (e.g., glutamate) release. Lorazepam and diazepam exhibit a similar clinical response time (i.e., time to cessation of seizure activity); however, lorazepam has been shown to have a longer duration of anticonvulsant effect (12–24 h vs. 15–30 min) and is the preferred initial drug choice in SE management according to some authorities [7]. The successful use of lorazepam in the treatment of seizures, myoclonus, and other neurologic manifestations of serotonin syndrome is discussed in ► Chap. 24, “Serotonin Syndrome” and elsewhere [98]. Based on other, more toxicant-specific information sources, diazepam is the initial treatment of choice for convulsions caused by nerve agents (e.g., soman) [53, 99], hydroxychloroquine [100], or chloroquine overdose [101]. This recommendation simply may reflect the lack of experience to date with lorazepam treatment of these particular toxins.

The initial dosing for benzodiazepines is given in Table 4 [102]. Intravenous administration of antiepileptic drugs should always be the preferred route of treatment. However, depending on the treatment setting (i.e., prehospital emergency department or intensive care unit), alternative routes of administration may be considered. In the pediatric population, diazepam may be administered intrarectally (IR) in the available gel form.

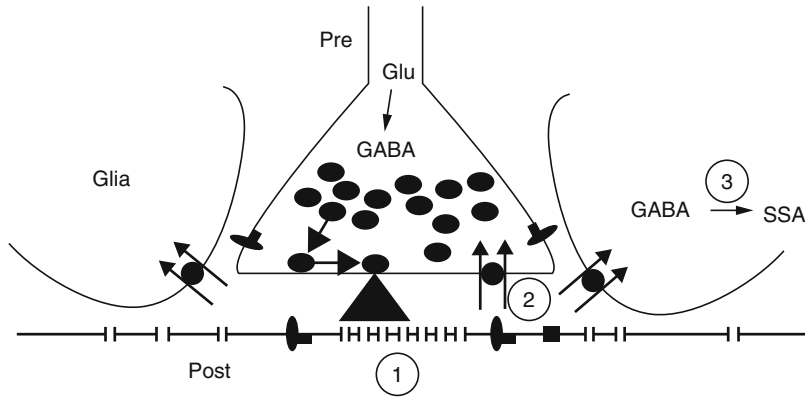


Fig. 5 The GABAergic synapse as a target of anticonvulsant drugs. GABA is synthesized from glutamate in the presynaptic terminal and is packed into small synaptic vesicles. After release, GABA activates postsynaptic ion channels (GABA_AR, marked “1”) which mediate the chloride influx and thereby the inhibition of the postsynaptic cell. From the synaptic cleft, GABA is removed into the presynaptic terminal and into an adjacent glial cells by GABA uptake (“2”). A fraction of the transmitter is

degraded into succinic semialdehyde by GABA transaminase (“3”), which is present in the glial cells as well as in neurons. Pre- and postsynaptic metabotropic GABA_BR are indicated by ellipsoid bodies in the cell membrane but are no major target for anticonvulsants presently in use. GABAergic drugs against epilepsy act as positive modulators of the GABA_AR (“1”), blockers of the GABA uptake (“2”) or inhibitors of GABA degradation (“3”) (From Offermanns and Rosenthal [95])

Table 4 Intermittent drug dosing for status epilepticus

Drug	Initial dosing	Administration rates and alternative dosing recommendations	Serious adverse effects
Diazepam	0.15 mg/kg IV up to 10 mg per dose, may repeat in 5 min Peds: 2–5 years, 0.5 mg/kg (IR); 6–11 years, 0.3 mg/kg (IR); greater than 12 years, 0.2 mg/kg (IR)	Up to 5 mg/min IV pump	Hypotension Respiratory depression
Lorazepam	0.1 mg/kg IV up to 4 mg per dose, may repeat in 5–10 min	Up to 2 mg/min IV pump	Hypotension Respiratory depression
Midazolam	0.2 mg/kg IM up to maximum of 10 mg, max 0.2 mg/kg IV	Peds: 10 mg IM (>40 kg); 5 mg IM (13–40 kg); 0.2 mg/kg (intranasal); 0.5 mg/kg (buccal)	Respiratory depression Hypotension
Phenytoin	20 mg/kg IV, may give an additional 5–10 mg/kg	Up to 50 mg/min IV, may give additional dose 10 min after loading infusion	Arrhythmias Hypotension
Phenobarbital	20 mg/kg IV, may give an additional 5–10 mg/kg	50–100 mg/min IV, may give additional dose 10 min after loading infusion	Hypotension Respiratory depression
Valproate sodium	20–40 mg/kg IV, may give an additional 20 mg/kg	3–6 mg/kg/min, may give additional dose 10 min after loading infusion Peds: 1.5–3 mg/kg/min	Hyperammonemia Hepatotoxicity Thrombocytopenia

Adapted from Brophy et al. [102]. IV intravenous, IR intrarectal, IM intramuscular

Intramuscular (IM) midazolam or lorazepam is also an alternative to intravenous diazepam or lorazepam. On the basis of the published case experience and at least one prospective randomized study (performed, however, in a nonpoisoned pediatric population), termination of seizure activity (within 1–10 min) was observed after IM midazolam (0.2 mg/kg, max 7 mg) and compared favorably with treatment with intravenous diazepam (0.3 mg/kg, max 10 mg) [103].

Second-Line Therapy

There is no high-quality clinical trial evidence with which to select a second-line treatment for toxicological seizures unresponsive to benzodiazepines and evolving to SE. When benzodiazepines have failed, the debate concerns the choice between barbiturates or other anticonvulsants as second-line agents. In a systematic review of the evidence concerning the choice of phenytoin or barbiturates as second-line therapy for toxicological seizures, Shah et al. were not able to find any RCT comparing both drugs [104]. Experimental data suggest that phenytoin is unlikely to be effective or may be proconvulsant in some instances. Phenobarbital or thiopentone is probably a better option, but scientific evidence is based only on a few experimental data with a limited number of toxins and a limited number of case reports.

Although phenytoin and its phosphoester congener fosphenytoin may be appropriate choices for the treatment of patients with idiopathic seizure disorders or patients with defined structural or electrical foci of seizure activity, they are not rational choices of therapy for toxicant-induced convulsions, which result from a diffuse lowering of neuronal seizure threshold, rather than a spread of electrical activity from a focal origin. Phenytoin frequently is recommended as a second-line and maintenance anticonvulsant in the treatment of SE of nontoxicant origin [7, 10, 25, 74]. Phenytoin-induced blockade of voltage-dependent sodium channels inhibits the propagation of seizure activity from active electrical foci but has limited ability to elevate the threshold for seizures induced by GABA-antagonistic or glycine-antagonistic convulsant drugs (e.g., strychnine, picrotoxin, pentylenetetrazol) [105, 106].

Although it may be effective at preventing the spread of abnormal electrical activity from a CNS focus, phenytoin would not be expected to suppress the characteristically diffuse lowering of seizure threshold or oppose the increase in neuronal excitability induced by proconvulsant drugs, chemicals, and toxins.

A considerable body of experimental evidence exists indicating phenytoin's lack of anticonvulsant efficacy in the suppression of seizures induced by a variety of proconvulsant substances, including penicillin [107–109], pilocarpine [110, 111], cocaine [112], pyrethroids (e.g., deltamethrin, permethrin) [113], local anesthetics (e.g., procaine, lidocaine) [114, 115], theophylline [116–118], pentylenetetrazol [119], picrotoxin [119], strychnine [119], NMDA [26], and organophosphate insecticides [53]. There is evidence in animals that administration of phenytoin may enhance the proconvulsant potency of theophylline [117]. Phenytoin use in experimental animals has been reported to increase mortality rate in cyclic antidepressant toxicity [120]. One exception to phenytoin's apparent lack of anticonvulsant efficacy in toxicant-induced convulsions seems to be 4-aminopyridine-induced seizures, wherein anecdotal clinical and experimental animal evidence suggests phenytoin is efficacious [63, 64]. The mechanism of 4-aminopyridine-induced neurotoxicity is not precisely known, but seems to be related to the blockade of potassium channel. There also are ample clinical data to support the lack of efficacy of phenytoin in the treatment of alcohol withdrawal seizures [121–123].

The clinical evidence available to support recommendations regarding the use of phenytoin in the management of toxicant-induced convulsions is far more limited. The Veterans Administration (VA) Status Epilepticus Cooperative Study Group compared the initial anticonvulsant efficacy of intravenous lorazepam, phenobarbital, phenytoin, and diazepam followed by phenytoin after treatments were assigned randomly to patients with generalized convulsive SE [10]. In this study, the definition of treatment success was cessation of clinical and electrical evidence of seizure activity within 20 min of the start of infusion, with no

further seizure occurrence during the first hour after initiation of treatment. The 43.6% success rate for patients treated first with phenytoin was the lowest of any of the treatment groups and was significantly lower than that for lorazepam, 64.9% ($p < 0.001$). The significant difference between the lorazepam and phenytoin groups in the length of time required to complete drug infusion (mean infusion times – lorazepam, 4.7 min; phenytoin 33 min) might explain the observed overall difference in efficacy. Phenobarbital, which was infused over a mean interval of 16.6 min, was as effective as lorazepam, however, in patients with overt generalized convulsive SE, suggesting an alternative explanation (i.e., other than difference in infusion time) for the observed differences in treatment success.

Although the VA Cooperative Study included a group of patients whose episodes of SE were deemed to have resulted from the “toxic effects of therapeutic or recreational drug” exposure, the relevance of the study’s conclusions to the current discussion is limited by the absence of comparisons made among the various treatments in this toxicologic substratum of patients. Given the small size of this group ($n = 31$), it is unlikely that meaningful comparisons could be made among its treatment subgroups.

In general, medications that cause neuronal hyperpolarization via increases in chloride influx (or potassium efflux) and that increase neuroinhibitory tone or reduce neuroexcitatory tone (or both) by suppressing NMDA-glutamate sodium and calcium influx are, in theory, rational choices of therapy for toxicant-induced convulsions. Consistent with this rationale and supported by previously cited clinical trial data [10], widely accepted anticonvulsant regimens for the general treatment of SE begin with parenteral benzodiazepines (diazepam or lorazepam or both) [2, 7, 74]. Phenobarbital, frequently a third-line agent in the broader treatment of SE, is a more appropriate second-line choice than phenytoin for toxicant-induced recurrent seizures or SE. This assertion is based on previously stated arguments against the use of phenytoin in toxicant-induced convulsions and on the rationale that barbiturates are more likely than phenytoin to act in an

additive or synergistic manner with other GABA agonists, such as diazepam and lorazepam, to suppress toxicant-induced diffuse increases in neuronal electrical excitability.

Adverse acute effects of intravenous benzodiazepines include hypoventilation, depressed sensorium, and hypotension. With prolonged continuous infusion of propylene glycol-containing formulations of some drugs, such as diazepam (45% propylene glycol by volume) or lorazepam (80% propylene glycol by volume), coma, hyperosmolality, anion gap metabolic acidosis, and hyperlactatemia may occur [124–126]. This is a possible reason to prefer intravenous midazolam. Barbiturates also bind to the GABA_A complex, enhancing the binding of GABA and increasing the duration of Cl[−] channel opening and Cl[−] influx [35]. At high concentrations, some barbiturates directly open the Cl[−] channel and exert a direct agonist action on chloride influx and neuronal hyperpolarization. Experimental evidence supports the superiority of phenobarbital over phenytoin in preventing theophylline-induced seizures and death [117, 118]. Recommended dosing for phenobarbital as a second-line anticonvulsant after diazepam or lorazepam is 20 mg/kg intravenously infused at a rate of 50–100 mg/min. The time required for safe administration of an intravenous loading dose of phenobarbital, roughly 20–30 min in a 70-kg individual, is potentially a disadvantage compared with other agents (e.g., benzodiazepines or other barbiturates, such as thiopentone or pentobarbital) in the initial treatment of sustained convulsive activity. As Treiman and colleagues [10] observed, however, there was no significant difference in the initial anticonvulsant success rate between phenobarbital-treated and lorazepam-treated patients with SE in their study. There also may be prophylactic anticonvulsant and other favorable (e.g., sedative) effects from administering phenobarbital to highly seizure-prone individuals, such as individuals who present with moderately severe theophylline toxicity (e.g., with agitation, tremor, tachycardia) [127]. Potential acute adverse effects of therapy with parenteral phenobarbital and other barbiturates, especially the higher-potency agents, such as

thiopentone and pentobarbital, include CNS and respiratory depression and hypotension. Because of the possibility of hypotension and respiratory depression with a full loading dose in barbiturate-naïve patients, a common, yet untested regimen, is to give an initial phenobarbital dose of 400 mg in adults and repeat as necessary.

Special Conditions

From a pathophysiological and therapeutic standpoint, isoniazid-induced convulsions represent a unique subset of toxicant-induced seizures. The underlying proconvulsant mechanism of isoniazid involves inhibition of GABA synthesis and decline in presynaptic and synaptic GABA. Anticonvulsant drugs that work via indirect GABA agonism and require the presence of GABA to exert an effect on GABA_A chloride channel conductance are relatively ineffective in situations of synaptic GABA deficiency. Administration of pyridoxine, an essential cofactor in GABA synthesis, effectively restores GABA synthesis to adequate levels and promotes a return toward normal GABAergic neuroinhibitory tone [38]. Pyridoxine hydrochloride should be administered intravenously for acute isoniazid-induced neurotoxicity and given in gram-for-gram amounts if the toxicant dose is known or in 5-g incremental bolus doses if isoniazid dose is unknown (level of evidence II-3). The experimental demonstration of synergism between diazepam and pyridoxine in the treatment of acute isoniazid toxicity in dogs and rats [128, 129] provides support for the administration of indirect GABA agonists such as diazepam along with pyridoxine to patients with isoniazid-induced convulsions. This combination may be particularly beneficial if the amount of pyridoxine available for use in the emergent treatment setting is limited (see ► Chap. 65, “Isoniazid and Related Hydrazines”).

Pharmacological antagonists, such as naloxone and flumazenil, employed in the emergent reversal of toxic effects of CNS-depressant agents, such as opiate μ -receptor and benzodiazepine receptor agonists, may oppose but more often enhance the proconvulsant risks associated with administration and withdrawal of these drugs [130]. Although naloxone, based on experimental evidence, may antagonize the convulsant effects of propoxyphene

[131, 132], it also has been observed to potentiate the proconvulsant effects of meperidine's major oxidative metabolite, normeperidine [133], and of pentazocine [134] and should be used with caution in these settings. It has been well substantiated by clinical experience that the use of flumazenil (see ► Chap. 148, “Flumazenil”) should be avoided in patients at risk for acute benzodiazepine antagonist-induced withdrawal or in whom the presence of benzodiazepine agonist effects may protect against the proconvulsant effects of other drugs (e.g., tricyclic antidepressants) [135]. Although some clinical studies suggest that flumazenil can be administered safely empirically in unclear cases of multiple drug poisoning [136, 137], the conclusions reached by other investigators about the relative safety of this approach are limited by the confounding and neuroprotective presence of other anticonvulsant agents (e.g., phenobarbital) [138].

The use of propofol, levetiracetam, or lacosamide in the treatment of toxicant-induced seizures and SE is discussed below.

Treatment of Refractory Status Epilepticus

In addition to prompting questions as to the underlying etiology and appropriate selection of first-line treatment, prolonged or recurrent seizure activity may warrant increases in the potency, duration, and attendant risks of anticonvulsant therapy. This approach may require further provision of aggressive supportive measures before and during treatment (e.g., neuromuscular blockade, intubation, mechanical ventilation, external cooling, intravenous vasopressor therapy). Supportive care should include, when indicated, supplemental thiamine (100 mg IV three times a day), if there is any reasonable risk of deficiency; intravenous dextrose, if objective evidence (e.g., rapid blood assay) or suspicion of hypoglycemia supports the need; intravenous bicarbonate for correction of severe metabolic acidosis; and maintenance of brisk urinary output, with urine pH greater than 6.5, in an effort to prevent myoglobinuric renal tubular injury.

Table 5 Dosing for refractory status epilepticus

Drug	Initial dosing	Continuous infusion dosing recommendations	Serious adverse effects
Midazolam	0.2 mg/kg; administer at an infusion rate of 2 mg/min	0.05–2 mg/kg/h CI Breakthrough SE: 0.1–0.2 mg/kg bolus, increase CI rate by 0.05–0.1 mg/kg/h every 3–4 h	Respiratory depression Hypotension
Pentobarbital	5–15 mg/kg, may give additional 5–10 mg/kg; administer at an infusion rate of <50 mg/min	0.5–5 mg/kg/h CI Breakthrough SE: 5 mg/kg bolus, increase CI rate to 0.5–1 mg/kg/h every 12 h	Hypotension Respiratory depression Cardiac depression
Propofol	Start at 20 mcg/kg/min, with 1–2 mg/kg loading dose	30–200 mcg/kg/min CI Use caution when administering high doses (>80 mcg/kg/min) for extended periods of time (>48 h) Contraindicated in young children Breakthrough SE: increase CI rate by 5–10 mcg/kg/min every 5 min or 1 mg/kg bolus plus CI titration	Hypotension Respiratory depression Propofol infusion syndrome (cardiac and renal failure, rhabdomyolysis, metabolic acidosis)
Thiopentone	2–7 mg/kg; administer at an infusion rate <50 mg/min	0.5–5 mg/kg/h CI Breakthrough SE: 1–2 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h	Hypotension Respiratory depression Cardiac depression

Adapted from Brophy et al. [102]. *SE* status epilepticus, *CI* continuous infusion

The global level of evidence for the pharmacological management of refractory status epilepticus is II-3 to III. Suggested dosing for refractory status epilepticus is illustrated in Table 5. A first recommended approach to refractory SE is the addition of midazolam, a potent, short-acting benzodiazepine, as an initial 0.2-mg/kg slow intravenous bolus followed by infusion at 0.75–10 µg/kg/min [74]. One of the advantages of this approach is that injectable formulations of midazolam do not contain propylene glycol and are not associated with propylene glycol toxicity during relatively prolonged infusion therapy.

As an alternative to phenobarbital, more potent barbiturates are frequently included in published regimens for refractory SE. Pentobarbital may be given at a recommended intravenous loading dose of 10–15 mg/kg administered over 1 h, followed by maintenance infusion at 0.5–1 mg/kg/h [74]. Thiopentone should be administered at a loading dose of 2–7 mg/kg (infusion rate < 50 mg/min), followed by maintenance infusion at 0.5–5 mg/kg/h.

The critical care provider should be prepared to institute pressor therapy, given the higher risk of

hemodynamic compromise with high-potency barbiturate anticonvulsants (see ► Chap. 46, “Barbiturates”).

Propofol is thought to act as a GABA agonist, with potent enhancement of chloride channel conductance in a manner that may be additive or synergistic with that of benzodiazepines or barbiturates [139]. A suggested propofol regimen for refractory SE that seems to be relatively widely endorsed by epileptologists consists of a 1–2-mg/kg loading dose, followed by infusion of 2–10 mg/kg/h [74]. The advantages of propofol and midazolam over other anticonvulsants include their rapid onset and short duration of action, allowing for prompt, continuous suppression of seizure activity during infusion and rapid assessment of neurologic status after discontinuation of treatment. Potential disadvantages of treatment with propofol include the associated high cost and elevated risks for hypertriglyceridemia and neuroexcitatory events, such as dyskinesias and convulsive movements, the latter being reported more frequently at doses less than 3 mg/kg [139]. Supporting clinical data include a published report that showed that intravenous

propofol bolus and maintenance infusion halted seizure activity in a 30-year-old woman who, after amoxapine overdose, had developed SE refractory to conventional therapy [140].

Adverse effects such as hypotension and bradycardia may be associated less frequently with propofol than with barbiturate anesthetic agents. This suggestion is challenged, however, by the findings of one clinical investigation comparing propofol with high-dose pentobarbital in the treatment of refractory SE [141]. Efficacy with regard to seizure control was not significantly different when the propofol and pentobarbital groups were compared, although the mean time to propofol-induced EEG burst suppression, approximately 2.5 min, was significantly shorter than that for pentobarbital, approximately 2 h. There was no significant increase in the incidence of adverse clinical effects, including hypotension, pneumonia, or prolonged intubation, in patients who received propofol compared with patients who received high-dose barbiturate treatment. The small number of patients (eight patients in each group) enrolled in this study and the severe systemic illness and multiorgan failure observed in both treatment groups limit interpretation of the outcome and dose–response data obtained in this study [139].

There is an increasing interest for an earlier introduction of more recent anticonvulsants (levetiracetam, lacosamide) as soon as benzodiazepines have failed. Besides promising data regarding efficacy, the main advantage of these recent drugs would be the absence of serious adverse effects and of significant drug–drug interactions. However, no data are available from poisoned population. In nonpoisoned patients, the relative effectiveness of five antiepileptic drugs (lacosamide, levetiracetam, phenytoin, phenobarbital, valproate) in the treatment of benzodiazepine-resistant convulsive status epilepticus was recently discussed from a meta-analysis of published studies. A total of 27 papers were available for data extraction. From the included studies, there was only one randomized double-blinded trial comparing valproate and phenobarbital. The levels of evidence of the studies were as follows: level 4 ($n = 18$), level 4- ($n = 3$), level 2b ($n = 5$), and level 1b ($n = 1$). Despite

numerous limitations (number of studies, bias, heterogeneity, etc.), the authors found that the highest efficacy was attributed to valproate, levetiracetam, and phenobarbital [142].

Key Points in the Management of Toxin-Induced Seizures

1. The fundamental pathophysiology of toxicant-induced convulsions involves relatively diffuse changes in central nervous system neurotransmitter balance, favoring neuroexcitatory over neuroinhibitory tone.
2. Risk factors for toxicant-induced convulsions include patient age, drug overdose or withdrawal, parenteral route of exposure (e.g., antibiotics), underlying seizure disorder, and impaired drug clearance.
3. As seizure activity becomes more prolonged, the risks of neuronal injury and systemic complications increase, clinical manifestations become less pronounced, and responsiveness to anticonvulsant treatment tends to decline.
4. Common systemic complications of toxicant-induced seizures include respiratory failure, aspiration pneumonitis, hyperthermia, rhabdomyolysis, and metabolic acidosis.
5. Subclinical status epilepticus occurs in a high percentage (26%) of critically ill patients with altered sensorium. Continuous electroencephalogram monitoring is essential in the management of patients at high risk for this occurrence (e.g., patients receiving neuromuscular blockers).

Special Populations

Age-related differences in general SE-related incidence, features, treatment, and outcome have been discussed thoroughly in the medical literature

[75, 143–145]. There is little published information, however, regarding such differences among various age groups of patients with toxicant-induced convulsive disorders. Nevertheless, it is appropriate to approach the evaluation and management of pediatric and geriatric patients with relatively high suspicion that age-related differences in risk factors (e.g., impaired drug clearance) and dose–response thresholds may predispose individuals in these age groups to the development of toxicant-induced seizures and related complications. Examples of clinical settings in which seizure occurrence has been observed to be age dependent include narcotic withdrawal [146], par-enteral propylene glycol administration [147], and parenteral antibiotic treatment [38].

There is a paucity of data describing which drugs are most commonly responsible for drug-induced seizures in children. Data obtained from a prospectively collected cohort of poisoned patients over a 2-year period showed that among 11,977 poisoning cases, pediatric patients (age < 18 years) represented 25.1% of the cases [148]. From these 3005 pediatric patients, 142 (4.7%) presented with drug-induced seizures. Most of the cases (75%) occurred in patients aged 13–18 years, and 61% resulted from intentional ingestions. Like in adults, antidepressants are the most common agent class, with a majority of the cases involving bupropion as etiologic agent. Anticholinergics and antihistamines were the second most common cause. Among infants and toddlers, sympathomimetics including illicit drugs were the leading agents.

Recommendations for the treatment of toxicant-induced SE in pediatric patients, based on recommendations for general management of pediatric SE, are essentially the same as for adults [75, 144]. Alternatives to intravenous anticonvulsant administration that are particularly appropriate considerations in younger pediatric patients include the intrarectal, intraosseous, and intramuscular (midazolam) routes.

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Management of a critically ill patient with cardiovascular disturbances requires the clinician to consider that a cardiac toxin may be involved. This chapter emphasizes recognition of cardiac arrhythmias, conduction abnormalities, and specific electrocardiogram (ECG) findings that might suggest the involvement of a cardiovascular toxin. First, relevant cardiac physiology and the toxic mechanisms pertinent to poisonings and overdose are reviewed. Next, we describe a clinical approach to the recognition and management of patients with rate and rhythm disturbances from cardiovascular toxins. Lastly, we discuss some specific cardiovascular toxins that show how autonomic disturbances, membrane-depressant effects, triggered rhythms, and systemic influences produce the protean manifestations of a patient with cardiac poisoning.

Cardiac Physiology

Understanding some basic principles of toxicity facilitates the management of critically poisoned patients with cardiovascular disturbances.

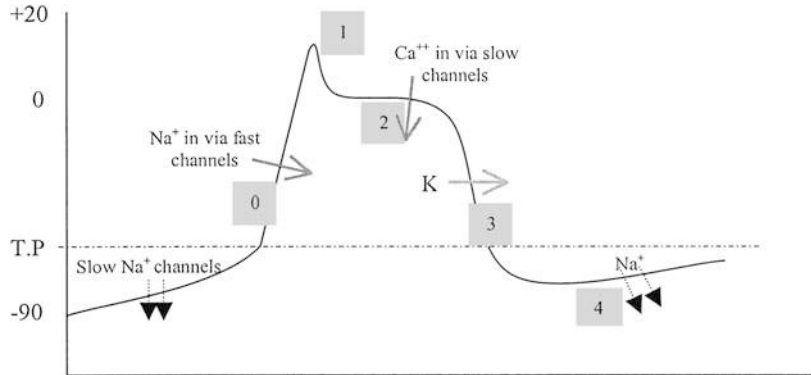
Myocardial Cell Physiology

Differing pharmacology of the three important transmembrane ion channels responsible for the cardiac cell action potential (AP) makes the myocardial cell unique with respect to therapeutic and

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Fig. 1 The five phases of transmembrane ion flow during action potential of an automatic myocardial cell with spontaneous diastolic depolarization. *TP* threshold potential



toxic actions of drugs and toxins. The three channels are (1) fast sodium channels, (2) slow calcium channels, and (3) outward potassium channels.

The AP of the cardiac cell has five phases (Fig. 1) [1]. When a cardiac cell AP reaches its threshold potential, opening of fast sodium channels results in a spikelike upward deflection due to the rapid influx of sodium ions (phase 0). The brief, rapid repolarization of the AP (the notch seen in phase 1) occurs via the efflux of potassium ions (and minimal influx of chloride ions) into the cell. This repolarization is attenuated by the opening of slow (L-type) calcium channels, which, despite their designation (which refers to rates of inactivation), facilitate rapid calcium entry. Together, the influx of calcium, ongoing efflux of potassium, and late sodium currents balance the cell's transmembrane potential to create and maintain a plateau phase (phase 2). Delayed inactivation of L-type calcium channels, combined with sodium channel closure and the opening of outward potassium channels, result in a rapid return to baseline transmembrane potential (phase 3). After repolarization, additional intracellular sodium is pumped out in exchange for extracellular potassium using sodium-potassium adenosine triphosphatase (ATPase) pumps, and the resting membrane potential (phase 4) is maintained by the inwardly rectifying potassium current until another impulse arrives to depolarize the cell or the cell spontaneously depolarizes. During phase 4, some cardiac fibers allow sodium ions to enter into the cell, raising the resting membrane potential, also known as spontaneous

diastolic depolarization. When the membrane potential reaches threshold, the fast sodium channels open, and another AP is generated.

Role of Calcium Ions in Myocardial Cells

A discussion of regional electrophysiological differences in the heart adds to the understanding of cardiotoxic actions of the various drugs. First, conduction in the His-Purkinje system and the atrial and ventricular myocardium depends on *sodium* entry via the fast sodium channels during phase 0. In contrast, conduction through the sinoatrial (SA) and atrioventricular (AV) nodes depends on *calcium* entry via the slow calcium channels during phase 0 (Fig. 2) [2]. Calcium influx also initiates myocardial contraction during the plateau phase 2; this calcium entry allows excitation-contraction coupling, the mechanism by which the depolarization of an AP results in the mechanical process of myocardial contraction.

Regulation of Cardiac Function

The Frank-Starling mechanism – defined as an increase in stroke volume in response to increased end diastolic volume – is one of the major determinants of cardiac output. In addition, the autonomic nervous system (ANS) has a significant effect on cardiac output. In the ANS, impulses are transmitted from the brain via the

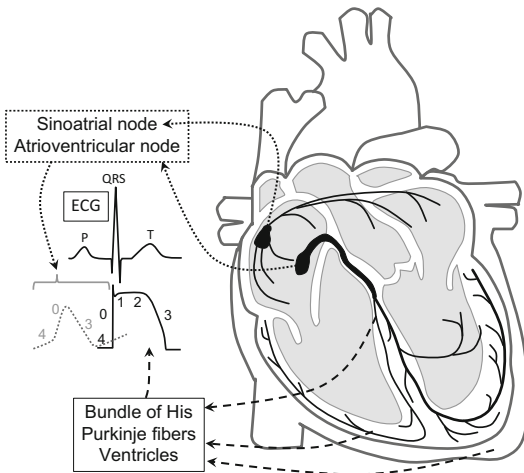


Fig. 2 Schematic demonstration of the typical action potential generated in the sinoatrial and atrioventricular nodes versus the conduction systems of the His-Purkinje and atrioventricular cells. Atrial depolarization on the electrocardiogram (ECG) results in the P wave. The impulse spreads to the atrioventricular node, where specialized cells delay the transmission to allow atrial contraction; the impulse then continues to the ventricles via the bundle of His and the Purkinje fibers. This delay results in the P-R interval on the ECG. The QRS complex represents conduction cell phases 0, 1, and 2 (ventricular depolarization); the T wave indicates phase 3 (ventricular repolarization). The QT interval represents phases 2 and 3 of the action potential

preganglionic fibers that synapse with the postganglionic fibers and subsequently innervate an end organ. Transmission of the impulse occurs primarily through the release of the neurotransmitters acetylcholine and norepinephrine (Fig. 3).

Sympathetic Nervous System

Sympathetic fibers innervate most parts of the heart and increase heart rate, the rate of AV nodal conduction, and myocardial contractility. Norepinephrine from postganglionic fibers interacts with the β_1 -adrenergic cardiac receptors to increase myocardial cell permeability to sodium and calcium, increasing excitability, conduction, and contractility [1, 3].

Parasympathetic Nervous System

In the heart, postganglionic parasympathetic fibers from the vagus nerve innervate the sinus and AV nodes, where they cause the local release

of acetylcholine. Vagal stimulation of muscarinic receptors in these nodes primarily decreases excitability of the atria and slows the conduction of impulse into the ventricles to a point where atrial arrest or complete blockade of transmission at the AV node is possible. Direct effects on myocardial contractility are modest [3].

Pathophysiology

Arrhythmogenesis caused by xenobiotics can be divided into three general mechanistic categories: (1) abnormal impulse initiation, (2) triggered rhythms, and (3) abnormal impulse conduction [4].

Abnormal Impulse Initiation

While all myocardial cells have the potential to generate an AP as outlined above, only specialized conduction cells exhibit automaticity, i.e., the ability to generate an AP without external stimulus. The sinus node is the normal pacemaker because it has the fastest intrinsic firing rate; signals are received from the SA node at a rate that suppresses the firing of other potential autonomic foci (overdrive suppression). The intrinsic firing rate depends on four factors: (1) the resting potential, (2) the refractory period, (3) the threshold potential, and (4) the slope of diastolic depolarization (Fig. 4). An alteration in any of these four factors can cause normal atrial and ventricular working myocardial cells, which do not manifest automaticity, to generate automatic impulses. When the firing rate of any part of the myocardium exceeds the SA node rate, a new site of pacing will result [4].

Triggered Rhythms

Afterdepolarizations (ADs), or positive deflections of the AP, can occur during phases 2 through 4 and can then result in the abnormal initiation of impulses; these abnormal impulses are called triggered rhythms. Two types of ADs are categorized

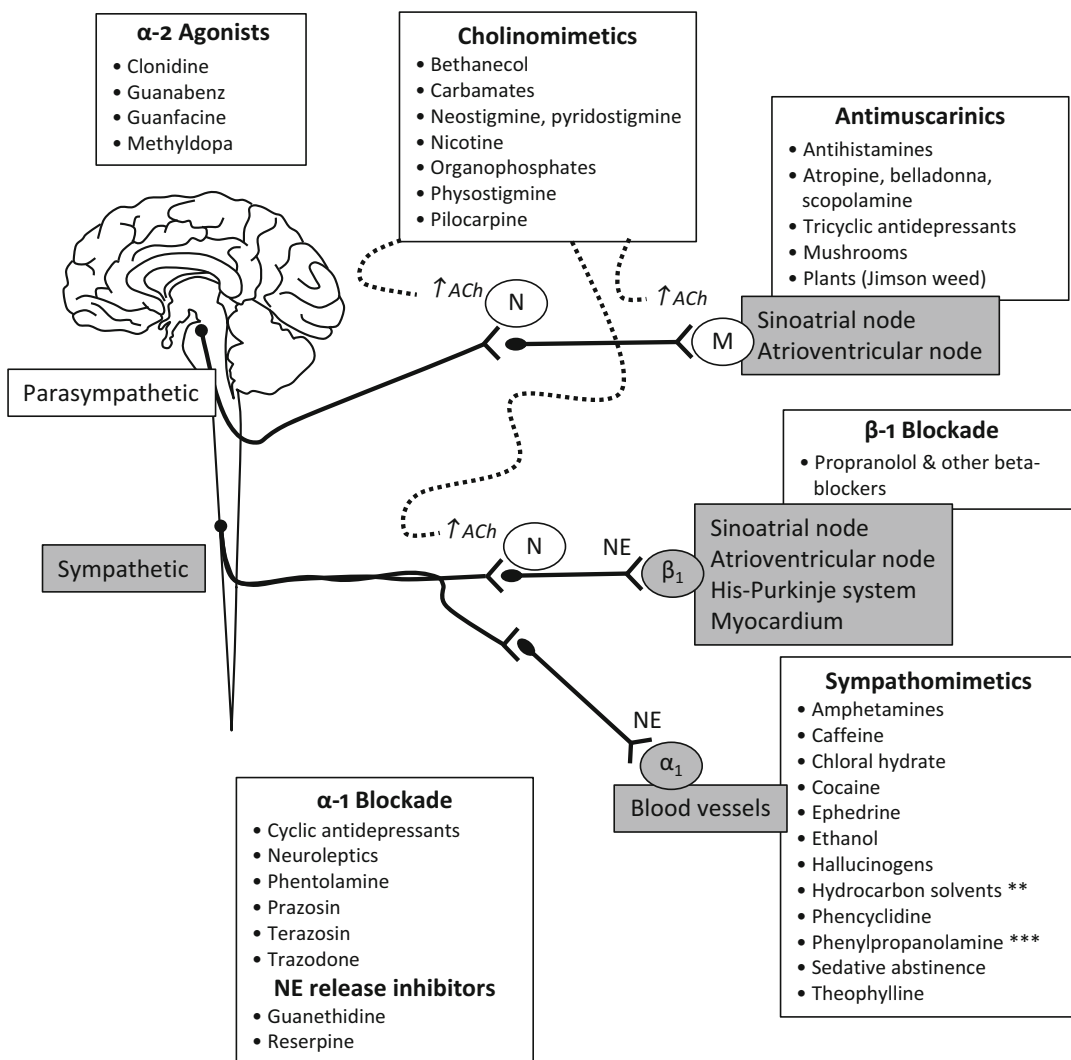


Fig. 3 The elements of the autonomic nervous system and its sites of cardiovascular action. The boxes list drugs or toxins that may influence the cardiovascular system through the autonomic nervous system at various sites.

*May cause reflex bradycardia. [†]Sensitizes myocardium to catecholamines. *N* nicotinic receptors, *M* muscarinic receptors, *ACh* acetylcholine, *NE* norepinephrine

based on their temporal relationship with the repolarization phase of the AP: (1) early ADs and (2) delayed ADs (Fig. 5) [4, 5].

Early ADs are the most common predecessors to triggered rhythms that result from poisoning. These result from outward potassium channel blockade (Fig. 5a). By preventing the efflux of potassium required for restoration of phase 4 resting potentials, this blockade causes a surplus of positive ions intracellularly, resulting in delayed

return of the AP to its baseline and upward oscillations in the AP above threshold. The ECG manifestation of an early AD is manifested on ECG as a prolonged QT interval. This finding can progress to ventricular tachycardia and torsade de pointes (TdP) [6], commonly thought to occur through the phenomenon of superimposition of an R wave on a T wave (referred to as the R-on-T phenomenon) [7, 8]. The amplitude of triggered rhythms associated with early ADs is inversely related to heart

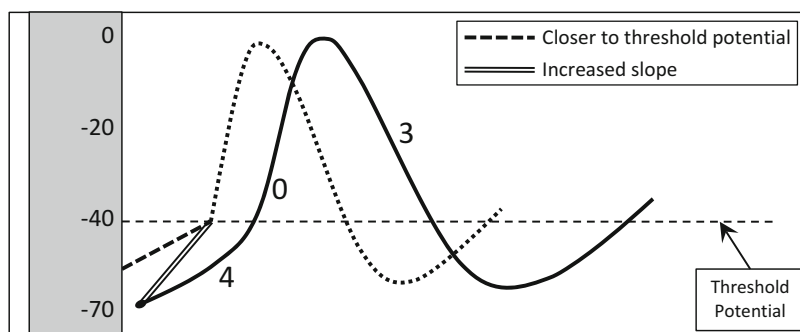


Fig. 4 An image depicting pacemaker cell membrane potential. Numbers represent phases of depolarization: resting potential (4), rapid depolarization (0), and repolarization (3). The solid line represents normal pacemaker cell membrane depolarization as the membrane potential approaches and crosses the threshold potential (dashed

line). Factors increasing the slope (double line) or increasing the resting potential (dark dotted line) of the cell will result in enhanced automaticity (pale dotted line). Conversely, decreasing the slope or decreasing the resting potential results in depressed automaticity and slowed pacemaker rate

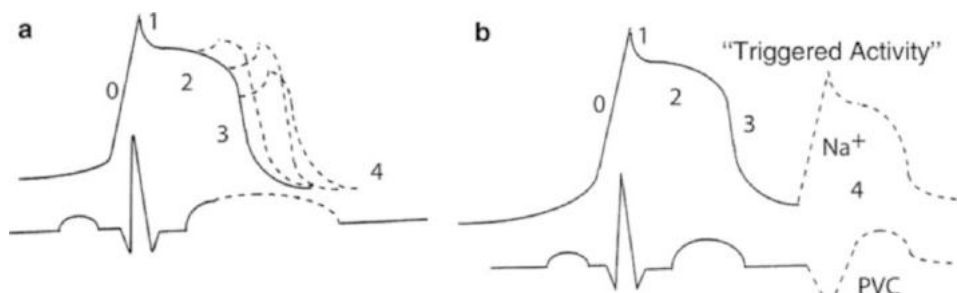


Fig. 5 (a) Cardiac action potential showing potassium flow blockade during phase 3 leading to membrane oscillations or early *afterdepolarizations*. Triggered activity occurs when oscillations reach threshold voltage. (b)

Delayed afterdepolarizations also result in triggered activity and dysrhythmias (i.e., premature ventricular contraction (PVC) and ventricular tachycardia) when they reach threshold voltage (From .Ref. [150])

rate; thus, bradycardia predisposes an individual to TdP and other ventricular arrhythmias, while tachycardia is protective [9].

Delayed ADs occur when repolarization of the AP is complete or nearly complete and can result in premature ventricular contractions (Fig. 5b) among other rhythms. Delayed ADs are observed in conditions of intracellular calcium overload. In poisonings, this overload is associated most commonly with digitalis toxicity or excess catecholamine states. Delayed ADs can also result in triggered activity and have been implicated in certain arrhythmias, especially digitalis-associated bigeminal and idioventricular rhythms [10]. In distinction to early ADs, the amplitude of triggered activity associated with delayed ADs increases with heart rate (see

Fig. 5b) [150]. It has been suggested that pacing-induced increase in heart rate may worsen digitalis toxicity in poisoned patients [11, 12]. Basic science studies on delayed ADs supports this hypothesis,⁷ although transvenous pacing for symptomatic bradycardia after accidental digoxin overdose was well tolerated in one retrospective series [13].

Abnormal Impulse Conduction

Under normal conditions, an impulse initiated in the sinus node travels down the conducting tissues into the ventricles [4]. If an impulse arrives at an area of refractoriness or conduction block (ischemia, scar, or toxin-induced), it may travel down an alternative conduction pathway. If the impulse returns to the area that initially was refractory

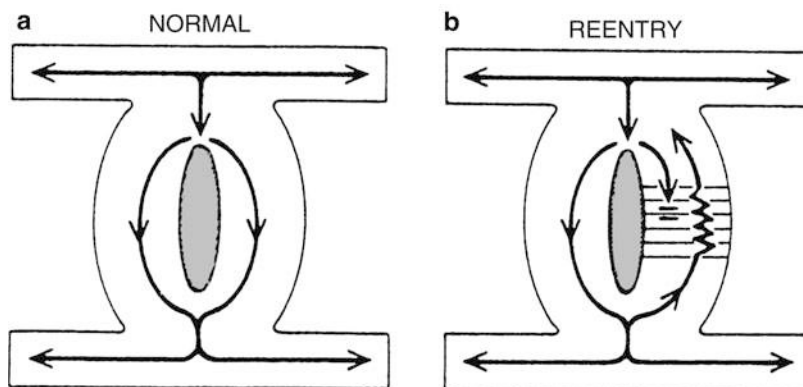


Fig. 6 *Reentry*: Schema of Purkinje fibers or ventricular muscle through which impulse transmission occurs. (a) Normal depolarization of a muscle segment. Impulses spread simultaneously down various conduction pathways to depolarize distal areas. Depolarization and repolarization proceed homogeneously. (b) Reentry. The hatched area represents a local area with depressed conduction, which might be produced by a membrane-depressant

drug or focal myocardial ischemia or necrosis. An impulse traveling antegradely in an area of depressed conduction is blocked (*dark horizontal lines*); impulses traveling in adjacent pathways can pass through the area of conduction delay, however, in retrograde fashion. If tissue proximal to the depressed area is already repolarized and is now excitable, restimulation (reentry) occurs (From Ref. [150])

but is now excitable, a reentry “circuit” results (Fig. 6). These reentry circuits are the most common source of clinically significant tachyarrhythmias in nonpoisoned patients. Many cardiotoxins, particularly inhibitors of fast sodium channels, cause nonuniform slowing of conduction and shortening of the refractory period – forming a milieu for unidirectional block and reentry [14].

Toxic Mechanisms of Arrhythmogenesis

A combination of membrane-depressant effects, autonomic disturbances, and systemic metabolic imbalances may occur during poisoning from cardiotoxins. Knowledge of various effects of drugs that contribute to arrhythmogenesis facilitates recognition and treatment of the manifestations of cardiotoxicity.

Membrane Depression

A toxin-induced block in conduction prevents the propagating impulse from exciting the tissue ahead

of it. The manifestations of a conduction block vary depending on the toxin and its site of action.

Sodium Channel Blockade

Inhibition of the fast sodium channels (Fig. 7 and Table 1) decreases the maximum rate of rise and amplitude of the AP in Purkinje fibers and in atrial and ventricular myocardial cells. As a result, more stimulus current is needed to propagate an impulse throughout the His-Purkinje system and myocardium. Clinically the ECG may reveal QRS prolongation and, rarely, AV block; other ECG features are listed in Table 1. Nonuniform drug-induced depression of conduction may result in unidirectional block and reentry in the conduction system, resulting in tachyarrhythmias [4, 14].

Slow Calcium Channel Blockade

In the pacemaker cells of the SA node and AV node, where the slow calcium channel is the primary ion channel controlling depolarization, inhibition of this channel results in a slowing or inability of the tissue to conduct a cardiac impulse (see Fig. 2) [2]. Calcium channel inhibition results in depression of the SA node discharge rate (negative chronotropy) and slowing of conduction through the AV node (negative dromotropy). The

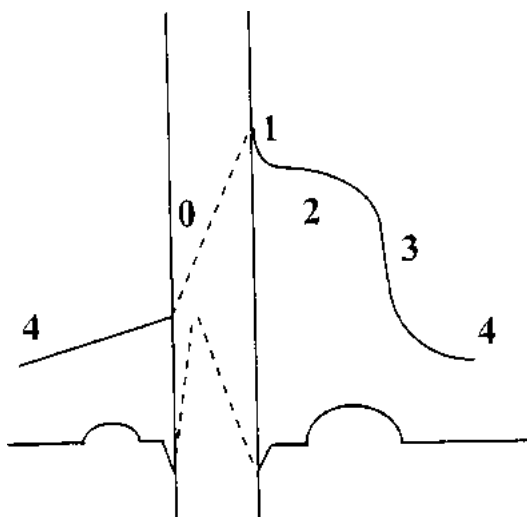


Fig. 7 Cardiac action potential showing that, when sodium channels are blocked, the rate or rise of phase 0 is decreased corresponding to a widening of the QRS complex on the electrocardiogram (From Ref. [150])

ECG manifestations may include sinus bradycardia (delay at the SA node), a prolonged P-R interval (delay at the AV node), or both [15]. Excessive delay prolongs AV conduction to the point of second-degree or complete heart block. Assuming that there is only isolated slow calcium channel inhibition of the pacemaker cells in an otherwise healthy heart, complete block in the pacemaker tissues is associated with an escape rhythm arising from the distal conduction tissues (His bundle, Purkinje fibers) or ventricular fibers. Patients dependent on ventricular or other escape rhythms are particularly sensitive to type I antiarrhythmics (e.g., lidocaine); the sodium channel blockade affected by these drugs impairs phase 0 depolarization and may thus abolish the only existing rhythm and cause asystole [16]. The slow calcium channels also are responsible for excitation-contraction coupling in the ventricular fibers. Impeding calcium entry into these cells results in a progressive depression of myocardial contractility (decreased inotropy). Similarly, vascular smooth muscle cells rely on calcium entry into the cells for contraction, and calcium blockade results in vasodilation. Combined, decreased myocardial contractility and vasodilation can result in significant hypotension.

Table 1 Selected fast sodium channel inhibitors and their consequences

Drugs and toxins	Electrocardiogram findings
Antidepressants	Rightward deviation of QRS axis
Cyclic antidepressants	Prominent R wave in AVR
Serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine)	Prolonged QRS and interventricular conduction delay
Bupropion	Ventricular tachycardia
Antihistamines	Ventricular fibrillation
Antiarrhythmics	Ventricular bradycardia (severe poisoning)
Type Ia	Asystole
Quinidine, disopyramide, procainamide	
Type Ib	
Lidocaine, bupivacaine	
Type Ic	
Flecainide, encainide, propafenone	
Type II	
Propranolol ^a	
Antipsychotics e.g., quetiapine, thioridazine, mesoridazine	
Carbamazepine	
Chloroquine	
Cocaine	
Marine toxins e.g., saxitoxin, tetrodotoxin	
Propoxyphene, tramadol	
Quinine	
Synthetic opioids e.g., loperamide, meperidine	

^aPropranolol and other membrane-depressant β -blockers may show fast sodium channel inhibition in poisoning. This is not a β -receptor mechanism

Outward Potassium Channel Blockade

The significance of potassium channel blockade in the creation of early ADs has been discussed in the previous section on triggered rhythms (see Fig. 5). Although our discussion focuses on drugs and toxins, various non-toxicologic conditions have been associated with triggered rhythms, including myocardial stretch, hypoxia, acidosis, hypothermia, hypokalemia, hypomagnesemia, and

Table 2 Selected causes of acquired long QT syndrome

Antiarrhythmic drugs
Type Ia (disopyramide, procainamide, quinidine)
Type III (sotalol, amiodarone)
Antibiotics
Antimalarials (chloroquine, halofantrine)
Macrolides (azithromycin, clarithromycin, erythromycin)
Pentamidine
Fluoroquinolones (levofloxacin, moxifloxacin)
Antiemetics (domperidone, ondansetron)
Cholinergic agonists
Cisapride, organophosphates
Histamine receptor antagonists
Terfenadine, astemizole
Illicits (cocaine)
Opioids (methadone)
Psychiatric drugs
Antidepressants (citalopram)
Antipsychotics (droperidol, haloperidol, ziprasidone)
Neuroleptics (thioridazine, mesoridazine, and other phenothiazines)
Plants and herbals
Aconitine, grapefruit juice, <i>Hyoscyamus reticulatus</i> , rhododendron
Toxins
Arsenic, fluoride
Metabolic conditions
Hypokalemia, hypomagnesemia, hypocalcemia

Modified from Ref. [151]. A full and continuously updated list is maintained by CredibleMeds® Worldwide and is available online (with free registration) at www.QTdrugs.org

hypocalcemia (Table 2) [6]. The development of toxin-induced long QT and torsade de pointes is more likely in the presence of one of the above conditions or a genetic predisposition.

Sodium-Potassium ATPase Blockade

The energy-driven sodium-potassium ATPase pump maintains a high sodium and potassium concentration gradient across cell membranes by pumping sodium out of and potassium into the cell [17, 18]. Inhibition of this pump by cardiac glycosides (e.g., digitalis) raises intracellular sodium concentrations, which increases intracellular calcium concentrations via the gradient-dependent sodium-calcium pump (Fig. 8a) [18].

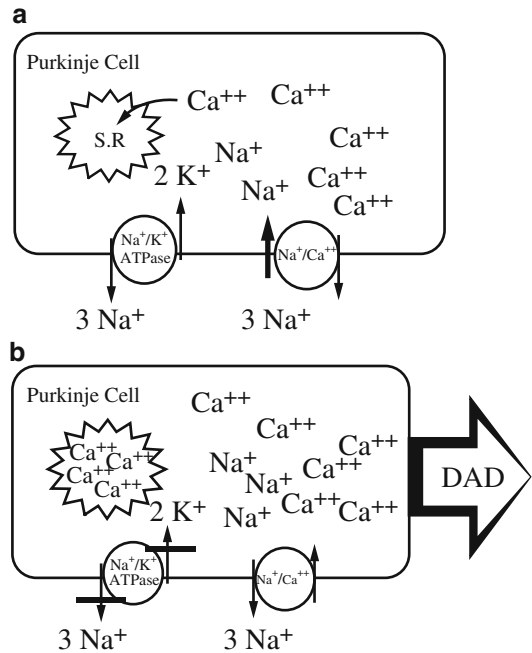
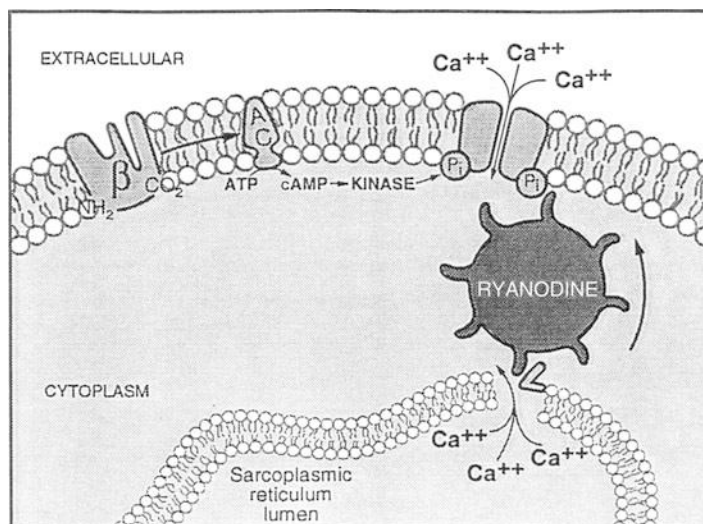


Fig. 8 (a) Purkinje cell's normal state: The Na⁺/K⁺-ATPase pump and the Na⁺/Ca⁺⁺ pump regulate the balance of cations, with excess Ca⁺⁺ sequestered in the sarcoplasmic reticulum (S.R.) (b) In the presence of cardiac glycosides (e.g., digoxin), the Na⁺/K⁺-ATPase is inhibited, and overaccumulation of Na⁺ within the cell reverses the activity of the Na⁺/Ca⁺⁺ pump, significantly increasing the amount of Ca⁺⁺ available with each depolarization. In digoxin overdose, these processes lead to increased internal charge, resulting in delayed afterdepolarizations. Inhibition of the Na⁺/K⁺-ATPase simultaneously results in extracellular hyperkalemia. (Adapted from Haddad LM, Shannon MW, Winchester JF, et al.: *Clinical Management of Poisoning and Drug Overdose*, 3rd ed. Philadelphia, 1998. WB Saunders Company.)

This increase in intracellular calcium concentration has been associated with delayed ADs (see “Triggered Rhythms” section above) and certain digitalis-induced tachyarrhythmias (Fig. 8b) [19]. Sodium-potassium pump blockade can also induce hyperkalemia due to loss of intracellular potassium to the extracellular environment. Evidence from animal studies suggests that potassium depletion results in modulation of sodium-potassium ATPase inhibition by digitalis, and persons with low serum potassium are more likely to develop digitalis-induced arrhythmias [10, 19]. See ► Chap. 38, “Digitalis Glycosides” for a further discussion of this topic.

Fig. 9 Schematic overview of Ca^{2+} homeostasis during myocardial contraction. The β -adrenergic receptor (β), when stimulated, increases adenylate cyclase activity (AC), leading to activation of kinases that phosphorylate the L-channel, increasing Ca^{2+} entry. Ryanodine is the receptor that couples plasmalemmal Ca^{2+} currents to the sarcoplasmic reticulum, allowing release of intracellular pools of Ca^{2+} .



Adrenergic Receptors

β -Receptors

Of the β -receptors, the β_1 -adrenoceptor is the predominant subtype involved in drug-related cardiac poisoning. β_1 -Adrenoceptor activation results in increased cyclic adenosine monophosphate (cAMP) synthesis, which initiates a cascade of events culminating in calcium entry into the myocardial cells and increased inotropic, chronotropic, and dromotropic effects (Fig. 9). Phosphodiesterase then hydrolyzes cAMP and terminates its activity. Poisonings from direct β -agonists, theophylline, and caffeine result in tachyarrhythmias and – in the context of significant overdose – hypotension. Although the caffeine in commercially available beverages rarely causes significant toxicity, higher doses of caffeine in over-the-counter stimulants and diet medications and recent availability of large quantities of anhydrous caffeine preparations on the Internet has resulted in severe adverse effects and fatalities [19, 20]. Sympathomimetic drugs (e.g., cocaine and amphetamines) increase release of or inhibit reuptake or degradation of catecholamines and cause diffuse activation of adrenoceptor. Typically, α_1 and β_1 effects predominate, resulting in hypertension and tachyarrhythmias (see Fig. 3). β_1 -Adrenoceptor blockade decreases cAMP and subsequently blunts chronotropic, dromotropic, and

inotropic effects of endogenous and exogenous catecholamines. Activation of β_2 -adrenoceptor on the peripheral vasculature causes vasodilation, whereas activation of cardiac β_2 -adrenoceptor increases ventricular contractility [21].

α -Adrenoceptor

In poisoning – e.g., imidazoline or yohimbine – clinically significant toxicity involves activation of the α_1 -adrenoceptor subtype in arterial vasculature and/or α_2 -adrenoceptor subtype activation in the brainstem. *α_1 -Adrenoceptor activation* results in elevated intracellular calcium levels and subsequent arterial constriction with a rise in blood pressure. *Central α_2 -adrenoceptor agonism* decreases cAMP levels and inhibits sympathetic output, increases parasympathetic output, and produces sedation (see Fig. 3). Notably, medications administered for one desired α -adrenergic effect can have severe effects on the opposing receptor type. In the case of the over-the-counter imidazolines tetrahydrozoline and oxymetazoline, the desired α_1 -mediated peripheral vasoconstriction obtained by topical application can become life-threatening with α_2 -mediated hypotension and bradycardia in supratherapeutic exposures [22]. α_1 -mediated agonist effects (notably, hypertension) can precede the α_2 effects (hypotension, bradycardia, and mental status depression); in the context of imidazoline poisoning in children, life-threatening

hypertension has been reported to precede hypotension [23]. α_1 -Antagonist activity results in decreased intracellular calcium with subsequent arteriolar relaxation and hypotension (see Fig. 3).

Cholinergic Receptors

Acetylcholinesterase is the enzyme responsible for degradation of acetylcholine. Toxins (e.g., organophosphates) that inhibit acetylcholinesterase result in elevated acetylcholine concentrations at muscarinic and nicotinic receptors. A variety of sympathetic and parasympathetic signs and symptoms may be present after toxicity. The cardiovascular effects of acetylcholinesterase inhibitors are mediated by actions both on nicotinic and muscarinic receptors.

Nicotinic Cholinergic Receptors

Shortly after exposure to acetylcholinesterase inhibition, cardiovascular toxicity results from agonist activity at the ganglionic nicotinic cholinergic receptor. Although these receptors are present on parasympathetic and sympathetic postganglionic fibers, sympathetically mediated effects (tachycardia and hypertension) predominate. With higher doses, parasympathetic stimulation and neuromuscular blockade are seen. These effects are seen after exposure to acetylcholinesterase inhibition, as well as in nicotine poisoning, the incidence of which – especially in pediatric patients – is expected to increase since the introduction of “e-cigarettes” to the consumer marketplace [24, 25].

Muscarinic Cholinergic Receptors

The delayed effects of acetylcholinesterase inhibition involve stimulation of muscarinic cholinergic receptors in myocardial tissue, which decrease SA node excitability and AV node conduction, resulting in sinus bradycardia and varying degrees of AV block (see Fig. 3). Inhibition of the cardiac muscarinic receptors – a phenomenon seen with exposure to antihistamines, tricyclic antidepressants, and other anticholinergic xenobiotics – prevents acetylcholine binding, reducing parasympathetic restraint of heart rate and resulting in unopposed sympathetic

stimulation. This stimulation causes a modest sinus tachycardia with heart rate generally less than 150 beats/min and a modest rise in blood pressure due to increased cardiac output (see Fig. 3).

Altered Central Autonomic Nervous System Activity

Many toxins suppress or enhance ANS activity through the central nervous system (CNS) and subsequently result in peripheral cardiovascular effects. Poisoning from clonidine, a central α_2 -agonist, often results in reduced CNS-mediated sympathetic activity and increased parasympathetic tone, causing a decrease in heart rate and hypotension. Conversely, many CNS stimulants (e.g., cocaine and amphetamines) cause an increase in CNS-mediated sympathetic tone, resulting in tachycardia and hypertension. In a healthy heart, sympathetic stimulation can increase cardiac output twofold to threefold.

Systemic Influences

Many critically poisoned patients have coexisting systemic factors that further influence and exacerbate cardiotoxicity. Hemodynamic changes resulting from hypovolemia, fever, electrolyte abnormalities, acidosis, and hypoxia also must be taken into consideration and corrected.

Clinical Manifestations of Toxic Effects: Cardiac Arrhythmias and Conduction Abnormalities

This section discusses the recognition of cardiac arrhythmias, conduction abnormalities, and specific ECG findings that might help the clinician narrow the differential diagnosis in an unknown overdose. Because most conduction abnormalities are accompanied by abnormalities in heart rate, our clinical approach to a patient begins with categorizing them as having bradycardia or tachycardia. Some toxins cause conduction disturbances without rate alteration and are considered separately.

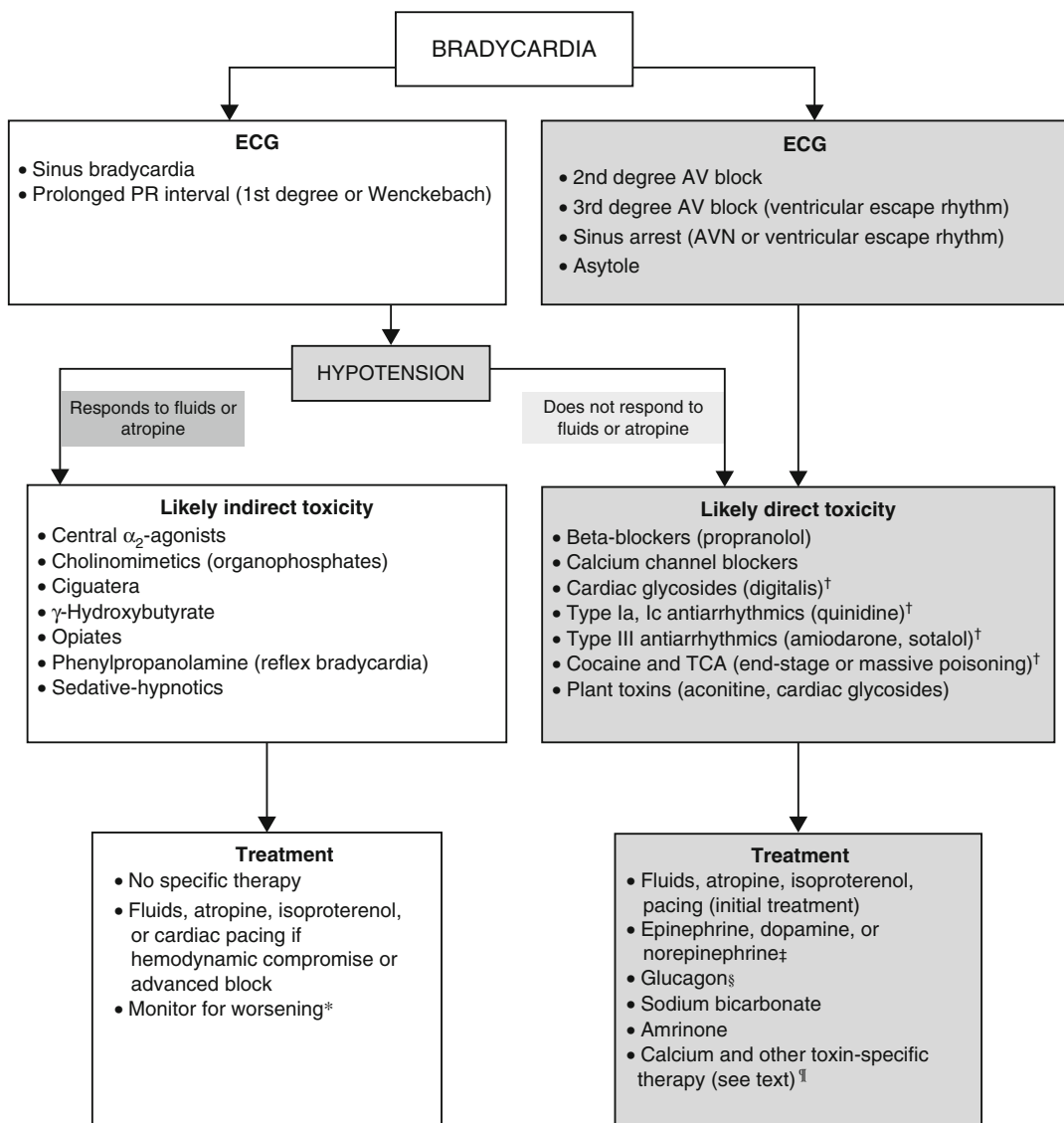


Fig. 10 Algorithm for determining causes and management of bradycardia. *Toxins with potential for direct toxicity may manifest only mild signs early in the course of poisoning. [†]Agents also may cause tachyarrhythmias (see Table 4). [‡]If low systemic vascular resistance.

[§]Glucagon is particularly helpful for β -blocker poisoning.

[¶]If signs of membrane depression. Helpful in suspected calcium channel overdose; may be harmful in digoxin overdose

Bradycardia

As outlined in Fig. 10, our approach to the diagnosis and management of bradycardia begins by classifying the patient into two broad categories based on ECG findings and perfusion status. Similarly, we separate cardiodepressant drugs

into two categories based on whether they directly or indirectly influence cardiovascular function. Drugs that directly impair cardiac function do so through their effects on myocardial membranes and receptors (e.g., calcium channel blockers and β -blockers). Drugs that have indirect effects on the cardiovascular system

typically function by altering autonomic output or causing reflex changes in heart rate (e.g., γ -hydroxybutyrate or phenylpropanolamine). It is important to note that there is significant overlap between mechanistic classification with respect to response to therapeutic interventions and that some exposures (e.g., organophosphates) may require significant administration of either fluids or atropine prior to resolution of clinical effects.

Bradycardia with Conduction Abnormality or Hypoperfusion

Agents that directly inhibit conduction and decrease contractility generally present with more profound ECG abnormalities and cardiovascular instability than agents with indirect toxicity. Bradyarrhythmias and hypotension are the hallmark of these toxins. Mild sinus bradycardia may be the only ECG abnormality despite clinical findings of hypoperfusion. Hypotension in these cases is evidence for depressed contractility from a direct myocardial toxin or vasodilation as opposed to rate-related shock. High-degree heart block (Mobitz II or third-degree AV block), sinus arrest with AV junctional or ventricular escape rhythm, widening of QRS, prominent R wave in EKG lead AVR, and asystole also suggest the presence of a direct myocardial toxin. Some agents that cause bradyarrhythmias (e.g., type IA antiarrhythmics, cardiac glycosides) predispose the patient to ventricular tachyarrhythmias through reentry mechanism or delayed ADs, as discussed above.

Bradycardia Without Conduction Abnormalities or Hypoperfusion

Patients who present with sinus bradycardia with first-degree or Wenckebach AV block may be manifesting signs of early poisoning from a direct myocardial toxin. More often, however, these findings suggest drugs and toxins with indirect toxicity that results in less myocardial depression and hemodynamic instability than direct effects on the conduction system. Most indirectly acting cardiodepressants either decrease sympathetic tone or increase parasympathetic tone, typically with heart rates of 40–60

beats/min, without causing severe hypoperfusion (see Fig. 10). Higher grades of AV block are seen infrequently.

Treatment

The goal of management in a patient with symptomatic bradycardia from an unknown poisoning is to improve perfusion by increasing cardiac output and reversing vasodilation. Treatment should focus on increasing heart rate if rate-related hypotension is suspected and/or improving inotropy if myocardial contractility is impaired. Atropine and pacing should be initiated and generally are sufficient for indirectly acting cardiodepressants, but may be ineffective in management of bradycardia associated with direct toxins. Specific antidotes to individual direct toxins should be considered based on clinical response to certain interventions and additional clinical history. With severe intoxication, heart block or asystole sometimes is associated with an inability to generate an impulse even with high-voltage pacing [26].

If hypotension is present despite normal or increased heart rate or in association with high-grade AV block, the clinician should assume contractile dysfunction and initiate treatment with crystalloid fluids and an inotropic agent. Epinephrine, dopamine, norepinephrine, or vasopressin should be started and titrated to a dose that restores perfusion (Level of Evidence [LOE]: III). Individual reports have indicated that glucagon can increase rate and contractility in poisonings from β -blocker, calcium channel blocker, and severe tricyclic antidepressant (TCA) poisoning (LOE: III) [27]; although given its use of cAMP-mediated processes to circumvent blocked β -adrenergic receptors, its effects are likely most pronounced in the context of β -blocker toxicity [27]. Outside documented effects in animal models, support for the clinical use of glucagon in cardiovascular poisoning is not strong [28]; however, in the context of life-threatening β -blocker toxicity, its use may be of potential benefit (LOE: III). Isoproterenol also may be used for unresponsive sinus, junctional, or ventricular bradycardia (LOE: III). If the ECG reveals a wide QRS, sodium bicarbonate boluses may

reverse the effects of cardiotoxins on fast sodium channels (LOE: II-2) (see Table 1). If appropriate, toxin-specific therapy, such as calcium (for negative inotropic effects of calcium channel blockers) and digoxin antibodies, should be instituted. Two additional therapies – hyperinsulinemia-euglycemia therapy and lipid emulsion – are described below and in more detail in the chapters specifically devoted to these interventions. As noted above, concomitant electrolyte abnormalities, hypoxia, and acidosis should be corrected because they may contribute to failure of pacing stimulus to depolarize cardiac cells (LOE: III).

Tachycardia

Our analysis of tachyarrhythmias in poisoned patients begins by classifying them into a wide-complex versus a narrow-complex rhythm. This distinction serves two primary purposes. First, it allows the clinician to narrow the differential diagnosis to a group of toxins responsible for the arrhythmia (Table 3). Second, the clinician can use the classification scheme to decide on initial therapy concomitant with an attempt to establish the diagnosis.

Wide-Complex Tachycardia

Monomorphic tachycardia of uncertain origin, polymorphic ventricular tachycardia (PVT), and bidirectional ventricular tachycardia (VT) are three types of wide-complex tachycardia (WCT) that are encountered in poisoned patients. When the patient is hemodynamically stable, therapy varies for the three types of WCT. In this section, we progress through a discussion on how to identify subtypes of WCT; subsequently, we present treatment options for each of these subtypes. Figure 11 provides a modified advanced cardiac life support (ACLS) algorithm for managing a patient with a WCT secondary to poisoning.

Monomorphic Wide-Complex Tachycardia. When an ECG reveals a wide-complex QRS with a uniform morphology and a constant RR interval, two common entities should be considered: VT and supraventricular tachyarrhythmia (SVT) with intraventricular conduction delay.

Table 3 Differential diagnosis of drug-induced or toxin-induced tachyarrhythmias

Narrow-complex tachyarrhythmias
Anticholinergic
Amantadine
Antihistamines ^a
Atropine, belladonna, scopolamine
Cyclic antidepressants ^a
Mushrooms (muscarine-containing, e.g., <i>Clitocybe dealbata</i>)
Neuroleptics (thioridazine ^a and mesoridazine ^a also are membrane depressants)
Plants (e.g., Jimson weed)
Sympathomimetic
Amphetamines and their congeners (e.g., ecstasy)
Caffeine
Chloral hydrate ^a
Cocaine ^a
Ethanol
Ephedrine and pseudoephedrine
Lysergic acid diethylamide (LSD) and other hallucinogens
Monoamine oxidase inhibitors
Phencyclidine
Scorpion or spider envenomation
Sedative-hypnotic withdrawal
Selective serotonin reuptake inhibitors
Theophylline ^a
Cholinomimetic
Organophosphates
ECG
Sinus tachycardia
Supraventricular tachycardia (normal conduction)
Treatment
Specific therapies include antidotes depending on xenobiotic
Correct hypotension, hypoxia, or electrolyte abnormalities
Esmolol or other short-acting beta-blocker infusion for intractable tachycardia in the absence of hypotension or other signs of myocardial depression
Wide-complex tachyarrhythmias
Antiarrhythmics (type Ia, Ic, III) ^c
Antihistamines ^c
Arsenic ^c
Carbamazepine
Cardiac glycosides
Chloral hydrate
Cocaine (high doses)
Cyclic antidepressants
Sodium fluoride ^c

(continued)

Table 3 (continued)

Freon (and other fluorocarbon aerosols)
Hydrocarbon solvents
Neuroleptics (thioridazine, mesoridazine) ^c
Propoxyphene
Quinine and related agents ^c
ECG
VT (monomorphic or polymorphic)
VF
<i>ECG signs preceding VF/VT</i>
Supraventricular tachyarrhythmias
Intraventricular conduction delay (QRS prolongation)
Prominent R wave lead AVR
Rightward deviation of QRS axis
QT prolongation (see Table 2)
Treatment
See treatment algorithm (Fig. 12)

ECG electrocardiogram, *VF* ventricular fibrillation, *VT* ventricular tachycardia

^aAny supraventricular arrhythmia can deteriorate to a ventricular arrhythmia, but this occurs more frequently with these agents

^bContraindicated if suspicion of membrane-depressant drug overdose

^cAgents that can cause torsade de pointes and monomorphic VT

Although implementing the optimal therapy can be facilitated greatly if VT is distinguished from SVT using published guidelines [29], previous studies in the general population with WCT have shown that even experienced physicians have difficulty in differentiating VT from SVT [30]. Hemodynamic stability or instability cannot be used to determine between the two arrhythmias [31]. In poisoned patients with a monomorphic WCT, initially, it is safer to assume and treat as if the arrhythmia is VT (see later). When initial treatment measures have been instituted and the patient is hemodynamically stable, attempts to differentiate between VT and SVT may be considered. In hemodynamically stable patients, carotid sinus massage or other vagal maneuvers can be applied and may indicate a supraventricular arrhythmia when it abolishes the rhythm or slows the rate. Although certain key ECG features suggest VT (Table 4), these features have not been validated in poisoned patients. Adenosine may provide useful diagnostic information in patients

with WCT of uncertain origin [32]. Table 3 lists toxic causes of WCT, and the later section on specific toxins discusses those that are commonly encountered in poisoning.

Impaired conduction in the His-Purkinje system resulting in QRS widening greater than 100 ms and/or rightward deviation of the terminal 40-ms frontal plane QRS vector (130–270°) suggests significant cardiotoxicity and is predictive of seizures from TCA poisoning (see Figs. 12 and 13) [33, 34]. An important electrocardiographic manifestation of this rightward deviation is the terminal R' in AVR: a positive deflection measuring greater than 3 mm is a significant predictor of seizures or arrhythmias in TCA poisoning (Fig. 14) [35]. Although these ECG findings in poisoning most commonly suggest antihistamine or TCA involvement, similar intraventricular conduction delay is evident with other toxins that impede fast sodium channels (see Table 1) [36].

Treatment. Because many overdoses resulting in a WCT are due to fast sodium channel inhibition, an important modification to the ACLS treatment algorithm (as shown in Fig. 11) involves the contraindication of type Ia and Ic antiarrhythmics (e.g., procainamide) and the introduction of sodium bicarbonate bolus therapy. The clinical status should dictate the initial method of treatment for the WCT. When associated with hemodynamic compromise, cardiac ischemia, or cerebral insufficiency, immediate termination of the arrhythmia should be attempted with direct current cardioversion and intravenous sodium bicarbonate. Magnesium administered empirically may be beneficial. The patient who is clinically stable can be treated with sodium bicarbonate and antiarrhythmic therapy. Lidocaine has been the antiarrhythmic of choice in this setting, although amiodarone may replace lidocaine as more evidence becomes available (see discussion below). Sodium bicarbonate has emerged to be the first line of treatment for membrane depression from diphenhydramine, TCA, and poisoning from other agents with fast sodium channel blockade activity (see Table 1) [37] (LOE: II-2). Sodium bicarbonate is believed to be beneficial as a result of increasing extracellular sodium, increasing

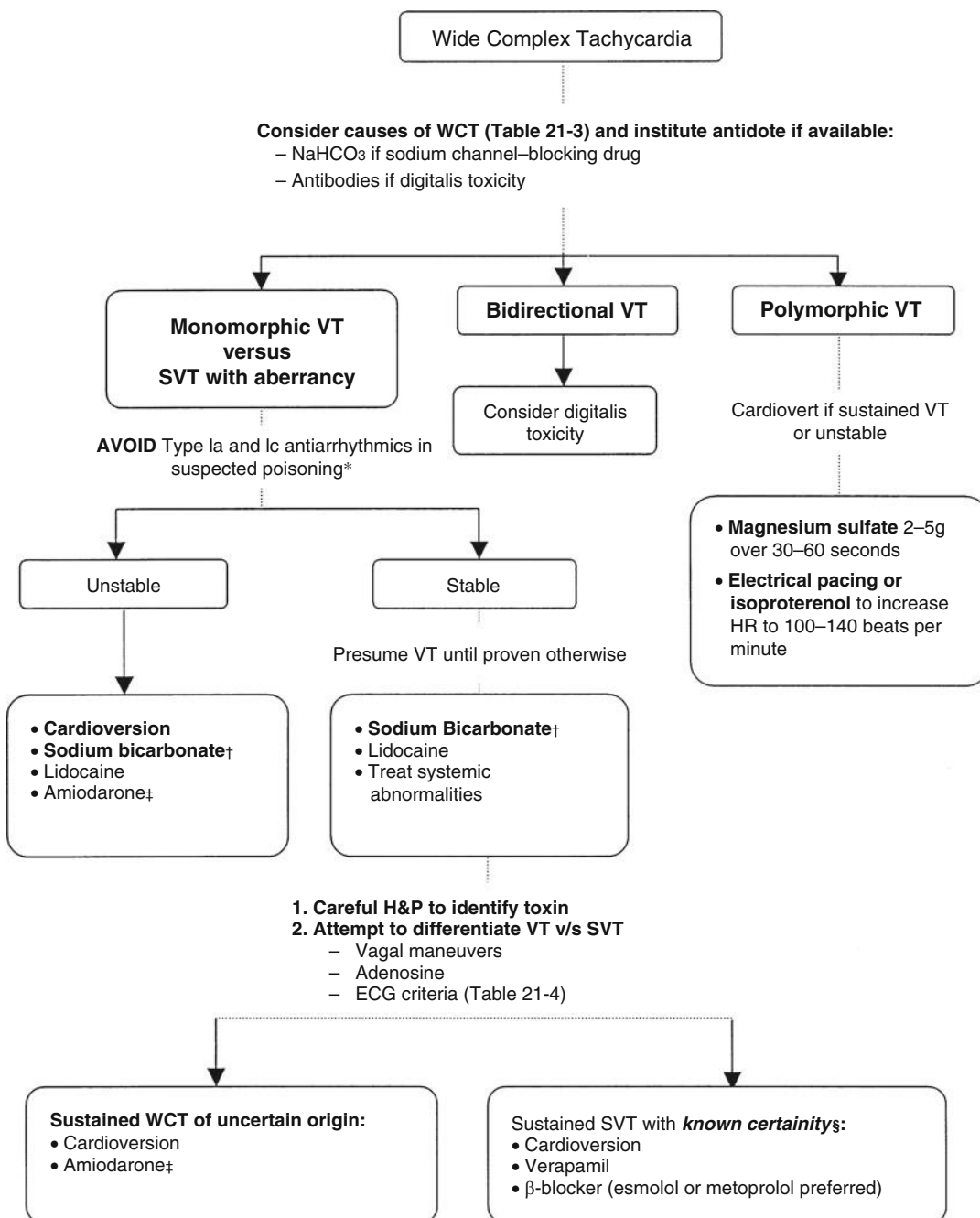


Fig. 11 Algorithm for management of wide-complex tachycardia (WCT) of uncertain origin in poisoning and drug overdose. *Quinidine, procainamide, disopyramide, flecainide, and propafenone. †Unless contraindicated by pH greater than 7.55, cerebral edema, or severe hypokalemia. ‡Use for refractory ventricular arrhythmias, but may worsen hypotension in poisoned patients. §Strongly

recommend use of a cardiology consultant or esophageal lead confirmation of atrial rhythm before use of calcium channel blockers, β -blockers, or digitalis in WCT. ECG electrocardiogram, H & P history and physical examination, HR heart rate, NaHCO_3 sodium bicarbonate, SVT supraventricular tachycardia, v/s versus, VT ventricular tachycardia

extracellular pH, and lowering extracellular potassium, all of which attenuate the effects of TCA and other fast sodium channel blockers [38–41]. There are further discussions of this topic in the chapters on sodium channel blocking antiarrhythmics and on sodium bicarbonate.

When these initial stabilizing measures have been implemented, further attempts to

differentiate the cause of WCT should be undertaken so that toxin-specific therapy can be administered (e.g., digitalis antibodies for digitalis overdose). Calcium channel blockers and β -blockers are contraindicated in WCTs of uncertain etiology because their vasodilatory or myocardial-depressant effects may cause sudden cardiovascular collapse. If pharmacological therapy is unsuccessful, sustained WCT, especially with a rate greater than 150 beats/min, should be treated with electrical cardioversion.

ACLS guidelines from 2010 recommend procainamide, amiodarone, or sotalol for the treatment of stable WCT [42]. Other than in case reports and a case series, the use of amiodarone has not been studied in poisoned patients [43–45]. In a small case series in which 13 of 17 patients with aconite poisoning had ventricular tachyarrhythmias, amiodarone suppressed VT in the five patients in whom it was used [45]. Further reviews of the management of aconite poisoning have also revealed a potential role of flecainide [46]. Lidocaine was used in 11 patients and was

Table 4 Electrocardiogram features strongly suggestive of ventricular tachycardia^a

Atrioventricular dissociation
QRS morphology
Upgoing in V1: qR, RR' (R taller than R'), R
Downgoing in V6: rS, QS
5/6 or 6/6 V leads positively or negatively concordant
Fusion beats or capture beats
Frontal plan QRS axis -90 to -180 (northwest or right upper quadrant)
Identical to previous PVC

PVC, premature ventricular contraction

^aThese criteria have not been validated in ventricular tachycardia associated with poisoning

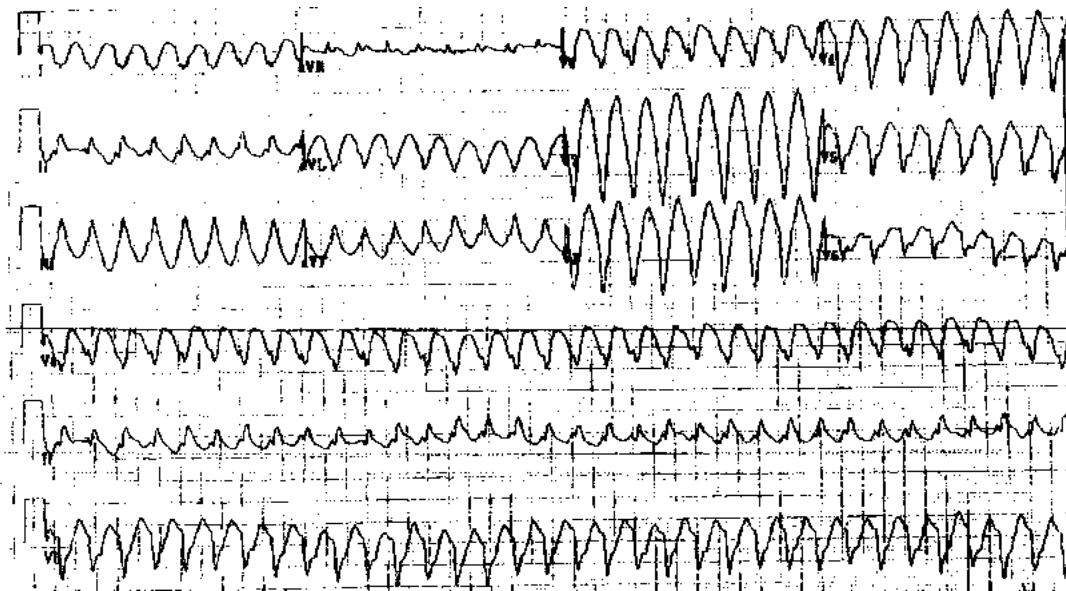


Fig. 12 Electrocardiogram (ECG) from a 53-year-old woman who ingested unknown quantities of a tricyclic antidepressant. The patient had a sustained wide-complex tachycardia with a normal blood pressure despite receiving multiple ampules of sodium bicarbonate boluses and a

lidocaine drip. After 17 h in this rhythm, sinus tachycardia returned spontaneously, and the patient fully recovered without any specific interventions. This ECG was interpreted as ventricular tachycardia by two separate cardiologists

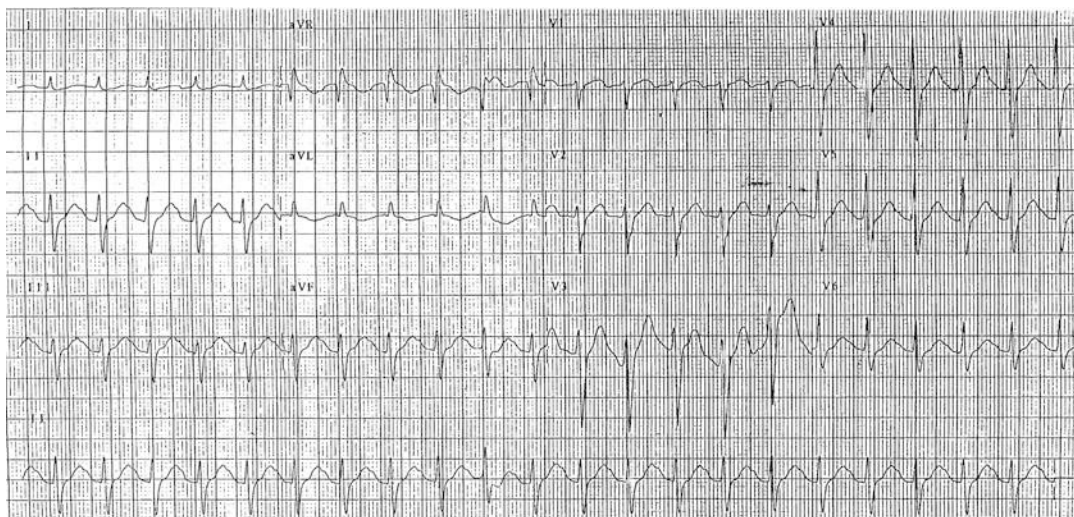


Fig. 13 Electrocardiogram (ECG) from a 39-year-old man after a tricyclic antidepressant overdose. The ECG shows signs of impaired conduction in the His-Purkinje system: QRS widening greater than 100 ms and rightward

deviation of the terminal 40-ms frontal plane QRS vector (aVR). In the presence of tricyclic antidepressant overdose, these ECG findings suggest significant cardiotoxicity

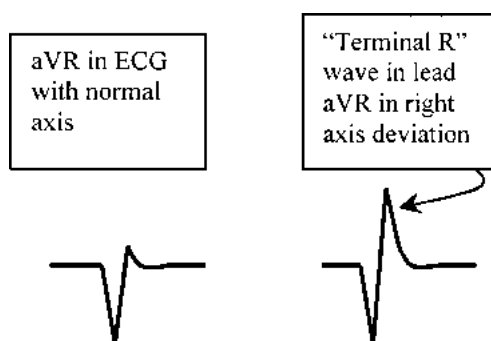


Fig. 14 A positive deflection greater than 3 mm of the terminal portion of lead AVR (R'), frequently called a *terminal R*, is a significant predictor of seizures or arrhythmias in tricyclic antidepressant poisoning. Similar intraventricular conduction delay suggests presence of a fast sodium channel blocker in a poisoned patient

ineffective in all cases. Additional publications supporting the use of amiodarone are mainly limited to case reports, including a 17-year-old patient with cardiac arrest secondary to butane abuse [44], a 45-year-old patient with cardiac arrest after ingestion of 2 g of flecainide [47], and a 26-year-old with ventricular fibrillation after ingestion of 25 mg of digoxin [48]. Although these reports and some animal studies [49] have analyzed the use of amiodarone in WCT due to

poisoning, current evidence does not indicate whether amiodarone or lidocaine would be preferable in these cases. Outside of poisoning cases, multiple studies have shown that amiodarone is preferred over lidocaine for refractory, shock-resistant ventricular tachycardia (LOE III) [50, 51]; however, current data do not indicate survival benefit from administration of antiarrhythmic drugs in refractory or pulseless ventricular tachycardia. Amiodarone should be considered for recalcitrant arrhythmias. Hypotension and bradycardia are the major acute adverse effects from amiodarone and are related to the rate of infusion. These adverse effects should be taken into consideration before its use in poisoned patients.

Extracorporeal life support is a further treatment modality to be considered for intractable toxin-induced cardiac failure; its use has been described in a variety of case reports. Several treatment modalities are included under the term extracorporeal life support, including extracorporeal membrane oxygenation (ECMO, further subdivided into venoarterial and venovenous modalities), emergency cardiopulmonary bypass, and intra-aortic balloon pumps. Case reports of severe toxin-induced cardiovascular compromise

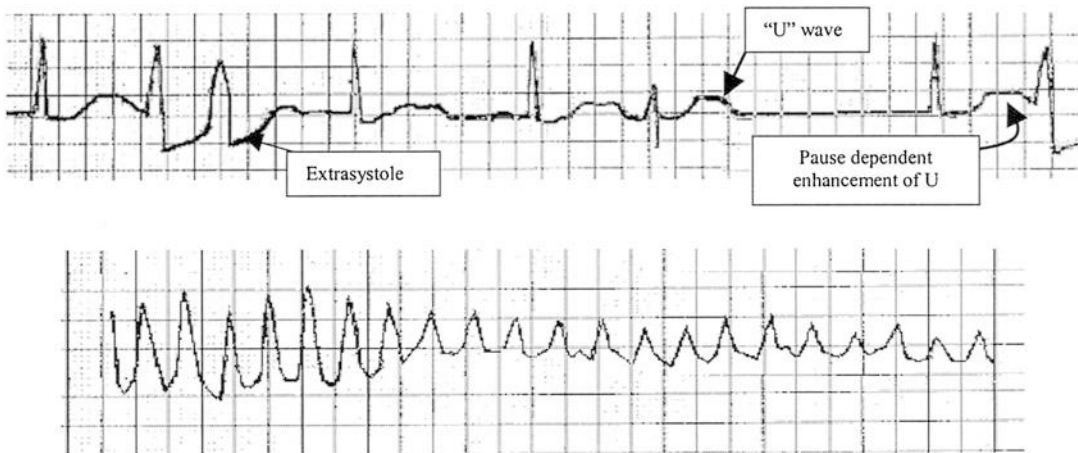


Fig. 15 Electrocardiogram (ECG) from a 63-year-old woman who had ingested unknown amounts of thioridazine. She presented with sinus bradycardia at a rate of 20–50 beats/min and hypotension requiring atropine and dopamine. Six hours after ingestion, she developed several episodes of torsade de pointes (TdP) shown in the lower panel, which was preceded by the strip in the upper panel.

(Note the presence of “warning signs” of TdP discussed in the text: giant U waves, bradycardia, extrasystoles, and pause-dependent enhancement of T-U wave). The patient was cardioverted and subsequently placed on an isoproterenol drip, and the ECG eventually became normal without any further episodes of TdP

describe treatment with venoarterial extracorporeal membrane oxygenation (VA-ECMO) – a modality that allows both pulmonary (oxygenation) and circulatory support – and intra-aortic balloon pumps. Cases in which these treatment modalities have been successful – including verapamil [52], flecainide [53], diltiazem [54], digoxin [55], propranolol, bupropion [56], and a variety of combined ingestions [57] – illustrate that VA-ECMO and intra-aortic balloon pumps show promise when other treatment modalities have failed.

Polymorphic Ventricular Tachycardia. With PVT, the ECG reveals a WCT with beat-to-beat variation in the QRS morphology and RR interval (Fig. 15). The pathophysiology of PVT, as discussed earlier, is different from monomorphic VT, and consequently therapeutic options differ. PVT often occurs in the setting of a prolonged QT_c interval, in which case it is referred to as TdP.

Agents that cause TdP typically lengthen repolarization as evidenced by prolongation of QT_c interval and appearance of U waves on the ECG (see Fig. 15). These U waves represent early ADs. Although QT_c greater than 500 ms after drug exposure places the patient at higher risk for TdP

(LOE III) [58], the arrhythmia can occur at shorter QT_c intervals as well [6]. These arrhythmias often are associated with and often precipitated by pauses due to sinus bradyarrhythmia or sinus arrest or a pause after a premature beat, because bradycardia enhances the ADs. Factors that are predictive of TdP in the setting of a prolonged QT_c interval are the presence of “warning signs,” such as giant U waves, ventricular bigeminy, pause-dependent lengthening or enhancement of T-U wave, extrasystoles, and bradyarrhythmias [6]. Ventricular bigeminy with prolonged QT_c interval has been called impending torsade [6]. The pathophysiology of TdP is discussed separately under section “[Triggered Rhythms](#)” above. A more detailed discussion of the pathophysiology of TdP can be found in the chapter on dysrhythmia. Of note, a QT nomogram has been developed that was shown in one study to accurately predict arrhythmogenic risk for drug-induced QT prolongation; this nomogram is shown in Fig. 16 [59].

Treatment. If TdP is sustained and causes hemodynamic compromise, it can be treated primarily with electrical cardioversion in conjunction with the administration of magnesium. In

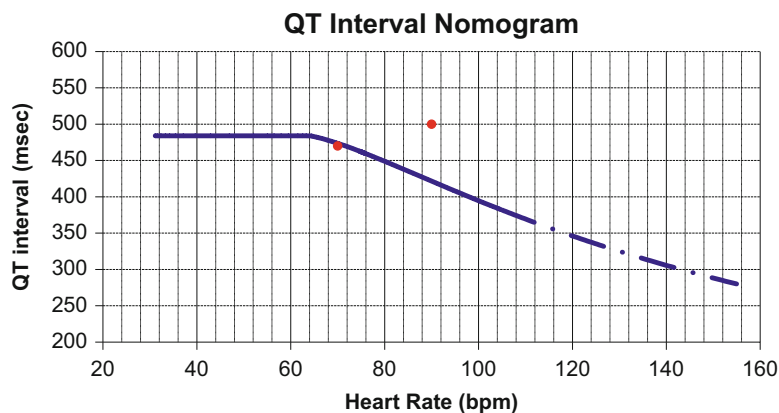


Fig. 16 QT nomogram, courtesy of Dr. Geoffrey Isbister. QT Interval Nomogram. The QT interval should be measured manually from the beginning of the Q wave to the end of the T wave in 6 leads; the median QT interval is then calculated. The QT interval thus obtained is plotted against the patient's heart rate in the nomogram; if the resulting

point is above the line, the patient is considered at risk for torsade de pointes. Of note, the information obtained from this nomogram may not be applicable in certain circumstances due to age- and sex-based QTc variability (Image from Ref. [59])

general, treatment of TdP or prolonged QT_c with the abovementioned warning signs is directed at suppression of early AD and acceleration of heart rate. Most often, the arrhythmia is not sustained and terminates spontaneously. The challenge lies, however, in prevention of its recurrence. TdP should be treated initially with a rapid bolus of magnesium sulfate (2–5 g over 30–60 s), which decreases the amplitude of early AD and suppresses triggered rhythms (LOE III). Treatment with a slower infusion of 2 g over 2 min should be considered in the presence of the warning signs (especially bigeminy) with a prolonged QT_c on ECG [5, 60]. Recurrent warning signs or arrhythmias can be treated with a second bolus in 5–15 min and, if necessary, a maintenance infusion at 3–10 mg/min. Bradycardia is associated with a more pronounced AD, and because toxin-induced TdP is pause-dependent, increasing the heart rate generally suppresses the AD and the emergence of TdP. If magnesium sulfate is ineffective or bradyarrhythmias occur, an isoproterenol infusion or electrical pacing can be instituted to accelerate the heart rate or shorten the QT interval (LOE III); overdrive pacing has been shown to be effective in terminating the recurrence of QT prolongation in drug-induced and genetically

determined torsade de pointes (LOE III) [61, 62], apparently through increased repolarizing potassium currents and thus shortening QT intervals [63]. The β₁- and β₂-adrenoceptor agonist isoproterenol (1–4 μg/min) may be used to accelerate the heart rate; the infusion should be titrated to a rate of 90–110 beats/min [61]. As noted above, tachycardia usually abolishes or prevents emergence of TdP [9], at which point the pacing rate should be decreased to the lowest rate that abolishes ventricular ectopy (usually 80–100 beats/min). Hypokalemia can exacerbate TdP, and potassium supplementation, even in normokalemic patients with drug-induced prolonged QT_c, has been shown to normalize repolarization abnormalities (LOE III) [60, 64]. Serum potassium should be checked and maintained in the high-normal range (4.5 mEq/L) in patients at risk for TdP [64].

Bidirectional Ventricular Tachycardia. ECG findings reveal a tachycardia with a wide QRS morphology that usually is alternating in direction with a constant RR interval (Fig. 17). In rare arrhythmia, bidirectional VT is almost pathognomonic for digitalis toxicity and should be treated with digoxin-specific antibodies [65] although this rhythm has also been associated with ingestion of aconite (see below) [66, 67].

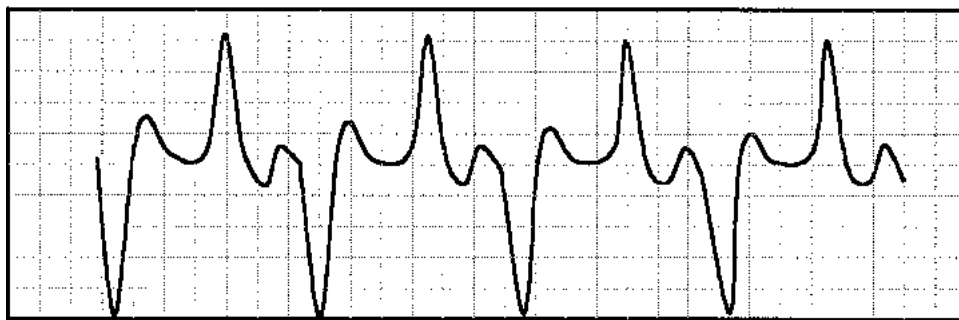


Fig. 17 Bidirectional ventricular tachycardia suggestive of digitalis toxicity

Narrow-Complex Tachycardia

Narrow-complex sinus tachycardia is probably the most common arrhythmia seen in poisoned patients. Sympathomimetic and anticholinergic drugs are common causes of supraventricular arrhythmias in poisoning, although other indirect influences – including fever, hypoxia, hypovolemia, and agitation – often contribute to toxicity. Toxin-induced SVTs generally resolve with supportive care. Some toxins that induce tachycardia also possess membrane-depressant properties with a potential to cause myocardial depression (Figs. 15 and 16). The clinician can risk stratify these patients by assessing the ECG for conduction abnormalities. The clinician should suspect digitalis toxicity in any patient with an atrial tachycardia and AV block (usually 2:1 AV block). Digitalis is well known to increase automaticity and cause AV nodal conduction blockade.

Treatment. Supportive therapy and cardiac monitoring usually are sufficient for a patient with narrow-complex tachycardia, because tachycardia frequently subsides when the offending agent is eliminated. Hypovolemia, hyperthermia, and hypoxia can exacerbate tachyarrhythmias in poisoned patients and should be corrected. Pharmacologic therapy or electrical cardioversion usually is reserved for SVTs or tachyarrhythmias associated with hemodynamic compromise, active myocardial ischemia, acute heart failure, or cerebrovascular insufficiency. When treatment is warranted for a narrow-complex supraventricular arrhythmia

and the toxin is unknown, one option is to use a relatively specific and short-acting β_1 -selective blocker, such as esmolol, because many arrhythmias are a result of excess sympathetic activity. Arrhythmias from stimulant abuse (i.e., cocaine, amphetamines) are predominantly β -adrenergic receptor mediated, and a β -blocking agent is preferred. A nonselective β -blocking drug (i.e., propranolol) could theoretically worsen vasoconstriction, however, by antagonizing β_2 -mediated vasodilation, resulting in unopposed α effects and aggravation of hypertension [68]. Although concerning in theory, studies attempting to identify adverse effects in patients with cocaine-related chest pain treated with nonselective β -blocking drugs have not demonstrated adverse clinical effects [69]. The use of cardioselective (β_1 -receptor-selective) drugs, such as esmolol or metoprolol, avoids this theoretical concern [70].

β -Blocking agents also are preferred for treating tachyarrhythmias from caffeine and theophylline toxicity. Case reports have illustrated that nonselective β -blocking agents can, however, provoke severe bronchospasm in patients with chronic obstructive pulmonary disease (COPD) and asthma [71–74]. Attempts to identify the safety data surrounding β -blockade safety in patients with asthma and COPD are predominantly based on meta-analyses and population-based studies, and their applicability to the treatment of acute poisoning is unclear. Studies of therapeutic administration of β -blocking agents for hypertension have not definitively shown an

adverse effect of β -blocker therapy on FEV1 or respiratory symptoms in patients with COPD [75, 76]. Some evidence exists that the bronchospastic risks associated with COPD may differ from those associated with patients diagnosed with asthma [77]. In the context of β -blocking agent use for control of hypertension in patients with asthma, literature reviews and meta-analyses of the use of these drugs for control of hypertension have demonstrated that although β 1-selective agents may be better tolerated in asthmatics, they are not completely risk-free [78, 79]. Patients with asthma (with or without chronic obstructive pulmonary disease) taking nonselective β -blocking agents may have increased hospitalizations and emergency department utilization [77].

In the absence of data specific to theophylline and caffeine poisonings, esmolol and metoprolol may be considered safer alternatives.

If anticholinergic poisoning is suspected and is associated with hemodynamic instability, β -blockers or physostigmine may be used. Physostigmine, a cholinesterase inhibitor, increases acetylcholine at the neuronal junction, reversing anticholinergic toxicity. Case reports have indicated that physostigmine use in the presence of AV conduction inhibition may worsen AV block, resulting in bradycardia and asystole [80]; however, multiple studies have now demonstrated the safety of physostigmine – in the absence of underlying conduction abnormalities, preceding seizures, or arrhythmias – in reversing delirium and agitation associated with anticholinergic toxicity [81]. Some authors have advocated for dismissal of electrocardiographic criteria entirely in considering the administration of physostigmine for antimuscarinic toxicity [82]; however, the safety of this intervention has not been thoroughly assessed in patients with severe cardiovascular depression from tricyclic antidepressant poisoning. A more extensive discussion of the safety of the use of physostigmine can be found in the chapters on the anticholinergic syndrome and on physostigmine.

Evidence of fast sodium channel blockade on the ECG should be treated with sodium bicarbonate bolus therapy as discussed earlier in the section on WCT and TCA poisoning.

Specific Toxins

Poisonings may result in cardiotoxicity by a variety of mechanisms. To facilitate diagnosis, we categorize the toxins based on manifestations of cardiotoxicity, specifically bradyarrhythmias, tachyarrhythmias, or both. Some poisoned patients also may have abnormalities in conduction without any abnormalities in rate, but the principles of treatment remain the same.

Drugs Causing Bradyarrhythmias

β -Adrenergic Receptor Blockers

β -Adrenergic receptor blockers, with the exception of pindolol, cause cardiac disturbances as a result of β -receptor blockade and typically present with sinus bradycardia and varying degrees of AV block in patients with healthy hearts. Junctional and slow ventricular escape rhythms (heart rate 20–40 beats/min) are seen in patients with underlying conduction disease or with massive overdose. Hypotension, shock, and pulmonary edema resulting from myocardial depression can be seen in any severe β -blocker poisoning but are more likely in patients after massive overdose, or in those with diseased myocardium that depends on sympathetic activity for contractility. Certain β -receptor-blocking drugs have sodium channel blocking effects (acebutolol, pindolol, and propranolol) or sympathomimetic activity (acebutolol and pindolol) that contribute to toxicity [83]. β -Receptor-blocking agents with sodium channel blocking and membrane-depressant effects can cause myocardial depression and conduction system abnormalities, resulting in widening of QRS and hypotension [84]. Sotalol, which has type III antiarrhythmic activity, prolongs the QT interval in a dose-dependent manner and may cause TdP and ventricular fibrillation, even at therapeutic doses [85, 86].

Crystalloid fluids, atropine, and cardiac pacing should be administered initially to patients with bradycardia and hypotension. Glucagon has been the most consistently useful agent in treating severe β -blocker poisonings; however, its efficiency is not based on high-level evidence, and

review articles have questioned its utility [27, 28, 87]. As described above, glucagon activates adenylate cyclase by a non- β -receptor mechanism, enhancing heart rate and myocardial contractility. Epinephrine, dopamine, and isoproterenol also have been used successfully in β -blocker poisoning [26, 88]. Further potential interventions include the administration of high-dose insulin therapy (hyperinsulinemia-euglycemia, HIE), which appears to have positive effects on intracellular glucose transport, vascular dilatation, and increased inotropy based on animal models and multiple clinical cases [89]. In the context of treatment-resistant cardiogenic shock resultant from β -blocker poisoning, animal models and multiple case reports indicate a possible role of intravenous lipid emulsion (ILE) therapy [90]; however, evidence to date is inconclusive to definitively support empiric use of ILE except as possible rescue therapy in severe beta-blocker poisoning refractory to other interventions described above [91, 92]. VA-ECMO has also been used in refractory cases of severe beta-blocker poisoning (see discussion above) [93, 94].

Calcium Channel Blockers

The hallmark of poisoning by verapamil and diltiazem is myocardial depression and hypotension [11]. Sinus bradycardia, varying degrees of AV block, sinus arrest with AV junctional rhythm, and asystole may be seen [95, 96]. Nifedipine, amlodipine, and other dihydropyridines predominantly cause peripheral vasodilation with a reflex tachycardia, but with severe poisoning, they also may reduce myocardial contractility and produce bradycardia [97].

No single treatment consistently reverses calcium channel blocker cardiotoxicity. Atropine, cardiac pacing, and crystalloids can be tried but are often ineffective [98]. Calcium chloride and calcium gluconate reverse the negative inotropic effects of calcium channel blocker toxicity but not AV blockade or peripheral vasodilation (LOE III) [99, 100]. Even high doses of calcium may not be successful in reversing toxicity [17, 101, 102]. Glucagon and epinephrine have produced favorable results in some cases [18, 83]. Based on current evidence from animal studies and case

series, HIE appears to be a superior antidote to calcium, glucagon, and epinephrine and should be considered in recalcitrant or severe cases of calcium channel blocker poisoning (LOE III) [89, 102, 103]. While the precise mechanism of this therapy remains unclear, it appears that the source of energy for the myocardium is altered from free fatty acids to carbohydrates in calcium channel blocker poisoning. High doses of insulin with euglycemia enhance carbohydrate use and the clearance of lactate, improving myocardial contractility in calcium channel blocker poisoning [103]. Calcium channel blockers also inhibit pancreatic insulin release through L-type channel blockade, leading to inadequate carbohydrate use by the myocardium, hyperglycemia, and acidosis. Hyperglycemia in the context of calcium channel blocker overdose – especially with non-dihydropyridines (e.g., diltiazem, verapamil) – is considered to correlate with the severity of intoxication, and has been shown to correlate with in-hospital mortality, the need for temporary pacing, and the need for vasopressor administration [104].

Intravenous lipid emulsion therapy, as discussed above for β -blocker poisonings, has been reported in animal models and case reports to reverse some of the toxicity associated with calcium channel blocker overdose. Although multiple theoretical mechanisms exist, the administration of a large amount of intravenous lipid is thought to form a “lipid sink,” binding, or sequestering lipid-soluble drugs, thereby decreasing their clinical effects. Given the lack of randomized trials and the paucity of specific data, however, this treatment modality should be reserved for cases where the other interventions listed above have been ineffective [90, 105]. A further discussion of this point can be found in the chapter on calcium channel blocking agents.

Studies in animals have found that methylene blue has the potential to increase heart rate, mean arterial pressure, and survival time in an experimental model of amlodipine overdose [106]. This phenomenon has also been illustrated with case reports and is postulated to relate to inhibition of the nitric oxide-cyclic guanosine monophosphate (cGMP) pathway [107, 108]. Recent case studies

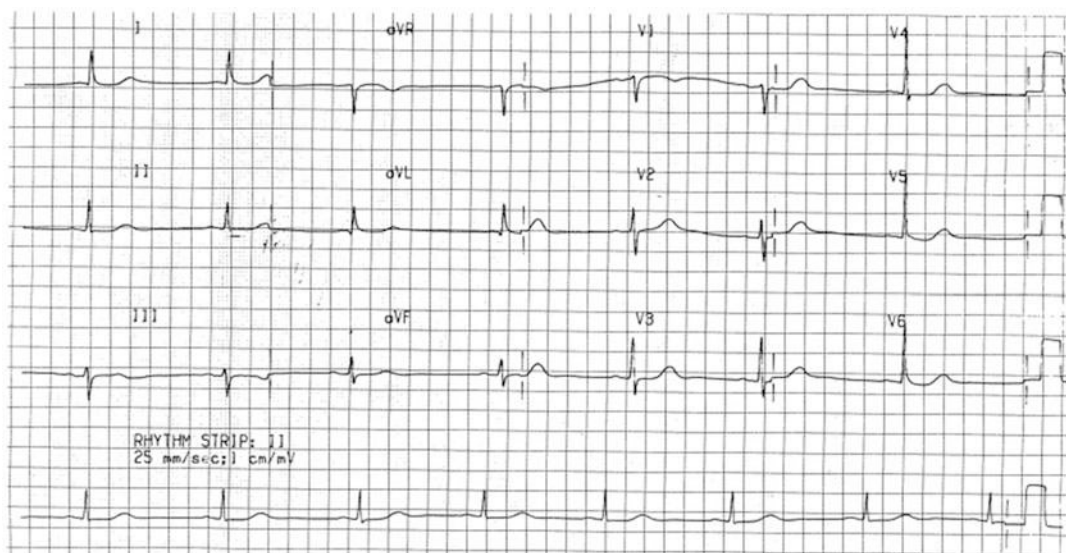


Fig. 18 A 73-year-old woman presented with syncope and hypotension after accidentally ingesting three times her normal dose of atenolol. Her initial sinus bradycardia of 36 beats/min did not respond to atropine, and there was no capture with transcutaneous pacing. Glucagon, 3 mg

intravenously followed by a 3 mg/h drip, increased heart rate and blood pressure. Bradycardia and hypotension recurred over the next 8 h with weaning of the glucagon infusion

[109, 110] and some animal data [111–113] have investigated the potential role for the calcium sensitizer levosimendan, currently available in Europe for the treatment of severe decompensated heart failure. VA-ECMO has also been used in the context of calcium channel overdose [54, 114]; please see discussion above. The role of these agents, if any, in the treatment of calcium channel blocker poisoning is discussed further in the chapter on calcium channel blocking agents.

Severe Cocaine and Tricyclic Antidepressant Poisoning

Although cocaine and TCAs primarily cause tachyarrhythmias, severe toxicity may result in ventricular bradycardia with reduced cardiac output and hypotension (Figs. 13 and 18). In addition to sodium bicarbonate, treatment should include cardiac pacing or isoproterenol in conjunction with pressors such as norepinephrine, phenylephrine, or vasopressin. Animal studies have supported the use of lipid emulsion therapy in cocaine toxicity [115]. Although this study involved pretreatment of research animals and is unlikely to translate easily to clinical scenarios

other than massive ingestions, single case reports have shown a potential role for lipid emulsion therapy [116, 117]. Antidotal research for cocaine reversal has been conducted – including cocaine hydrolase, butyrylcholinesterase, and bacterial cocaine esterase – however, novel treatments have yet to be fully studied or marketed [118].

Drugs Causing Tachyarrhythmias

Amphetamines and Cocaine

Amphetamine and many of its analogues release catecholamines from the presynaptic terminals, producing effects through direct stimulation of postsynaptic adrenergic receptors. Cocaine is a potent inhibitor of catecholamine reuptake, which results in increased levels and longer persistence of catecholamines at the adrenergic receptors. Sympathetic overactivity causing sinus or atrial tachycardia and hypertension are common cardiac findings after cocaine or amphetamine use. Compared with amphetamines, cocaine is associated more commonly with cardiovascular complications, such as acute myocardial infarction,

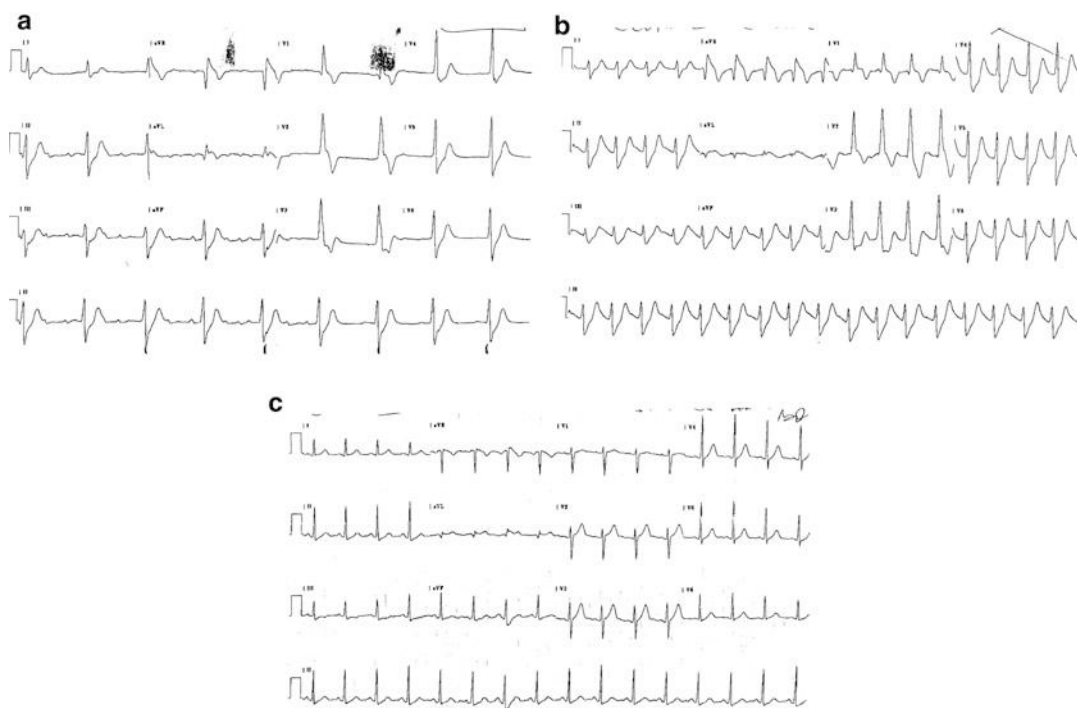


Fig. 19 A 28-year-old man had a seizure in jail 1 h after ingesting crack cocaine. The patient was asystolic when the medic arrived. **(a)** The first electrocardiogram (ECG) was taken on presentation to the emergency department and showed atrioventricular dissociation. **(b)** The second ECG revealed a QRS of 160 ms and a terminal R greater than 3 mm in lead AVR after intravenous fluids and

2 ampules of sodium bicarbonate. **(c)** The third ECG showed sinus tachycardia with resolution of the conduction disturbances. It was recorded after 8 ampules of sodium bicarbonate over 3 h with an improvement of arterial pH from 6.39 to 7.30. The patient recovered fully and was discharged after 5 days of hospitalization

myocardial necrosis, and dissecting aortic aneurysm [119]. Cocaine was implicated in 1.8% of cases from an international aortic dissection registry [120]. Increased myocardial work in the presence of fixed coronary artery disease, cocaine-induced coronary vasospasm, or thrombosis may be responsible for myocardial infarction [121–124], which has been shown to affect up to 6% of cocaine abusers presenting for emergency department care with chest pain [125]. Cocaine use has been associated with premature development of aortic atherosclerosis and hypertension [126]. Cocaine-induced vasoconstriction is augmented by tobacco use [127] and has been experimentally blocked by the α_1 -adrenergic blocking drug phentolamine, suggesting a significant role for α -adrenergic stimulation [128]. Patchy myocardial necrosis and contraction band necrosis as a

result of intense catecholamine stimulation have been described with acute and chronic use of cocaine [122, 123]. The focal areas of necrosis may form a substrate for arrhythmias, which may lead to sudden cardiac death. Myocarditis and cardiomyopathy also have been reported after acute and chronic use of amphetamines and cocaine. Additionally, high doses of cocaine may impede fast sodium channels, resulting in widening QRS, myocardial depression, and hypotension (Fig. 19) [40].

Reported effects of cocaine on cardiac rhythm are listed in Table 5 with a list of proposed underlying mechanisms.

Management of cocaine and amphetamine intoxication should be directed toward specific cardiovascular manifestations [70], including sodium bicarbonate for any ECG manifestations

Table 5 Cardiac dysrhythmias reported with cocaine use, with proposed underlying mechanisms [124]

Dysrhythmias	Mechanisms
Sinus tachycardia	Increased ventricular irritability [129]
Sinus bradycardia	
Supraventricular tachycardia	Sodium channel blockade with inhibition of action potential generation and conduction [130, 131]
Bundle-branch block	
Complete heart block	
Accelerated idioventricular rhythm	
Ventricular tachycardia	Increased intracellular calcium, resulting in afterdepolarizations and triggered ventricular arrhythmias [132]
Ventricular fibrillation	
Asystole	
Torsade de pointes	
Brugada pattern (right bundle-branch block with ST-segment elevations in leads V ₁ , V ₂ , V ₃)	Reduced vagal activity, thus decreasing parasympathetic control of tachycardia [133]

of sodium channel blockade (LOE III). Animal studies have shown benzodiazepines to reduce mortality from psychomotor agitation as a result of cocaine toxicity [134]. Benzodiazepines should be first-line therapy for treatment of agitation, tachycardia, and hypertension in these patients (LOE III) and should be accompanied by intravenous fluids, oxygenation, and cooling, as clinically indicated [135]. Persistent severe hypertension or hypertension with end-organ damage can be treated with vasodilators, such as sodium nitroprusside or α - and β -blocking drugs. Treatment for arrhythmias has been discussed in a prior section.

Anticholinergics

Anticholinergic drugs competitively inhibit acetylcholine at its muscarinic receptor sites and produce the well-described anticholinergic syndrome. By blocking the cholinergic effects on the heart, these drugs cause sinus tachycardia with mild hypertension. Serious arrhythmias from anticholinergic agents are rare, unless patients have underlying cardiac disease (i.e., severe coronary artery disease with tachycardia-induced ischemia), or the ingested compound has other

cardiotoxic properties in addition to muscarinic blockade. Common medications with anticholinergic effects that also cause conduction abnormalities in overdose include TCAs, phenothiazines, and antihistamines, all of which are discussed individually elsewhere in this book. Management of tachyarrhythmias from anticholinergic toxicity has been discussed previously.

Antihistamines

Most antihistamines have some degree of anticholinergic activity and produce varying degrees of the anticholinergic syndrome after overdose. Additionally, other properties of these agents can cause primary cardiac disturbances. Fast sodium channel blockade may result in slowing of conduction and wide QRS, which should be treated similar to TCA poisoning. This condition has been reported most commonly with diphenhydramine. Two antihistaminic agents, terfenadine and astemizole, inhibit outward potassium currents, causing QT interval prolongation and occasionally TdP. This condition can occur if the parent compound builds up as a result of impaired metabolism secondary to hepatic dysfunction or drug interaction or in overdose. For example, terfenadine produces dose-related QT prolongation. Terfenadine concentrations are normally below the arrhythmia-inducing threshold due to rapid metabolism via cytochrome P450 CYP3A4. Coadministration of CYP3A4 inhibitors (e.g., ketoconazole) increases concentrations of terfenadine, which may result in significant QT prolongation and torsade de pointes. Although terfenadine and astemizole have been withdrawn from US markets, they serve as an example of adverse cardiovascular effects that can be precipitated by drug-drug interactions. Management of prolonged QT interval and TdP is described elsewhere in this chapter.

Tricyclic Antidepressants

Hypotension, tachyarrhythmias, and seizures are the most frequently encountered signs of toxicity from TCA poisoning [136]. Manifestations of toxicity are a result of various mechanisms, including anticholinergic properties, catecholamine reuptake

inhibition, fast sodium channel blockade, and peripheral α_1 -blockade [137, 138]. Early in overdose, patients usually manifest sinus tachycardia as a result of anticholinergic effects and increased circulating catecholamines. With more severe poisoning, patients manifest signs of fast sodium channel blockade with impairment of conduction and myocardial depression. Peripheral α_1 -blockade, depressed inotropy, and catecholamine depletion all may contribute to hypotension.

ECG changes often precede cardiovascular deterioration, and the ECG is used widely as a bedside tool in assessment and risk stratification of patients with possible TCA poisoning [35]. Aside from anticholinergic effects causing sinus tachycardia, most other ECG findings in TCA poisoning (e.g., wide QRS, prominent R wave in AVR) result from fast sodium channel blockade and have been discussed in a prior section. Bundle-branch block-like pattern, AV block, ventricular bradycardia, and asystole also may be seen with severe toxicity [33]. The absence of conduction inhibition does not rule out TCA poisoning because hypotension can occur with or without conduction inhibition [139].

WCTs and intractable hypotension are the two most common reasons for death after TCA poisoning [138]. As described previously, manifestations of membrane depression that benefit from sodium bicarbonate include QRS widening greater than 100–120 ms, hypotension, and ventricular arrhythmias. Hyperventilation may be beneficial, but only transiently and only in cases in which sodium bicarbonate is not readily available or contraindicated (i.e., pulmonary edema).

Hypotension without evidence of conduction inhibition often can be treated with isotonic crystalloids [138]. If pressors are required, norepinephrine, phenylephrine, and/or vasopressin is the recommended vasoconstrictor agent. Profound cardiogenic shock with intractable hypotension is encountered occasionally in TCA poisoning and is associated with a high mortality. Intra-aortic balloon pump or arteriovenous extracorporeal membrane oxygenation/cardiopulmonary bypass may be the only means to stabilize these patients until their bodies can metabolize the TCA [140].

In addition to TCAs, several other drugs possess “quinidine-like,” membrane-depressant properties (see Table 1). Many of these other agents do not possess anticholinergic or sympathomimetic properties and do not manifest sinus tachycardia as with TCAs, cocaine, or antihistamines.

Caffeine and Theophylline

Caffeine and theophylline poisoning cause nonselective β -adrenergic stimulation through systemic and local catecholamine release. Additionally, at high concentrations, they inhibit phosphodiesterase, an enzyme that degrades cAMP, synergistically enhancing β -adrenergic stimulation. Cardiovascular manifestations of caffeine or theophylline intoxication commonly include SVTs and VTs in addition to hypotension. Early in the course of poisoning, hypotension may be due to direct vasodilation, but prolonged catecholamine stimulation resulting in myocarditis and impaired contractility can occur later. Additionally, older patients with ischemic heart disease can have myocardial depression as a result of ischemia aggravated by tachycardia and hypotension. Convulsions and metabolic abnormalities (hypokalemia, acidosis) also contribute to arrhythmias and hypotension.

Management is often difficult because patients on theophylline are generally older and have chronic lung disease. Management of tachyarrhythmias has been discussed. Hypotension may resolve with judicious use of fluids, treatment of arrhythmias, and correction of metabolic abnormalities. Pressors may be required for recalcitrant hypotension. Nonselective β -blockers, such as propranolol, can reverse hypotension by blocking β_2 -mediated vasodilation. β_1 -Selective blockers, such as esmolol and metoprolol, are preferred in the presence of bronchospastic lung disease; in addition, infusions of esmolol are easily titrated and are thus preferred in the context of acute severe caffeine ingestion.

Drugs Causing Either Tachyarrhythmias Or Bradyarrhythmias

Cardiac Glycosides

Digitalis has a variety of pharmacologic properties that result in protean manifestations of

toxicity. In overdose, morbidity and mortality may result from arrhythmias, heart block, and hyperkalemia. Disruption of sodium and potassium transport, with the associated hyperkalemia, depresses conduction velocity [14]. Increased rate of diastolic depolarization and delayed ADs may cause ventricular ectopy or tachyarrhythmias. Additionally, digitalis may enhance sympathetic activity, causing increased automaticity while decreasing parasympathetic activity and consequently accelerating conduction velocity. Resultant arrhythmias in overdose often are characterized by increased automaticity and depressed intracardiac conduction. The development of an atrial tachycardia with 2:1 or higher-degree AV conduction block suggests digitalis toxicity. AV junctional tachycardia and ventricular ectopy, tachycardia, or fibrillation may be more common in patients with diseased hearts [15]. Bradyarrhythmias, including sinus bradycardia, second-degree and complete AV block, atrial fibrillation with slow ventricular response, idioventricular rhythm, and asystole, also can occur with digitalis poisoning. Hyperkalemia, resulting from inhibition of sodium-potassium exchange, can contribute to AV block and depressed excitability and is an indicator of poor prognosis.

First-line treatment for arrhythmias or hyperkalemia in digitalis poisoning is administration of digoxin-specific antibodies (LOE I) [141]. If the antibodies are not immediately available, temporizing measures should be directed at the specific arrhythmia and normalization of serum potassium levels. Insulin, glucose, and bicarbonate are preferred treatment for digitalis-induced hyperkalemia. Lidocaine and phenytoin may ameliorate tachyarrhythmias by increasing AV conduction and depressing automaticity (LOE III) [15]. Cardiac pacing should be reserved for high-grade AV blocks and bradyarrhythmias with hemodynamic compromise because some evidence suggests that pacing may enhance triggered rhythms due to delayed ADs [8, 9]. Although esmolol can be used for tachyarrhythmias, other β -blockers, calcium channel blockers, and type Ia antiarrhythmics should be avoided because they can worsen conduction

disturbances [15]. These poisonings are discussed in greater detail in the chapter on digitalis glycoside poisoning.

Type I Antiarrhythmics

In overdose, type Ia antiarrhythmic drugs block fast sodium channels, impede slow inward calcium and outward potassium channels, and reduce the rate of spontaneous depolarization [142]. ECG findings may include QRS widening, bundle-branch block, SA or AV block, and marked QT prolongation. Patients may present with bradycardia resulting from conduction delay and block [36]. Monomorphic VT from reentry as a result of membrane depression and PVT as a result of prolonged repolarization can occur with type IA (quinidine) poisoning (overdose and sometimes with therapeutic doses). Hypotension also is a common manifestation secondary to depressant actions on the heart. Similarly, type IC antiarrhythmics (flecainide, propafenone) cause bradyarrhythmias with conduction delays, depressed inotropy, and shock and monomorphic VT in overdose. The effects of these agents on cardiac conduction are rate dependent, so the extent of QRS widening is greater at faster heart rates. Recognition and management of conduction inhibition and hypotension are similar to that discussed in the previous section on TCAs. Treatment of PVT also is described elsewhere in this chapter. Poisoning by these agents is discussed in greater detail in ► [Chap. 39, “Sodium Channel-Blocking Antidysrhythmics”](#).

Antipsychotic Drugs

Cardiovascular manifestations of antipsychotic agents in overdose result from a combination of α -adrenergic blockade, anticholinergic activity, and “quinidine-like,” membrane-depressant effects. Although these properties appear to be similar to TCAs, individual antipsychotic agents have varying potencies and different degrees of concentration in the myocardium. Most predominantly possess α -adrenergic and anticholinergic properties, the cardiovascular toxicity of which generally is not difficult to treat. Thioridazine and mesoridazine are the most cardiotoxic neuroleptics and have been responsible for most

deaths from this group [143]. Their membrane-depressant effects and ECG manifestations are similar to those described for type IA antiarrhythmics. Bradycardia with SA or AV block, prolonged QT interval, QRS widening, and bundle-branch blocks may occur in overdose [144]. Sinus tachycardia due to anticholinergic properties also may be seen with thioridazine and mesoridazine but not as predictably as with TCAs or with some of the other neuroleptics. Monomorphic VT and PVT have been reported with these neuroleptics [145]. TdP is reported more commonly with neuroleptics than with TCA overdose [143]. A likely explanation is that TCA-poisoned patients are frequently tachycardic because of the anticholinergic effects, which may be less prominent in thioridazine or mesoridazine overdose and are absent in quinidine poisoning. Because TdP is “pause dependent,” and repolarization time is inversely proportional to heart rate, patients with bradyarrhythmias in the presence of these neuroleptics may be more likely to develop PVT (see Fig. 13). Treatment for PVT is described elsewhere. Conduction abnormalities and hypotension should be treated as with type Ia antiarrhythmics and TCA poisoning. Second-generation or atypical antipsychotics – including aripiprazole, risperidone, ziprasidone, quetiapine – have a broad range of pathophysiologic effects but have much fewer adverse cardiovascular effects in overdose when compared to earlier antipsychotics. A systematic review of the toxicity associated with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone found some cases associated with QTc prolongation and dysrhythmias but concluded that the cardiotoxicity of these compounds is overall quite low [146]. Quetiapine in particular has been associated with QTc prolongation and torsade de pointes [147] and has been associated with sometimes profound, transient hypotension and tachycardia in multiple cases [148, 149], presumably due to this compound’s alpha-adrenergic and histamine blockade.

Poisoning with antipsychotic drugs is discussed in greater detail in the chapter on antipsychotic agents.

Summary

Central to the treatment of critically poisoned patients is initial stabilization using the clinical approach outlined in this chapter followed by a thorough history, physical examination, and evaluation of the ECG. Autonomic disturbances, membrane-depressant effects, triggered rhythms, and systemic metabolic influences may contribute to cardiac conduction and rate disturbances in poisoned patients. Recognition of these disturbances facilitates further management of patients manifesting signs and symptoms of cardiotoxicity from an unknown drug or a poison.

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Torsade de pointes (TdP) is a rare but potentially life-threatening event in poisoned patients. The medical toxicologist must identify high risk patients and recognize preattack electrocardiographic (ECG) signs and be able to rapidly distinguish this arrhythmia from other ventricular arrhythmias as the treatment of TdP is unique. This chapter emphasizes the pathophysiology, risk factors, ECG signs, and clinical management of TdP in the poisoned patient as well as the clinical approach to QT-prolongation in poisoned patients.

Background

Dessertenne introduced the term “torsade de pointes” in 1966 when he described the strange appearances of an intermittent rapid arrhythmia in a woman with bradycardia [1]. TdP implies a continual change in the amplitude of the QRS complexes, which appear to twist around an isoelectric line (Fig. 1). He also described T wave abnormalities in the ECG before and in between the bouts of TdP. The striking ECG features of this arrhythmia had been previously reported in the 1920s [2]. TdP is a pulseless polymorphic ventricular arrhythmia that occurs in patients with a significantly prolonged repolarization phase reflected electrocardiographically as a prolonged QT interval. Prolonged QT intervals (reflecting prolonged repolarization) may be due to drugs,

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Fig. 1 An arrhythmia recording of a woman 5 h after an acute overdose of citalopram showing sinus rhythm with a prolonged QTc-time and frequent extrasystoles followed

by a typical TdP. The patient was later diagnosed with a congenital LQTS

congenital, electrolyte abnormalities, cardiac disease, or often a combination of these etiologies [3]. There is a growing list of drugs that have been associated with QT prolongation. Some of these drugs have also been associated with TdP, and recent drug withdrawals in several countries because of this severe side effect (quinidine, thioridazine, cisapride, and terfenadine) have underscored the importance of recognizing the potential of some QT prolonging drugs to cause TdP.

Pathophysiology

Action potentials reflect the diffusion of ions across the cardiac cell membrane from areas of high concentration to areas of low concentration. The movement of ions creates a current which determines the morphology and duration of the cardiac action potential. An action potential is initiated when a resting myocyte is depolarized causing the sodium channels to open and sodium ions to move into the cell. The resulting change in transmembrane potential generates a series of subsequent openings and closings of other ion channels. Action potential duration (APD) is heterogeneous throughout the anatomic regions of

the heart due to variability of genetic expression of both ion channels and transport pumps. The ECG intervals are a surface reflection of cardiac ionic movements. The duration of the QT interval on the ECG is representative of the time required by the ventricular myocytes to repolarize. A prolonged QT interval is seen when the repolarization time is increased in a significant number of myocytes (Fig. 2).

Implications of drugs: Some drugs may increase repolarization time (and therefore APD) by blocking the outward potassium rectifier current (IKr) leading to a decreased outward potassium flow during phase 2 or phase 3 of the action potential (Fig. 3). The net outward current is decreased, yet the inward cationic current continues to increase (as voltage decreases at the end of phase 2 and during phase 3) causing an early after depolarization (EAD) to be propagated [4]. The prolonged refractory period resulting from delayed repolarization renders the myocardium vulnerable to reentrant tachyarrhythmias. If an EAD reaches threshold value, premature ventricular contractions (PVC) occur. The PVC propagates slowly through incompletely recovered myocardium potentially forming a functional reentrant circuit and triggered automaticity. If a drug causes EADs and dispersion of cardiac repolarization (so-called heterogeneity

Fig. 2 Ionic movement across cardiac membranes associated with prolonged QT interval

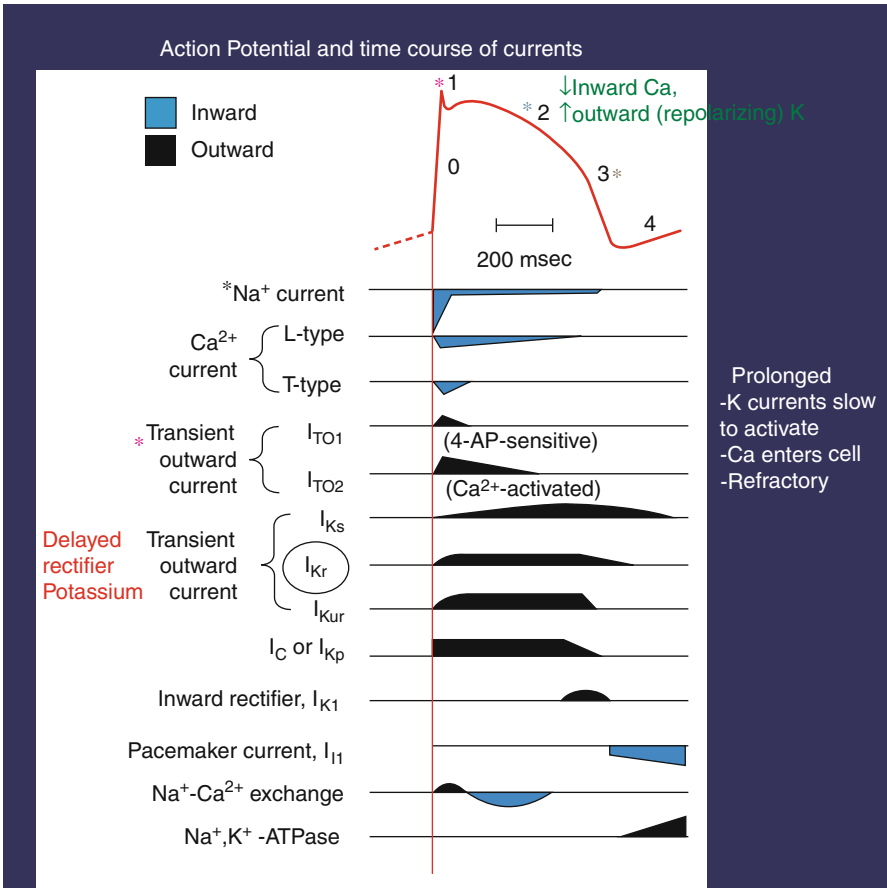
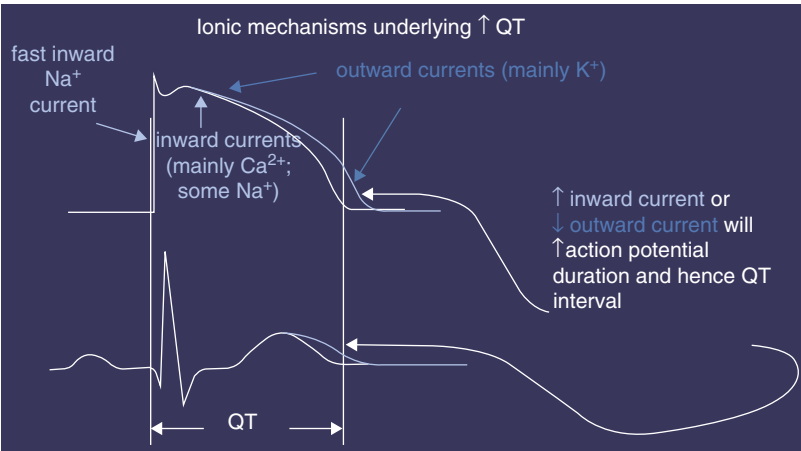
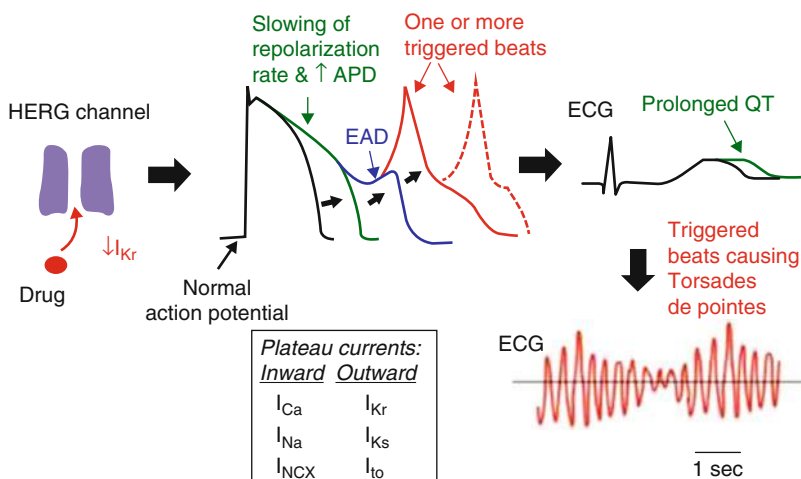


Fig. 3 Time course of currents during the action potential. Note drugs block delayed K rectifier current

Fig. 4 Pathogenesis of early after depolarizations (EADs)

EAD's - Mechanism



of intracardiac repolarization), TdP may occur [5] (Fig. 4).

The three cell types in the ventricular myocardium normally have different repolarization characteristics and therefore differing APDs. This intrinsic difference is termed intrinsic transmural heterogeneity of cellular repolarization. Drugs that block I_{Kr} do so to varying degrees in each cell type. The resulting increased differences in repolarization rate and APD among the cell types may cause unidirectional conduction block and intramural reentry, so-called torsade de pointes.

Risk Drugs for Torsade de Pointes

An immense number of drugs prolong repolarization and increase the QT interval [6], but few actually cause TdP. Risk drugs are listed on the credible Meds website, which has become the standard reference (<https://www.crediblemeds.org>) [7]. Several drugs that cause TdP have been removed from the market. In Sweden, for instance, only a handful drugs that have the potential to cause TdP are still available for oral use, namely, sotalol, disopyramide, chloroquine, quinine, methadone, and citalopram. Drugs such as amiodarone, erythromycin and haloperidol have a strong ability to prolong the QT interval, but do not induce TdP after an oral overdose in the

absence of other major risk factors. It should be noted, however, that a few other true risk drugs, as for example amisulpride, may be available in other parts of the world. Most of the drugs that have been associated with QT prolongation in therapeutic dosage or overdose, e.g., quetiapine, olanzapine, risperidone and lithium, do not induce TdP even in overdose [8, 9].

Risk Factors for Torsade de Pointes in Poisoned Patients

Major risk factors: Clinically, the most important risk factors for TdP are as follows:

- A prolonged QT interval is a prerequisite of development of TdP, and at least for some drugs (e.g., amisulpride), it has been shown that also the extent of the QT prolongation is a risk factor [10].
- Bradycardia [11]. The majority of published cases of drug-induced TdP had a heart rate below 80 beats per minute (bpm) when the torsade occurred [12].
- Hypokalemia [12, 13].
- Multiple major risk factors in a single patient [14].

An important risk factor in the setting of poisoning is the specific drug and the dose that has

Table 1 Major risk factors for torsade de pointes in poisoned patients

Ingestion of a toxic dose of a high risk drug
QTc >500 ms or a QT–HR pair above the QT nomogram “risk line”
Bradycardia
Hypokalemia
Multiple major risk factors

been ingested. This implies that at a certain degree of QTc prolongation, the risk for TdP is much greater if a patient has overdosed on a high risk drug such as sotalol or amisulpride compared to a drug with a lesser risk of causing TdP such as haloperidol (Table 1).

Other risk factors: Examples of other risk factors for TdP are as follows:

- Female gender. Many studies have shown an approximately twofold higher risk for drug-induced TdP among women [14, 15].
- Hypomagnesemia and hypocalcemia [14, 16]. A low serum calcium will prolong the QT interval, but the evidence for hypocalcemia being a significant risk factor for TdP is weak [14].
- Structural heart disease such as congestive heart failure or cardiomyopathy increases risk [11, 14].
- Congenital long QT syndrome and other genetic susceptibilities. Approximately 10–15% of patients with drug-induced TdP have been shown to have some genetic marker [14, 17]. Thus, genetic susceptibilities for TdP may be an important risk factor among poisoned patients even though the genetic disturbance is often unknown at presentation.
- Finally, advanced age and ingestion of more than one QT prolonging drug increases the risk for TdP [15, 18] (Table 2).

Methods for Measurement of the QT Interval

Manual or automatic: There are several manual and automatic methods described for accurate measurement of the repolarization duration on

Table 2 Other risk factors for torsade de pointes

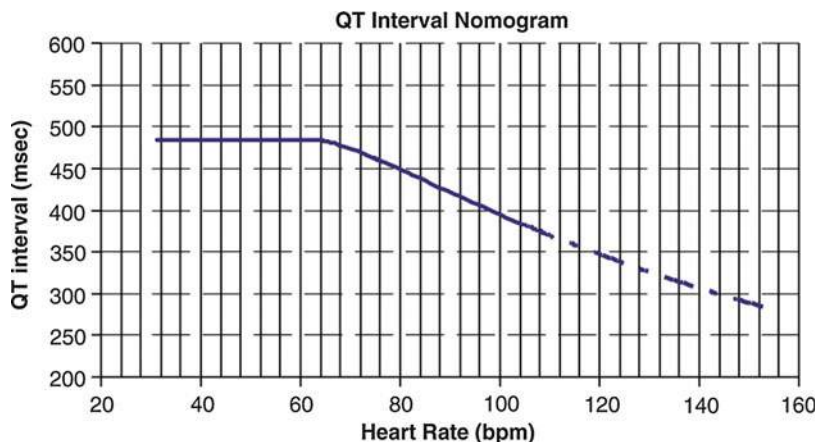
Female gender
Advanced age
Hypomagnesemia
Structural heart disease
Congenital LQTS
Ingestion of several QT prolonging drugs

the ECG. A major problem for all methods is defining the end of the T wave, especially in tachycardia. Other controversial issues for all approaches are: should measurement be performed in one or multiple ECG leads and in one or multiple beats in each lead, and if multiple leads and beats should be measured, which value should be used, the highest, the mean or the median? The manual approach has the advantage of more accurately determining the end of the QT interval, but is considerably more time-consuming as measurements in up to 6 different ECG leads and 3–5 beats in each lead are often recommended. Contemporary automatic QT-monitoring systems allow the rapid measurement of large numbers of QT intervals but may be inaccurate in determining the end of the T wave, and some serious miscalculations by different ECG monitors have been published [19, 20].

Heart rate correction: The strong effect of the heart rate on the QT interval makes heart rate correction necessary. The by far most commonly used correction method worldwide is “Bazett’s QTc” ($QTc = QT \text{ interval (ms)} / RR \text{ interval (s)}^{0.5}$) [21, 22]. Other less common methods are Friderica’s, Hoge’s and Framingham’s formulas. Most experts consider a QTc value above 500 ms as a significant risk of TdP [11, 14, 19]. The weakness of Bazett’s method in particular is that the QTc value is overestimated in tachycardia and underestimated in bradycardia [19].

The QT interval nomogram: To overcome the weaknesses of the different correction formulas, Chan and colleagues developed a QT interval nomogram [12] (Fig. 5). The nomogram is based on a cloud diagram produced by Fossa and colleagues [23]. Chan and coworkers evaluated the performance of this QT nomogram by comparing

Fig. 5 The QT interval nomogram. The “risk-line” separates QT-HR pairs below the line from those above which are associated with an increased risk of TdP (Reproduced from Ref. [12], with permission)



QT-HR combinations from 129 published cases with drug-induced TdP and 318 control cases poisoned by noncardiotoxic drugs [12]. This study reveals that the QT nomogram has a high sensitivity and specificity, somewhat better than Bazett's QTc equal to 500 ms, but it also shows that Bazett's correction formula with a risk cutoff at 500 ms also do quite well and, in fact, is similar to the QT nomogram for heart rates between 70 and 100 bpm. Moreover, the study reveals that a vast majority of all cases of drug-induced TdP occur in patients with a heart rate below 80 and that extremely few occur in tachycardic patients.

How to Best Measure the QT Interval

Isbister concluded in a recent review [19] that the most accurate method is to perform manual measurements of QT intervals. He recommends measurements in six different ECG leads and then using the median value for insertion into the QT nomogram. While this method may be used in clinical studies, and by consulting medical toxicologists and cardiologists, this rather time-consuming approach is not practical in the acute clinical setting of the poisoned patient. It is reasonable that the routinely performed supervision and monitoring of poisoned patients include automatic measurements of QTc values. However, for patients with a suspected overdose of a high risk

drug or with a QTc value above 500 ms at a heart rate below 100 bpm, Isbister's method may be preferred. Irrespective of the chosen method for measurement of the QT interval, one must realize the fact that the QRS complex is included in the calculation. This “weakness” of the QT interval per se becomes obvious in patients with bundle branch block or poisoning with drugs that also have membrane stabilizing properties.

Management of QTc Prolongation in Poisoned Patients

If a poisoned patient has overdosed on a drug known to carry a risk of TdP or display a QTc prolongation on the 12-lead ECG, continuous ECG monitoring and repeated measurements of the QT interval are imperative. Serum levels of potassium and calcium should be checked and corrected to the mid-reference range. Other possible risk factors should be considered. Drug-drug interactions and heart rate must be considered. An external defibrillator should be readily available. The patient should not be transported from the unit for diagnostic or therapeutic procedures unless monitored and accompanied by personnel able to respond to the development of TdP.

Prophylactic treatment: Recommendations regarding prophylactic pharmaceutical treatment of poisoned patients with a presumed high risk of developing TdP are controversial and almost

lacking [24, 25]. However, several clinicians and clinical toxicologists agree that magnesium administration may be indicated in certain high risk cases [22, 24]. If, for example, a patient has ingested a toxic dose of a high risk drug such as methadone or sotalol and displays a QTc-time above 500 ms at a heart rate below 80 bpm, it seems reasonable to administer 2 g magnesium (8 mmol) as an intravenous bolus injection over 5 min followed by an infusion of 1 g magnesium/h for 4–6 h. Arguments for this approach are that magnesium therapy is an effective treatment of TdP, suppresses EADs, and is well tolerated in the recommended dose range. In these relatively few high risk cases, there may also be a role for the administration of atropine and isoproterenol if significant bradycardia is present (see “Guidelines” section below). However, the routine use of magnesium in every patient with a QTc interval over 500 ms or with a QT–HR pair above the “risk line” is definitely not justified. For example, magnesium supplementation would not be indicated if the patient is tachycardic or if a nonrisk drug such as quetiapine, olanzapine, or risperidone has been overdosed.

Management of Toxicant-Induced Torsade de Pointes

The attack: The characteristic pattern of an attack of TdP is a pulseless polymorphic ventricular tachycardia, typically with short-lived intermittent runs interspersed with pulse-yielding beats (Fig. 6a and b). This means that the patients are most often asymptomatic during the arrhythmia, although they may experience palpitations, dizziness, or short-lived syncope [3, 14, 15, 26]. Cardioversion is seldom needed, indicated, or successful as long as the TdP-runs may not become persistent or degenerate to ventricular fibrillation.

Management of torsade de pointes: Because of the rarity of TdP, there is no evidence regarding its treatment derived from controlled trials. Magnesium (Mg) suppresses TdP although its mechanism of action is not fully understood. Magnesium

is a potassium channel blocker. As the electrochemical gradient of the cardiac cell promotes outward movement of potassium via IKr, Mg blocks the outward flow of potassium maintaining the action potential plateau. Nevertheless, magnesium is also a natural calcium channel blocker. Decreasing the inward calcium current suppresses EADs without affecting the QT interval. Magnesium also homogenizes transmural ventricular dispersion which causes repolarization to approach the normal intrinsic variability [27].

Guidelines: Published recommendations and guidelines for the management TdP recommend slight variations of the following protocol which is supported by numerous clinical observations and case series [3, 5, 14, 15, 28, 29].

- The first appropriate action, after basic life support procedures have been initiated, is to administer an intravenous bolus of 2 g (8 mmol) magnesium over 2 min, irrespective of the serum Mg concentration (Level of Evidence [LoE]: II-3).
- Secondly, correct hypokalemia (LoE: II-3), with the aim of achieving a serum potassium concentration of 4.5–5.2 mmol/L (LoE: III) [3, 29].
- If the TdP-runs do not resolve after these measures, we recommend an additional 2 g of Mg to be administered over 5 min (LoE: II-3).
- In cases where the preattack heart rate was slow, for example, below approximately 70 bpm, a dose of atropine can be administered and an isoproterenol infusion should be initiated (dose range: 0.03–0.3 µg/kg/min) (LoE: II-3). Overdrive pacing is indicated if the TdP continues or isoproterenol is contraindicated or not tolerated (LoE: II-3).
- It is often appropriate to start an intravenous infusion of 1 g (4 mmol) magnesium/h as the half-life of magnesium is only approximately 4 h.
- If pulseless unconsciousness occur, immediate cardioversion is indicated (Table 3). Transcutaneous pacing pads, placed after the first sign of TdP, are useful to have in place in case they are needed for the management of a sustained event.

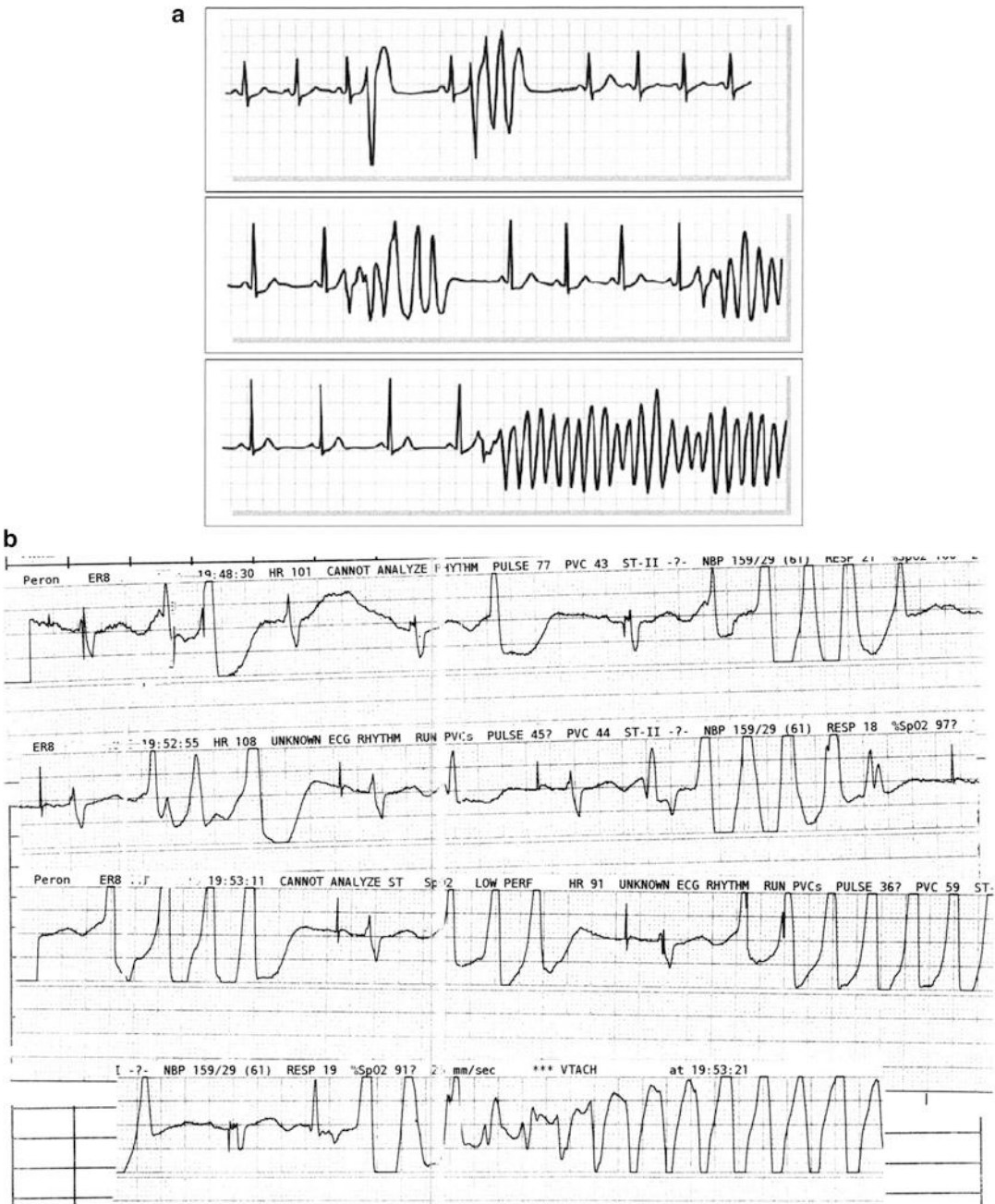


Fig. 6 (a and b). Two arrhythmia recordings showing the characteristic pattern of torsade de pointes with short-lived runs interspersed with pulse-yielding beats

Table 3 Treatment of toxicant-induced torsade de pointes

Slow iv. injection of 2 g magnesium (8 mmol)
Correct hypokalemia to the upper reference limit
If TdP-runs proceed, give another 2 g magnesium iv.
If preattack HR is slow, start isoproterenol and consider overdrive PM
Consider an infusion of 1 g magnesium per hour for 6 h
If prolonged pulseless unconsciousness occur, defibrillate

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The anticholinergic syndrome is common and may result from exposures to many drugs or natural substances (Table 1). Anticholinergic effects are desired or intended effects for certain drugs (i.e., antispasmodics, mydriatics, and belladonna alkaloids) and are undesired or side-effects for other drugs (i.e., antihistamines, antidepressants, antipsychotics, and antiparkinsonians). Both prescription and over-the-counter drugs may have anticholinergic effects. Combined use of more than one drug with anticholinergic effects increases the risk of anticholinergic toxicity. The anticholinergic syndrome, also called the *anticholinergic toxidrome*, has peripheral and central manifestations. The more serious adverse effects associated with large exposures to these agents are often a result of other physiologic properties of these agents rather than the anticholinergic effects.

Granacher and Baldessarini [3] and Hall and colleagues [4] were among the first to describe the central anticholinergic syndrome (CAS), a sometimes dramatic form of anticholinergic toxicity in which central nervous system (CNS) effects occur in the absence of peripheral anticholinergic manifestations. As with all anticholinergic syndromes, CAS may result from abuse, intentional or unintentional overdoses, or adverse drug reactions. A moderate stage of anticholinergism with euphoria and hallucinations is the desired end point of certain forms of substance abuse, but achieving the desired stage of intoxication and avoiding toxicity is difficult.

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Table 1 Anticholinergic drugs and natural substances^a

Belladonna alkaloids
Atropine sulfate
Belladonna extract
Belladonna tincture
Levo alkaloids of belladonna (Bellafole)
Clidinium (Quarzan)
Homatropine hydrobromide
Hyoscine N-butylbromide
Hyoscyamine sulfate
Hyoscyamine
Scopolamine hydrobromide
Gastrointestinal antispasmodics
Anisotropine methylbromide (Valpin)
Butylscopolamine bromide (Buscopan)
Clidinium bromide (Librax)
Dicyclomine hydrochloride (Bentyl)
Glycopyrrolate (Robinul)
Hexocyclium methylsulfate (Tral)
Isopropamide iodide (Darbid)
Mepenzolate bromide (Cantil)
Methantheline bromide (Banthine)
Atropine/diphenoxylate (Lomotil)
Methscopolamine bromide (Pamine)
Oxyphencyclimine hydrochloride (Daricon)
Oxyphenonium bromide (Antrenyl)
Propantheline bromide (Pro-Banthine)
Genitourinary antispasmodics
Flavoxate hydrochloride (Urispas)
Oxybutynin chloride (Ditropan)
Tolterodine tartrate (Detrol)
Cycloplegics
Cyclopentolate (Cyclogyl)
Tropicamide (Mydriacyl)
Other drugs
Cyclobenzaprine (Flexeril)
Mefloquine
Diphenidol (Vontrol)
Ipratropium bromide (Atrovent)
Antihistamines
Acrivastine
Antazoline
Azatadine
Bromodiphenhydramine
Brompheniramine
Bucizine
Carbinoxamine
Cetirizine

(continued)

Table 1 (continued)

Chlorcyclizine
Chlorpheniramine
Clemastine
Cyclizine
Cyproheptadine
Dexbrompheniramine
Dexchlorpheniramine
Dimenhydrinate
Dimethindene
Diphenhydramine
Diphenylpyraline
Doxylamine
Fexofenadine
Hydroxyzine
Loratadine
Meclizine
Methapyrilene
Phenindamine
Pheniramine
Phenyltoloxamine
Promethazine
Pyrilamine
Pyrrobutamine
Tripelennamine
Tripolidine
Antiulcer drugs
Cimetidine
Famotidine
Propantheline
Ranitidine
Antiparkinson drugs
Benzotropine mesylate (Cogentin)
Biperiden (Akineton)
Orphenadrine hydrochloride (Disipal)
Orphenadrine citrate (Norflex)
Procyclidine (Kemadrin)
Trihexyphenidyl hydrochloride (Artane)
Neuroleptics [1]
Chlorpromazine (Thorazine)
Prochlorperazine
Fluphenazine
Clozapine (Clozaril)
Prochlorperazine
Olanzapine (Zyprexa)
Thioridazine
Thiothixene

(continued)

Table 1 (continued)

Tricyclic antidepressants [2]
Amitriptyline (Elavil)
Clomipramine (Anafranil)
Imipramine (Tofranil)
Desipramine (Norpramin)
Doxepin (Sinequan)
Nortriptyline (Pamelor)
Protriptyline (Vivactil)
Trimipramine (Surmontil)
Plants
<i>Atropa belladonna</i> (deadly nightshade)
<i>Brugmansia arborea</i> (angel's trumpet)
<i>Brugmansia suaveolens</i> (angel's trumpet)
<i>Cestrum diurnum</i> (day jessamine)
<i>Cestrum nocturnum</i> (night jessamine)
<i>Cestrum parqui</i> (willow-leaved jessamine)
<i>Datura metel</i> (Hindu datura)
<i>Datura stramonium</i> (Jimson weed, thorn apple, locoweed)
<i>Duboisra</i> spp.
<i>Hyoscyamus niger</i> (black henbane)
<i>Lantana camara</i> (yellow sage)
<i>Lycium halimifolium</i> (matrimony vine)
<i>Mandragora officinarum</i> (mandrake)
<i>Scopolia atropoides</i> (crazy plant)
<i>Solandra</i> spp. (trumpet flower)
<i>Solanum dulcamara</i> (woody nightshade)
<i>Solanum nigrum</i> (black nightshade)
Mushrooms
<i>Amanita cothurnata</i>
<i>Amanita gemmata</i>
<i>Amanita muscaria</i>
<i>Amanita pantherina</i>
<i>Amanita smithiana</i>

^aBrand names given are examples of those in the United States. Other countries may use similar or different brand names.

Overview and Incidence

Data from the American Association of Poison Control Centers National Poison Data System indicate that anticholinergic exposures are common but usually not severe or fatal (Table 2) [5]. Of the more than 97,000 exposures reported in the United States in 2013, only one third of cases were treated in a healthcare facility (Table 3). These data, compared to AAPCC data from 2002,

demonstrate a marked decrease in reported exposures and deaths from anticholinergic exposure in 2014 [5, 6]. Use of drugs with anticholinergic activity is the most common cause of pharmaceutical-induced delirium [7]. Differences in clinical effects result from not only the dose but also variability in the degree of muscarinic receptor blocking among agents [1, 2]. Large intentional ingestions of sleeping pills, antihistamine-type sleeping pills, and tricyclic antidepressants (TCAs) are common causes of serious toxicity within these groups. Antihistamine exposure is the most common cause of unintentional anticholinergic toxicity, whereas cyclic antidepressants and atypical antipsychotics are proportionally larger origins of intentional exposures and toxicity [6]. Many anticholinergic-type adverse drug reactions and abuse are not reported to poison centers or adverse drug reaction programs, and their true incidence is unknown. In one study, 60% of elderly nursing home patients were taking at least one anticholinergic agent, and 13% of patients on anticholinergic drugs in one geriatric unit had significant adverse effects [7]. Data from the American College of Medical Toxicology's Toxicology Investigators Consortium (ToxIC) Case Registry reveal that of patients requiring medical toxicologist-directed treatment, 6% of patients age 19–65 years and 4% of patients age greater than 66 years had anticholinergic toxicity [8].

History

Natural substances with anticholinergic properties, such as nightshade plants, have long been used for their mind-altering properties by different cultures [9]. The Solanaceae alkaloids, primarily atropine and scopolamine, have been the active ingredients of ancient witches' brews and ointments (Pharmaka diabolica), love potions, intoxicants, hallucinogens, knockout agents, and poisons. British soldiers were described as "natural fools" for 11 days after consuming a salad containing leaves of *Datura stramonium* (Jimson weed) (see ► Chap. 111, "Anticholinergic Plants") [10].

Table 2 Anticholinergic exposures and intent reported to US poison centers in 2014 (Extracted from Mowry et al. [6])

Agents	Exposures	Unintentional	Intentional	Other/adverse reaction
Natural substances				
Mushroom ^a	37	12	21	4
Plant ^b	610	454	133	18
Medications				
Anticholinergic	8,271	7,774	336	137
Antihistamine ^c	66,784	52,722	12,774	957
Gastrointestinal antispasmodics ^b	1,325	1,022	221	68
Cyclic antidepressants	4,414	1,636	2,515	178
Phenothiazine	1,806	774	804	191
Atypical antipsychotics	15,907	5,822	9,103	753
Total	99,154	70,216	25,907	2,306

^aIbotenic acid group^bAnticholinergic type^cNot including H₂ receptor antagonists**Table 3** Anticholinergic exposures and outcomes reported to US poison centers in 2014 (Extracted from Mowry et al. [6])

Agents	Health care facility presentation	Outcome				
		None	Minor	Moderate	Major	Death
Natural substances						
Mushroom ^a	28	4	4	19	5	0
Plant ^b	191	164	71	80	8	0
Medications						
Anticholinergic	721	1,052	255	200	16	1
Antihistamine ^c	18,147	15,115	7,255	4,412	390	17
Gastrointestinal antispasmodics ^b	456	387	193	110	4	0
Cyclic antidepressants	3,215	677	961	1,188	341	12
Phenothiazine	1,248	327	414	463	41	1
Atypical antipsychotics	11,816	2,850	4,481	3,639	399	15
Total	35,822	20,576	13,634	10,111	1,204	46

^aIbotenic acid group^bAnticholinergic type^cNot including H₂ receptor antagonists

Pathophysiology

Acetylcholine (ACh) is a key neurotransmitter in both the central and peripheral nervous system. When released, ACh may activate either nicotinic or muscarinic receptors (Fig. 1). Nicotinic receptors (12 types: α_2 – α_9 and β_2 – β_5) are located in the CNS (mainly spinal cord), on postganglionic autonomic neurons (sympathetic and parasympathetic), and neuromuscular junctions. These receptors are ligand-gated ion channels for sodium (Na⁺) and calcium (Ca²⁺), activation of

which leads to rapid cell membrane depolarization and cellular excitation.

Muscarinic receptors, however, are located in the CNS (mainly brain (Fig. 2)), end-organ parasympathetic nerve endings, sympathetically innervated sweat glands and, to a lesser extent, autonomic ganglions and the adrenal medulla [11, 12]. There are five types of cloned muscarinic receptors (M₁ through M₅), whose effects are mediated more slowly than nicotinic receptors through guanosine triphosphate-binding proteins (G proteins). The primary intracellular messengers

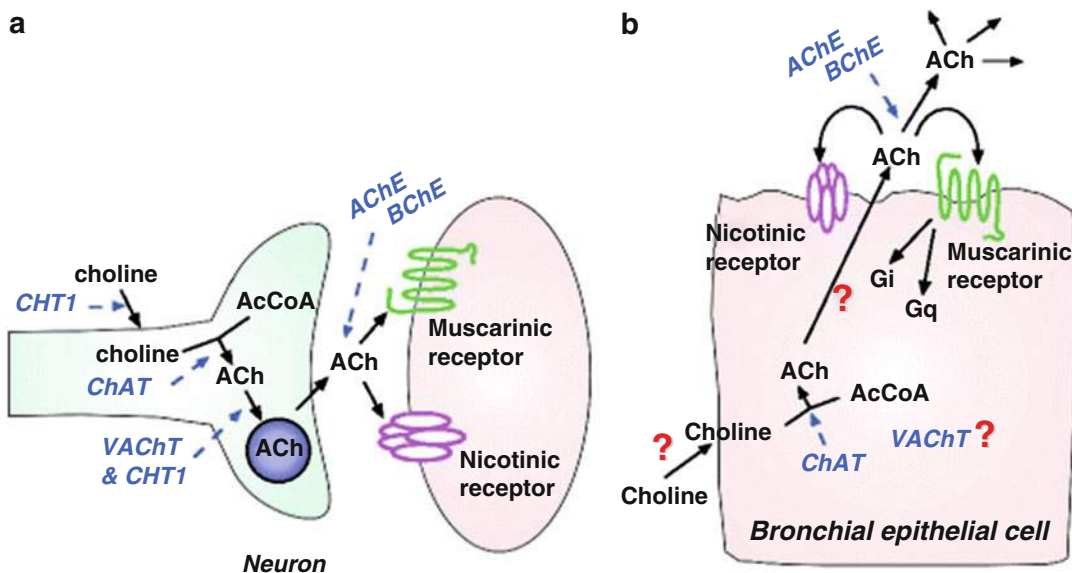


Fig. 1 Cholinergic signaling in neurons and bronchial epithelial cells. **(a)** In neurons, choline for ACh synthesis is transported by the choline high-affinity transporter (CHT1). ACh is then synthesized by the action of choline acetyltransferase (ChAT) and packaged into synaptic vesicles by the action of the vesicular acetylcholine transporter (VACHT) and CHT1. ACh is then secreted by the complex processes that control synaptic release. Released ACh then interacts with postsynaptic nAChR and mAChR as well as presynaptic receptors. Signaling is terminated by acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Key signal transduction events lead to the generation of action potentials, opening of membrane and internal ion channels, muscle contraction and kinase activation. **(b)** In bronchial epithelial cells (BEC), though CHT1 is present,

CHT1 does not appear necessary for choline transport for ACh synthesis. In BEC, as for neurons, ChAT is utilized for ACh synthesis; though there are multiple isoforms of ChAT, different splicing products may be utilized in different cell types. Since CHT1 is not required and BEC do not have synaptic vesicles, the role of VACHT and CHT1 in ACh secretion is unknown, though both are expressed in BEC. ACh released by BEC is inactivated by the same cholinesterases as expressed in neurons. A key difference is that released ACh is not limited just to synaptic communication but can also signal multiple neighboring cells as a paracrine factor or more distal cells as a hormone (From Handbook of Experimental Pharmacology Vol 208. Fryer AD et al. eds, 2012, Springer, Munich, with permission)

affected by muscarinic stimulation are Ca^{2+} and cyclic adenosine monophosphate (cAMP). Odd-numbered receptors (M_1 , M_3 , M_5) activate a G protein that leads to the release of intracellular calcium, resulting in smooth muscle contraction and gland secretion. Even-numbered receptors (M_2 , M_4) activate a G protein that inhibits adenylyl cyclase, leading to reduced levels of cAMP. Thus, the intracellular effects of muscarinic stimulation may lead to either stimulatory (depolarizing) or inhibitory (hyperpolarizing) effects on membrane potentials depending on the receptor types present on any particular structure [13]. After release, ACh undergoes synaptic degradation via acetylcholinesterase (AChE) into the inactive products choline and acetate.

Toxic Mechanism

Anticholinergic agents antagonize the effect of ACh by competitively blocking its binding to either nicotinic or muscarinic ACh receptor sites. Clinically significant nicotinic ACh receptor blockade results in neuromuscular paralysis and is most commonly encountered with the usage of paralytic agents including depolarizing agents (e.g., succinylcholine) and nondepolarizing curare-mimetic agents (e.g., pancuronium). Symptoms of nicotinic ACh antagonism may also arise from elapid envenomation due to the effect of α -neurotoxins [14].

Until recently, significant nicotinic ACh antagonism from nicotine ingestion was uncommon.

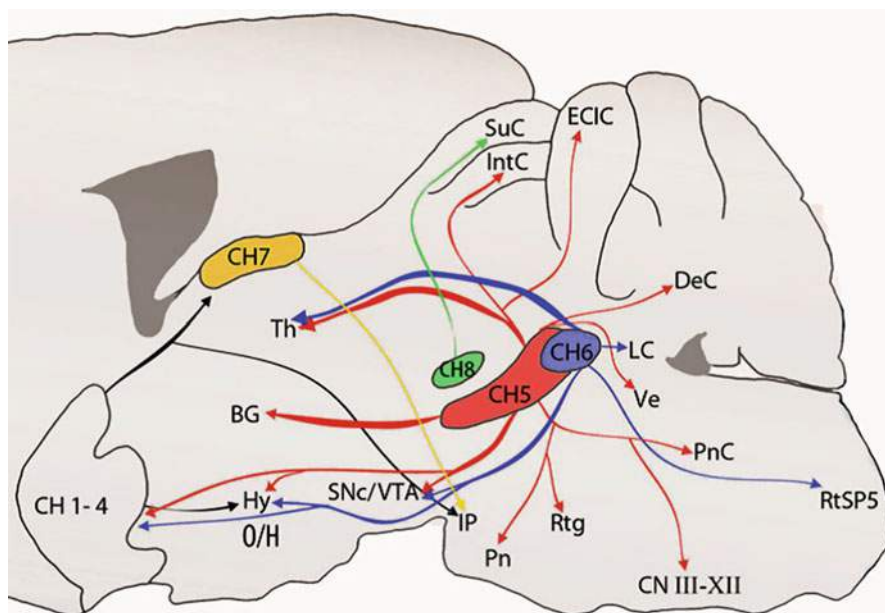


Fig. 2 Cholinergic cell groups (*Ch1–8*) and their brain stem projections collapsed onto a schematic parasagittal mouse brain section. *Th* thalamus, *BG* basal ganglia, *Hy* hypothalamus, *O/H* orexin/hypocretin neurons, *SuC* superficial layers of superior colliculus, *IntC* intermediate layers of superior colliculus, *ECIC* external cortex of inferior colliculus, *IP* interpeduncular nucleus, *Pn* pontine nuclei,

Rtg rostral tegmental nucleus, *DeC* deep cerebellar nuclei, *LC* locus coeruleus, *Ve* vestibular nuclei, *PnC* nucleus reticularis pontis caudalis, *CN* cranial nerves, *RtSP5* spinal nucleus of the 5th nerve (From Handbook of Experimental Pharmacology Vol 208. Fryer AD et al. eds, 2012, Springer, Munich, with permission)

However, between 2010 and 2016, there has been rapid development and expanded use of electronic nicotine delivery systems (e.g., electronic cigarettes). These systems vaporize liquid nicotine preparations from chambers that are often filled by hand from a commercially available bottle of concentrated nicotine fluid. Appealing flavorings and colorful labeling conflict with poor regulation of packaging, likely contributing to a staggering rise in liquid nicotine exposure reporting to the AAPCC, with more than half of the 3,073 exposures in 2015 occurring in children under 6 years of age. These figures are compared to 2011 in which there were only 271 total reported exposures [15]. Unfortunately, there has been similar rise in published case reports of pediatric ingestions resulting in significant toxicity and death [15, 16].

Muscarinic ACh receptor blockade is commonly encountered and makes up the bulk of clinically significant exposures, so much so that

the so-called anticholinergic toxidrome may be more appropriately characterized as an *antimuscarinic toxidrome*. Effects of muscarinic ACh blockade may be divided into central and peripheral effects (Table 4). Generally, central antimuscarinic activity results in changes in mentation including agitation, picking movements, and hallucinations and peripheral antimuscarinic activity results in anhidrosis, mydriasis, tachycardia, and urinary retention. These effects are often dose-dependent, with low level antagonism resulting in decreases in sweating as well as bronchial and salivary secretion production. Moderate antagonism may result in tachycardia and mydriasis with resultant loss in visual accommodation [17]. Urinary retention and intestinal/gastric atony result from high degree peripheral muscarinic ACh antagonism [12]. Muscarinic receptor antagonists (e.g., atropine) are generally ineffective at blocking nicotinic sites. Tertiary agents more readily cross the blood–brain barrier and are

Table 4 Signs and symptoms of anticholinergic (antimuscarinic) toxicity

Peripheral anticholinergic signs
Dry skin, mouth, and axilla
Flushing
Hyperthermia
Urinary retention
Diminished bowel signs
Mydriasis
Loss of accommodation
Myoclonus
Tachycardia
Hypertension
Peripheral vasodilation
Dysrhythmias
Cardiogenic shock
Central anticholinergic signs
Agitation
Altered mental status
Amnesia
Anxiety
Ataxia
Cardiorespiratory arrest
Choreoathetosis
Coma
Delirium
Disorientation
Dysarthria
Extrapyramidal reactions
Auditory and visual hallucinations
Incoherent speech
Lethargy
Paranoia
Psychosis
Seizures
Stereotypy (i.e., repetitive gesturing or movements)

more likely to result in central anticholinergic toxicity, whereas the converse is true of quaternary agents (Table 5). Atropine typically causes predominantly peripheral anticholinergic effects at low doses and additional central anticholinergic effects at higher doses [17]. Still higher doses of atropine may result in shock, coma, and respiratory failure [18]. Quaternary antimuscarinic compounds do not readily cross the blood–brain barrier and are unlikely to result in central ACh nicotinic blockade.

Table 5 Tertiary and quaternary anticholinergic compounds

Tertiary amines	Quaternary ammonium
Naturally Occurring Alkaloids	
Atropine	
Belladonna	
Hyoscyamine	
Scopolamine	
Semisynthetic derivatives	
Homatropine	Homatropine methylbromide
Methscopolamine	
Synthetic amine compounds	
Dicyclomine	Clidinium
Oxybutynin	Glycopyrrolate
Pirenzepine	Ipratropium
Tolterodine	Mepenzolate
	Propantheline

Clinical Presentations and Life-Threatening Complications

The anticholinergic toxidrome is a constellation of signs and symptoms potentially involving many different organ systems (see Table 4). Signs of peripheral anticholinergic toxicity characteristically, but not always, accompany central anticholinergic toxicity. The authors of a carefully controlled clinical study meticulously described the onset and course of iatrogenic central anticholinergic toxicity and its reversal by the cholinergic agent physostigmine [19]. They described three phases: induction, stupor, and delirium. In the induction phase, peripheral anticholinergic effects predominated. The stupor phase was characterized by somnolence, restlessness, ataxia, hyperthermia, and hypertension. The third phase, delirium, was characterized by amnesia, confusion, incoherent speech, and hallucinations. These phases represent an overlapping continuum of toxicity rather than distinct transition points. Importantly, the delirium phase often outlasted the first two phases. These phases were described in the setting of central anticholinergic toxicity from atropine, scopolamine, and ditran. They may differ somewhat in the setting of other anticholinergic agents [19].

The characteristic general appearance of the anticholinergic syndrome is a restless, delirious patient who is picking at the bed sheets, clothing, and imaginary objects in the air. Speech is characteristically rapid, mumbling, and incomprehensible [20]. Hallucinations are usually visual but sometimes may be auditory. Dilated pupils and tachycardia are often present, but neither is essential to the diagnosis. Public disrobing is a common feature (particularly in plant-based toxicity), possibly due to the delirious uninhibited patient's sensation of flushing and hot skin [20].

Routes of Exposure

The anticholinergic syndrome may result from oral, pulmonary (smoking), ocular, dermal, buccal, rectal, or vaginal routes of exposure to anticholinergic agents. Oral exposures are most common in reported cases and include intentional ingestion of pills, seeds, or teas. Pulmonary or inhalational exposures usually are associated with substance abuse, although nebulized atropine treatment of asthma is an exception [21, 22]. Ocular and dermal exposures more commonly are unintentional exposures and are difficult to recognize. Witches' ointments were applied intentionally to the whole body, including the axillae, rectum, and vagina [9]. Horse traders rolled *Datura* leaves together and inserted them into the rectums of old nags to make them appear to be as fiery as thoroughbreds [9]. Exposure to ophthalmologic drops has resulted in the anticholinergic syndrome as an adverse effect of therapeutic use and has been an agent of drug-facilitated assault or robbery. Dermal exposures to topical diphenhydramine and scopolamine patches are well-known causes of systemic anticholinergic effects [23–26].

Intention or Cause of Exposures

Adverse Drug Reactions

Many authors have stated empirically that anticholinergic syndrome occurs frequently as an

adverse drug reaction, but few data have been published to support this. Anticholinergic adverse drug reactions occur most frequently as a result of increased sensitivity to a therapeutic dose or as a result of combinations of anticholinergic agents. Very young and very old individuals and patients with underlying organic brain syndromes are said to be more susceptible to CAS [4, 27, 28]. For unknown reasons, some patients have developed the anticholinergic syndrome from exposures to anticholinergic skin patches that most patients tolerate without problems. [29]

Unintentional Overdose

Toddlers and mentally infirm people are common victims of unintentional or accidental overdose. Use of combinations of prescribed or over-the-counter anticholinergic agents is a common cause of unintentional overdose.

Intentional or Suicidal Overdose

Suicidal ingestions of over-the-counter sleeping pills usually involve anticholinergic antihistaminic agents. Although these exposures are common and usually mild to moderate in severity, severe outcomes or death occasionally results [30, 31].

Recreational Abuse

Self-administration of anticholinergic agents to induce the desired euphoria, stupor, and hallucinations through induction of anticholinergism is well described [32, 33]. Abuse of anticholinergic drugs or natural substances is a particular problem of adolescents who are too young to buy alcoholic beverages legally [34–36]. In the fourteenth and fifteenth centuries, henbane often was added to beer for its hallucinogenic and mind-altering properties [9]. Anticholinergic agents prescribed to prevent or treat extrapyramidal or dystonic reaction due to neuroleptics have been abused by schizophrenics and individuals without psychiatric illnesses. In one study of schizophrenic patients, careful scrutiny revealed that 6.5% of 214 consecutively admitted schizophrenic patients abused trihexyphenidyl [36]. Emergency department physicians in the 1980s often gave a placebo saline injection to patients with suspected

dystonic reactions in hopes of discovering individuals with feigned dystonia who were seeking intravenous anticholinergic drugs [37–39]. The delayed absorption associated with these agents plus the biologic variability in natural substances makes it particularly difficult for users to titrate the dose of these agents to reach the desired end point of hallucinations while avoiding more severe toxicity.

Malicious Use

The addition of anticholinergic agents such as scopolamine to other substances of abuse may lead to unusual or serious toxicity. Substitution of scopolamine for cocaine [40] and addition of scopolamine to heroin [41] have been reported. Surreptitious addition of scopolamine to beverages is a well-known method of drug-facilitated sexual assault or crime [42–44]. The German term *Altsitzerkraut*, meaning “old sitter herb,” refers to the use of henbane to induce a lethal form of anticholinergic toxicity to murder an inactive old person [9]. Because there is no history of exposure in these cases and the usual simple toxicologic screens are negative, misdiagnosis is common.

Toxic Causes or Sources

Many types of prescription and over-the-counter medications and natural substances have anticholinergic properties (see Table 1). The anticholinergic syndrome may result from intentional or unintentional exposure to toxic amounts of these individual agents or in combinations. Many members of the plant family Solanaceae contain tropane or belladonna alkaloids. Plants that can cause the anticholinergic syndrome contain variable amounts of the following toxic alkaloids: solanine, atropine, and scopolamine. Anticholinergic plant toxicity is discussed in detail in the chapter devoted to that topic. Scopolamine is the primary tropane in Jimson weed. Toxin concentrations of specific types of plants and mushrooms are well known to vary with location, climate, and season. Natural brews, such as teas or wines made from these plants, are notorious for their intoxicating abilities [45–48]. Mushrooms containing muscimol/ibotenic acid are often described as capable of causing hallucinations and a syndrome

with some features that resemble the anticholinergic syndrome. However, muscimol and ibotenic acid are actually pharmacologic modulators of the gamma amino butyric acid – glutamic acid neurotransmitter system. Intentional (recreational) and unintentional (toddler ingestions) exposures to these types of mushrooms only rarely produce severe anticholinergic-like syndrome [49].

Range of Toxicity

Toxicity varies greatly among the various substances with anticholinergic properties. Toxicity is greatest for the TCAs primarily because of their α -adrenergic receptor-blocking and sodium channel-blocking effects rather than their anticholinergic properties. In a pediatric series of auto-injector atropine exposures, lower injected doses resulted mainly in mild peripheral effects, whereas higher doses resulted in hyperthermia and central effects [50]. In adults, atropine doses of 0.032 mg/kg caused peripheral effects and doses of 0.13–0.17 mg/kg caused central effects [19]. These studies suggest that peripheral effects occur at lower doses than do central effects. As little as 4–5 eye drops (probably less in children) containing 4% atropine or 0.25% scopolamine has been reported to cause the anticholinergic syndrome [51, 52].

Organ System Effects

Seizures

Anticholinergic poisoning is a common cause of drug-induced seizures, the risk of which may be agent-dependent. Seizures were not observed in a series of 20 cases of severe atropinization secondary to mostly unintentional auto-injector discharge during the Persian Gulf War [50]. In TCA overdose, the prevalence of seizures has been reported to be 3–30% [53–55]. However, the pathophysiology of TCA-induced seizures is poorly understood and may not be entirely due to their anticholinergic effects. In nine children hospitalized after ingesting *Amanita pantherina* or *Amanita muscaria* mushrooms, seizures or myoclonic

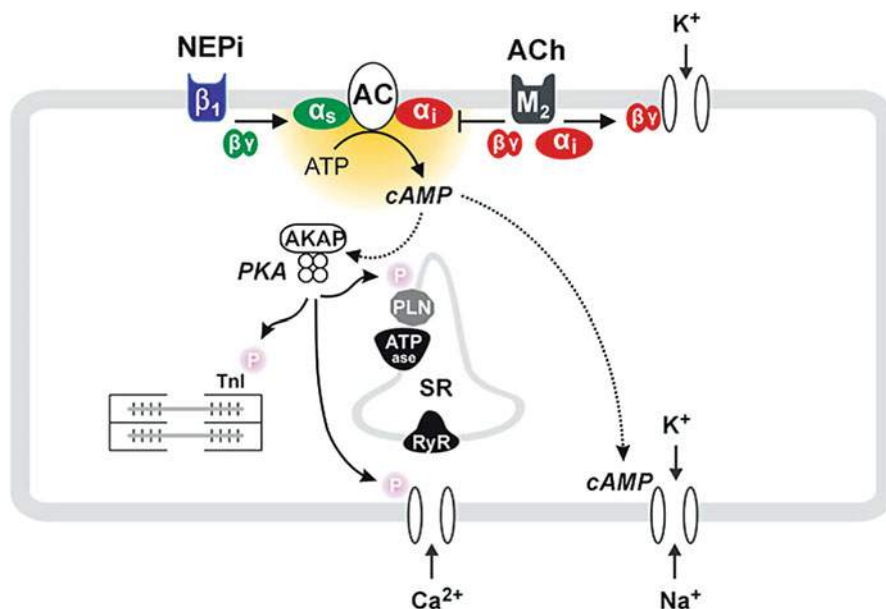


Fig. 3 Muscarinic signaling pathways in supraventricular (sinoatrial, atrial, and atrioventricular) myocytes. Acetylcholine (ACh) acts through M_2 receptors to regulate ACh-activated K^p channels via a membrane-delimited mechanism involving direct activation by the $\beta\gamma$ subunits of the inhibitory G protein G_i . ACh also acts through M_2 receptors to inhibit adenylyl cyclase (AC) activity via the α subunit (α_i) of G_i , resulting in a decrease in cAMP production. This may occur in the absence or presence of agonists that stimulate cAMP production. Norepinephrine (NEPi) acts through b_1 -adrenergic receptors to stimulate cAMP

synthesis by directly activating all isoforms of adenylyl cyclase (AC) via the α subunit (α_s) of the stimulatory G protein G_s . Changes in cAMP affect targets of protein kinase A (PKA)-dependent phosphorylation such as troponin I (TnI), phospholamban (PLN), and the L-type Ca^{2+} channel. Changes in cAMP also directly regulate pacemaker channels, which are permeable to both Na^+ and K^+ (From Handbook of Experimental Pharmacology Vol 208. Fryer AD et al. eds, 2012, Springer, Munich, with permission)

twitching occurred in 44% [49]. Understanding the true incidence of seizures may be clouded by abnormal muscle activity (e.g., jerks, twitches, rigidity) secondary to anticholinergic toxicity that may be confused with seizures by laypersons and less experienced health care providers. Because seizures have been considered by some to be a relative contraindication to physostigmine use, the reported observation of seizures by less experienced or trained personnel must be evaluated carefully.

Cardiovascular Effects

Mild to moderately severe anticholinergic syndrome is associated with sinus tachycardia and hypertension. The tachycardia may result primarily from blocking of the M_2 -receptors on the sinoatrial node.(Fig. 3). Hypertension results from

antagonism of the ACh-induced peripheral vasodilation (Fig. 4). However, anticholinergic agents that possess sodium channel or α -adrenergic antagonistic properties may result in hypotension due to direct vasodilation. Cardiotoxicity may further complicate hemodynamic instability due to development of advanced heart block or ventricular dysrhythmia. Together, these effects may lead to cardiovascular collapse and refractory shock. Of note, moderate anticholinergic exposure in a susceptible host may also lead to severe toxicity [56].

Gastrointestinal Effects

Anticholinergic agents may decrease intestinal peristalsis and delay gastric emptying [57]. For antispasmodic drugs, this is a desired effect and leads to decreased intestinal spasms. When

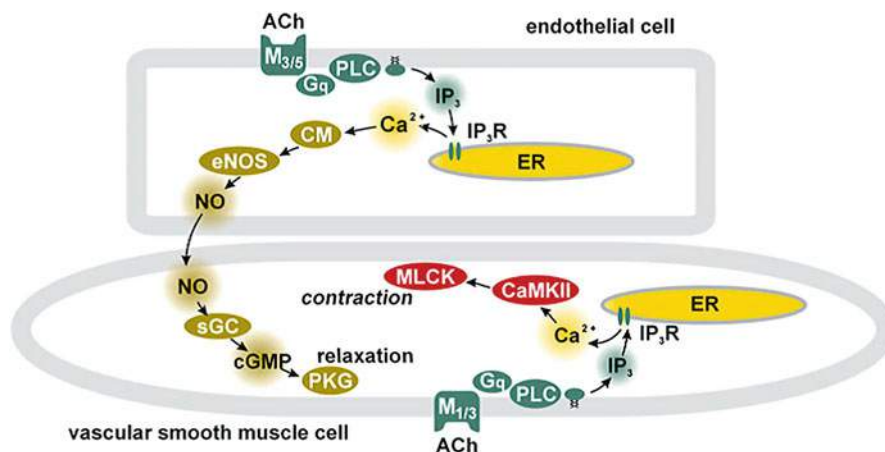


Fig. 4 Muscarinic signaling pathways in the vasculature. In endothelial cells, acetylcholine (*ACh*) acting through M_3 or M_5 receptors stimulates phospholipase C (*PLC*) activity through the G protein G_q . Subsequent production of inositoltriphosphate (IP_3) acts on the IP_3 receptor (IP_3R) in the endoplasmic reticulum to release Ca^{2+} . The resulting rise in cytosolic Ca^{2+} activates endothelial nitric oxide synthase (*eNOS*) via a calmodulin (*CM*)-dependent mechanism. Activation of *eNOS* leads to the production of nitric

oxide (*NO*), which can diffuse into adjacent vascular smooth muscle cells, where it stimulates soluble guanylyl cyclase (*sGC*) to produce cGMP. Protein kinase G (*PKG*) activated by cGMP promotes relaxation. In vascular smooth muscle cells, *ACh* acting through M_1 or M_3 receptors stimulates *PLC*-dependent production of IP_3 and the subsequent release of Ca^{2+} from the ER. This results in Ca^{2+} and *CM*-dependent kinase (*CaMKII*) activation of myosin light chain kinase (*MLCK*), which promotes contraction

undesired or excessive, these effects may lead to constipation or drug-induced ileus. This effect also may lead to delayed peak absorption and prolonged toxicity of anticholinergic agents as well as other co-ingestants.

Skeletal Muscle Effects

Severe forms of the anticholinergic syndrome may be associated with rhabdomyolysis resulting in release of myoglobin into the blood and nephrotoxicity [58–62]. Rhabdomyolysis in this setting may be a result of hyperthermia, excess motor activity or muscle tone, or dependent-type pressure injury secondary to deep coma.

Temperature Effects

Anticholinergic agents inhibit sweating, which reduces one's ability to dissipate excess body heat. Excess motor activity or muscle tone increases body heat. Hyperthermia can result from increased heat generation and impaired cooling secondary to sweating inhibition. This is especially true in environments with high ambient temperatures.

Urinary Tract Effects

Anticholinergic agents reduce bladder tone and may lead to urinary retention. This is especially a problem for an elderly man with prostatic hypertrophy and increases the risk of urinary tract infections. In many patients with anticholinergic toxicity, urinary retention may necessitate the use of bladder catheterization. If not addressed early, significant urinary retention may further contribute to agitation.

Diagnosis

Laboratory Tests

In the United States, many toxicologic screens are immunoassays designed to detect common drugs of abuse at levels above the US Substance Abuse and Mental Health Services Administration thresholds. This type of drug of abuse screen does not detect any of the anticholinergic agents listed in Table 1. Some immunoassay screens also provide qualitative or semiquantitative detection

of TCAs or other analytes, such as methylenedioxymethamphetamine (“ecstasy”). Gas chromatography combined with mass spectroscopy is a commonly employed technique in comprehensive drug and substance screening that can detect many but not all of these agents [63, 64]. Although quantitative assays are available for most anticholinergic agents, they are usually unnecessary in the clinical management of patients with anticholinergic syndrome and rarely can be done in a clinically useful time frame. In certain cases (e.g., in fatalities or atypical presentations), other laboratory techniques (e.g., gas–liquid chromatography, high-pressure liquid chromatography, or high-pressure thin-layer chromatography) may be required to identify the anticholinergic agent.

Differential Diagnosis

The differential diagnosis includes many conditions that resemble the anticholinergic syndrome (Table 6). Many of these diagnoses can be eliminated by a careful history and physical examination combined with routine laboratory tests. A history of anticholinergic exposure, typical manifestations of peripheral and central anticholinergic toxicity, and a typical time course for resolution of clinical effects are adequate for most clinical diagnoses of anticholinergic syndrome. In some cases, little to no peripheral anticholinergic findings are noted [4]. Although several physical findings, such as dry skin and decreased bowel sounds, are said to be useful in distinguishing anticholinergic syndrome from other causes of agitated delirium, the sensitivity and specificity of these findings are not well documented. Hall and colleagues [4] stated that hyperthermia was seen in only 20% of adults and 25% of children and that fewer than 10% of patients with central anticholinergic toxicity manifest constipation, ileus, urinary retention, and convulsions. These percentages appear to be estimates, and the number of cases on which they were based was not provided. This report also stated that the most reliable signs of the anticholinergic syndrome

Table 6 Differential diagnoses of anticholinergic syndromes

Intoxications
Caffeine
Dextromethorphan
Ketamine
Lithium
Lysergic acid diethylamide (LSD)
Monoamine oxidase inhibitors (MAOI)
Phencyclidine (PCP)
Salicylates
Selective serotonin reuptake inhibitors
Sympathomimetics (e.g., cocaine, amphetamines, methamphetamines)
Theophylline
Withdrawal syndromes
Ethanol
Barbiturates
Sedative-hypnotics
Dysautonomia
Malignant hyperthermia
Neuroleptic malignant syndrome
Serotonin syndrome
Metabolic diseases
Disulfiram (Antabuse) reactions
Hepatic failure
Hypercapnia
Hyperthyroidism
Hypoglycemia
Hyponatremia
Hypoxia
Pheochromocytoma
Uremia
Wernicke’s syndrome
Infections
Encephalitis
Meningitis
Sepsis
Psychiatric illnesses
Schizophrenia
Dementia
Other causes
Cerebral vasculitis
Cerebrovascular accident
Cerebral contusion
Postictal state
Postconcussive syndrome
Partial complex seizures
Anti-NMDA-receptor encephalitis

were dilated and sluggishly reactive pupils, confusion, disorientation, incoherence, memory impairment, facial flushing, dry mucous membranes, tachycardia, agitation, picking or grasping movements, ataxia, motor incoordination, and visual and auditory hallucinations [4]. In eight victims of surreptitious scopolamine use, dry mouth and skin were noted in 100% and decreased bowel sounds were noted in 25% [42]. Published reviews of *Datura stramonium* (Jimson weed) intoxication signs report wide ranges of clinical antimuscarinic features with dry mucous membranes and dry skin present in 46–94% of patients [65, 66]. In unknown cases, comprehensive laboratory testing can be used to detect some of the more commonly used drugs and abused substances.

Diagnostic Studies

Toxicologic Analyses

Most of the common causes of the anticholinergic syndrome are not detected on routine toxicologic screens, which usually consist of immunoassays to detect drugs of abuse. An exception is the qualitative immunoassay for TCAs, which also can yield false-positive results in the presence of other anticholinergic drugs, such as diphenhydramine and certain phenothiazines and anticonvulsants such as carbamazepine. Although quantitative levels of most of the drugs and anticholinergic alkaloids in Table 1 are available from reference laboratories, they are rarely necessary. Because of variable susceptibility to these agents, quantitative levels for diagnostic confirmation may not be reliable [67]. Quantitative levels of other agents may be useful in ruling out the anticholinergic syndrome.

Abnormal Routine Laboratory Test Findings

Many standard laboratory tests may be abnormal in patients with the anticholinergic syndrome. Patients who are agitated or delirious may have a mild increase in white blood cell counts secondary to demargination. Increases in serum sodium,

urine osmolality, blood urea nitrogen, and creatinine may occur as a result of prerenal azotemia secondary to poor fluid intake and increased insensible losses associated with agitation and hyperthermia. Increased creatinine also may occur with rhabdomyolysis-induced acute renal failure. Hyperthermia and agitation may lead to rhabdomyolysis, which is associated with increased amounts of myoglobin in the serum and the urine. Urine with excess myoglobin appears brown or pink and tests positive on a urine orthotolidine test for blood, but no red blood cells are seen in the microscopic urinalysis. Quantitative serum concentrations of skeletal muscle enzymes, particularly creatinine phosphokinase, and urinary myoglobin levels can confirm the diagnosis of rhabdomyolysis. Rhabdomyolysis also may increase the serum potassium and phosphate concentrations and decrease the serum calcium levels. Marked agitation may be associated with an increased anion gap metabolic acidosis, increased serum lactate, and decreased serum bicarbonate. Sustained or severe hyperthermia may result in disseminated intravascular coagulation, characterized by increased coagulation times, increased D-dimer and fibrin split products, and decreased platelets and fibrinogen levels.

Differential Features

The anticholinergic syndrome may be characterized by the mnemonic “*mad as a hatter, red as a beet, dry as a bone, blind as a bat, hot as a hare and tachy as a leisure suit.*” The syndrome is usually, but not always, a combination of peripheral and central anticholinergic toxicity (see Table 4). When it occurs without signs of peripheral anticholinergic toxicity, the anticholinergic syndrome may be misdiagnosed as a primary psychiatric disease, especially without a history of excess anticholinergic exposure and with a negative toxicologic screen [68]. Misdiagnoses are more common in very young and very old patients [23, 69, 70]. Anti- *N*-methyl-D-aspartic acid receptor encephalitis is an important recently described syndrome occurring primarily in young females that may closely mimic features of both central and peripheral anticholinergic

toxicity as a result of paraneoplastic effects (most commonly ovarian teratoma) [71, 72]. Many other toxicities and medical problems may also resemble the anticholinergic syndrome and may be difficult to distinguish clinically (see Table 6). Although it is said that dry skin and absent bowel sounds distinguish anticholinergic syndrome from stimulant poisoning, there are few published data to evaluate the sensitivity or specificity of these findings. Ophthalmologic preparations are particularly problematic because many patients do not include them when listing their current medications [28]. In a suspected case of anticholinergic syndrome, a diagnostic challenge with physostigmine doses may be attempted as long as contraindications (see ► Chap. 161, “Physostigmine”) are not present [73].

Treatment

Most cases of the anticholinergic syndrome are not life-threatening and require little more than observation and general supportive care. Because these patients are at risk of hurting themselves or others and of sudden deterioration due to seizures or respiratory distress, they should be observed carefully until major signs of toxicity have dissipated. Less commonly encountered severe cases may require complicated and expert supportive care [74, 75]. More severe cases of the anticholinergic syndrome usually are seen with agents that have other important, potentially toxic properties, such as sodium channel or α -adrenergic receptor blockade (e.g., TCAs, neuroleptics, diphenhydramine). Delayed gastric emptying and drug absorption are major concerns. In a reported case of severe benztropine toxicity, severe anticholinergic poisoning persisted for 9 days after a large single ingestion [76]. Anecdotally, one author reported recovery of Jimson weed seeds 23 h after ingestion [77]. A review of 15 cases of anticholinergic plant poisoning reported a mean latency to onset of symptoms of 2.7 h [78]. Based on these reports, gastrointestinal decontamination with activated charcoal may be useful for a longer time after ingestion of these agents than for the usual types of acute overdose

(Grade III recommendation). However, activated charcoal has not been shown to affect the outcome of these patients. The administration of activated charcoal should be done cautiously, if at all, in patients with altered mentation or risk of seizures, unless their airways are mechanically protected. Patients with severe toxicity and patients who are unable to protect their airway should undergo rapid-sequence intubation.

Patients who are significantly agitated must be protected from hurting themselves or others. Significant agitation associated with the anticholinergic syndrome should be treated by reversal with either an anticholinesterase (i.e., physostigmine) or a sedating agent (chemical restraint) (Grade I recommendation). The use of physical restraints alone may result in significant rhabdomyolysis if the patient fights vigorously or persistently against them. Physical restraint should be used only as an adjunct to chemical restraints, in case the latter wear off unexpectedly. Large amounts of sedatives may be required to achieve adequate chemical restraint or sedation in anticholinergic syndrome cases. In a comparative study of physostigmine versus benzodiazepines for the anticholinergic syndrome, the mean total benzodiazepine doses were diazepam, 53.1 mg; lorazepam, 35.5 mg; and midazolam, 31.7 mg [79]. Watkins et al. demonstrated the use of physostigmine alone resulted in significantly lower rates of intubation compared to benzodiazepines alone or a combination with other sedating agents [80]. Haloperidol can be used to calm delirious patients, but concerns about QT_c interval prolongation and proarrhythmias warrant QT_c monitoring during its use [81, 82]. Because haloperidol has some mild anticholinergic properties, many medical toxicologists believe it should be avoided in patients with the anticholinergic syndrome. However, published systematic reviews have not demonstrated any significance difference in outcomes or adverse effects between typical and atypical antipsychotics in the setting of all-cause delirium [83, 84]. As there exist no published clinical studies with respect to typical or atypical antipsychotic use in the specific setting of acute anticholinergic-induced delirium, the above concerns remain theoretical.

Seizures may be seen in severe cases of anticholinergic toxicity. Although apparent successful terminations of anticholinergic-associated seizures with physostigmine have been reported [85, 86], seizures believed to be secondary to physostigmine use also have been reported [87–89]. Animal studies suggest that physostigmine has limited efficacy against seizures secondary to anticholinergic toxicity [90–93]. Because of concerns over limited efficacy and even enhancing propensity to seizures, physostigmine is not indicated as an anticonvulsant therapy. Benzodiazepines are the primary anticonvulsants for anticholinergic-induced seizures. Seizures refractory to benzodiazepines may be treated with barbiturates or propofol as a second line agents (Grade III recommendation). Patients not responsive to those agents may be treated as described in ► Chap. 20, “Toxicant-Induced Seizures.”

Severe hyperthermia (temperature $>40^{\circ}\text{C}$) may result in direct tissue injury and rapid cardiovascular collapse and therefore should be treated aggressively. In addition to liberal doses of benzodiazepines to decrease adrenergic tone, rapid cooling is mandatory (Grade II-2 recommendation). Ice water immersion provides the most rapid reduction in core body temperature, albeit potentially limited by logistical constraints [94]. Other methods of cooling include ice-cooled saline infusion, evaporative methods (wet sheets and fans), and ice packs to the axilla and groin. Novel cooling devices developed for post-cardiac arrest target temperature management have received limited study but appear to be inadequate [94]. Dantrolene sodium occasionally appears as a recommended adjunctive agent for toxicant-induced hyperthermia. While there appears to be some evidence in its use for neuroleptic malignant syndrome, there is no published data supporting its use in anticholinergic-induced hyperthermia [95–99]. Instead, severe muscular rigidity that does not respond to benzodiazepines should be met with neuromuscular paralysis to eliminate continued thermogenesis [94].

Rhabdomyolysis may occur secondary to marked agitation, increased muscle tone, or severe hyperthermia. In the absence of renal failure, rhabdomyolysis treatment includes early liberal

administration of intravenous fluids (Grade I recommendation), though the benefit of adding mannitol or sodium bicarbonate is less clear. Myoglobin is less likely to precipitate in the renal tubules and cause nephrotoxicity when the urine is dilute and alkaline [100, 101].

Specific Treatment

Some physicians prefer to treat the anticholinergic syndrome primarily with supportive care, carefully titrated sedation, and intubation and artificial ventilation if necessary [102]. Other physicians prefer to use physostigmine for cases of severe anticholinergic poisoning presenting without significant cardiovascular toxicity, in hopes of avoiding the need for excess sedation, intubation, and artificial ventilation [70]. This is further supported by Watkins et al. who found that, in patients with severe anticholinergic-induced agitation, the use of physostigmine alone resulted in significantly lower rates of intubation compared to benzodiazepines (1.8 vs. 8.4%, respectively) [80]. Physostigmine is a short-acting, nonselective cholinesterase inhibitor that is a tertiary amine capable of crossing the blood–brain barrier. It has been reported to be effective in reversing anticholinergic toxicity from drugs [79, 103–105] and natural substances. (The clinical pharmacology of this agent is discussed in detail in ► Chap. 161, “Physostigmine.”) [106, 107] Although physostigmine was popular in the 1970s and early 1980s, its use diminished after reports of serious adverse effects in TCA overdoses [108–110]. Currently the use of physostigmine to reverse central anticholinergic toxicity remains somewhat controversial among some emergency medicine physicians.¹¹² Many of these perceived risks seem to be unfounded in the eyes of the medical toxicology community.¹¹² Doses of 2 mg (or 0.02 mg/kg) of physostigmine over 2 min will reliably reverse anticholinergic syndromes. The pharmacokinetic half-life of physostigmine is approximately 20 min, although the pharmacodynamic effect lasts longer. Nevertheless, it is not uncommon for the clinical effect of physostigmine to wear off before the

anticholinergic delirium resolves. In these cases, physostigmine can be readministered. Because of its cholinergic properties, physostigmine is best avoided in patients with significant bradycardia or active bronchospasm. Further details regarding the use of this agent are provided in ► **Chap. 161, “Physostigmine.”** Neostigmine is a quaternary amine, unable to cross the blood–brain barrier. It has been reported to be more efficacious than physostigmine in the treatment of paralytic ileus and other peripheral anticholinergic effects, but supportive care, supplemented by physostigmine as necessary, is preferable [96].

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Key Points

- Serotonin syndrome can occur with the initiation, dose escalation, or an overdose of serotonergic agents.
- The diagnosis of the serotonin syndrome is based on an accurate history of exposure to a serotonergic agent and bedside clinical exam.
- Rapid control of muscle rigidity and clonus is accomplished through administration of benzodiazepines.
- Hyperpyrexia is a marker of worsening serotonin syndrome and should be aggressively corrected by musculoskeletal paralysis and orotracheal intubation.

Common Errors

- Failure to recognize development of mild serotonin syndrome after change in dosage of serotonergic agents
- Failure to recognize the rapid progression of serotonin syndrome
- Misdiagnosis of anticholinergic toxidrome, neuroleptic malignant syndrome, or malignant hyperthermia

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Criteria for ICU Admission

- Significant clonus, tachycardia, and altered mental status unresponsive to benzodiazepines
- Muscle group rigidity and hyperthermia (temperature $>41^{\circ}\text{C}$) requiring active cooling

Criteria for ICU Discharge

- Resolution of clonus and altered mental status
- Resolution of hyperthermia and decreasing benzodiazepine requirement

The serotonin syndrome (SS) is a triad of altered mental status, autonomic instability, and neuromuscular abnormalities that presents following overdose, inadvertent dose escalation, or drug-drug interaction. While many cases can be self-limited and benign, severe cases of serotonin syndrome can be confused with neuroleptic malignant syndrome and severe metabolic and infectious etiologies.

Rarely referred to as serotonin toxicity, SS was first described in 1982 by Insel et al. who reported two patients who developed confusion, myoclonus, and fever after being treated with clomipramine, a tricyclic antidepressant [1]. Because of under-recognition and misdiagnosis, the true incidence of SS is hard to estimate [2]. The most recent toxicovigilance report from the American Association of Poison Control Centers (AAPCC) in 2014 demonstrates that poisoning from antidepressant agents (most commonly serotonin reuptake inhibitors) was the third most common reported exposure [3]. In addition, both antipsychotics and antidepressant medications that tend to have serotonergic activity were among the top ten of substances with greatest rate of increase in exposures. Selective serotonin reuptake inhibitors (SSRIs) accounted for 99 fatalities in the United States in 2014, the eighth-most common agent implicated in fatalities reported to AAPCC.

Biochemistry and Clinical Pharmacology

Serotonin syndrome is the result of excessive serotonin (5-hydroxytryptamine, 5-HT) at the synapse. Only about 5% of the body's 5-HT is located in the central nervous system, with most of the remainder being stored in enterochromaffin cells in the small intestine and circulating platelets. Serotonin is synthesized in the brain and in enterochromaffin cells from the amino acid L-tryptophan (Fig. 1)). L-tryptophan is transported across the blood-brain barrier through a nonspecific amino acid transporter and is hydroxylated to form 5-hydroxytryptophan which is then decarboxylated to 5-hydroxytryptamine. Serotonin is secured in intracellular vesicles through transport from the vesicular monoamine transporter (VMAT2). During neuronal depolarization, vesicles fuse with the presynaptic cleft and release 5-HT which binds to specific serotonin receptors at the postsynaptic junction. To date, there are seven known families of serotonin receptors (5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇) [4–6]. Some of these families contain separate subtypes of receptors. Six of these families are composed of G-coupled receptors with protein channels that respond to binding of 5-HT by altering neuronal membrane potential [5]. In contrast, the 5HT₃ receptor is a ligand-gated ion channel. 5-HT₁ receptors located within somatodendritic cells in the central nervous system (CNS) regulate mood. The 5-HT_{1B} receptor subtype is found peripherally on smooth muscle cells in vasculature. Agonism of 5-HT_{1B} receptors by triptans produces vasoconstriction, thus mitigating headaches. 5-HT₂ receptors are also found centrally and work in conjunction with 5-HT₁ receptors to regulate mood, nociception, and muscle tone [7]. 5-HT_{2A} and 5-HT_{2B} receptors are found in the gut and cardiac myocytes and may function to mediate long-term cardiac remodeling [8–10]. Agonism of 5-HT₂ receptors may also be responsible for cardiac valvulopathies associated with the use of some medications [11]. 5-HT₃ receptors in the gastric fundus, ileum, and the brainstem's dorsal vagal complex modulate

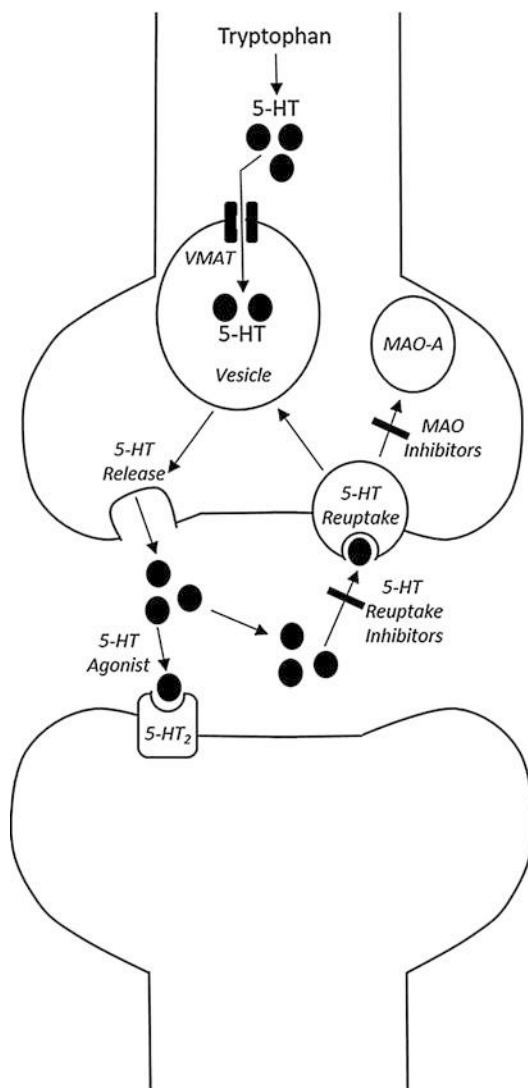


Fig. 1 Serotonin receptors and drug targets

nausea [4]. Of the families of serotonin receptors, activation of 5-HT_{1A} and 5-HT_{2A} receptors is largely responsible for the autonomic and neurologic manifestations seen in SS [8, 12, 13]. In overdose, however, the loss of receptor selectivity from binding at multiple 5-HT receptors contributes to the development of SS [14] (Fig. 2).

Regulation of serotonin concentrations in the synapse is accomplished by two methods: (1) release of serotonin from the afferent neuron into the synaptic junction inhibits further vesicular

fusion and release of 5-HT, and (2) degradation by monoamine oxidase A (MAO-A), an intraneuronal enzyme with affinity for 5-HT and norepinephrine [15]. Disruption in this cycle (e.g., excessive release of neurotransmitter, decreased reuptake of serotonin into the afferent neuron, and inhibition of metabolism) causes persistent stimulation of serotonin receptors and the clinical effects observed in SS.

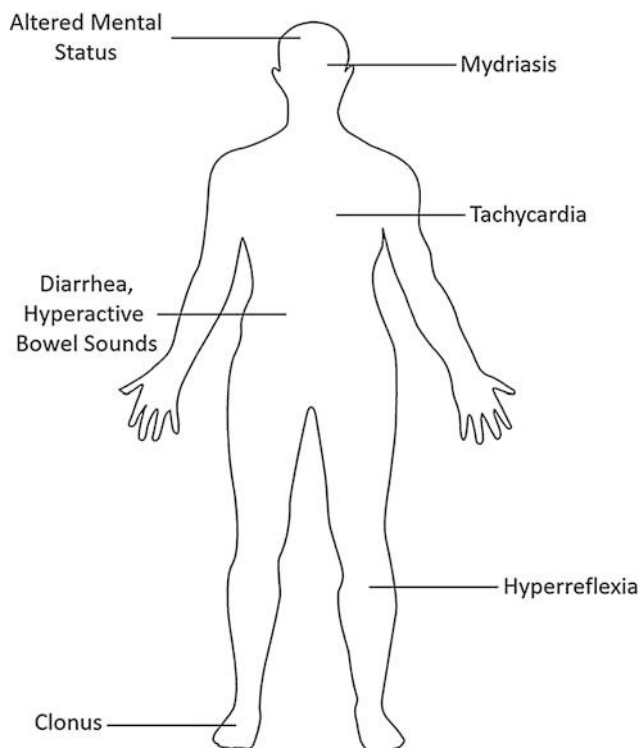
Most serotonergic xenobiotics modulate serotonin expression within the CNS in a variety of ways (Table 1) [16]. While overdose of a single serotonergic agent may be sufficient to induce SS, most cases arise from combinations of xenobiotics that affect serotonin in a different ways [17]. For example, cocaine can cause an increase in release of 5-HT (also dopamine and norepinephrine) by inducing vesicle fusion with the presynaptic junction. It also prevents reuptake of HT, a combination of actions that can induce SS [18, 19]. Combinations of drugs that both prevent reuptake and decrease metabolism of 5-HT can also produce SS. For example, patients on therapeutic dosing of SSRIs who receive the MAO-A inhibiting antibiotic linezolid, or are placed on other MAO-A inhibitors, can experience serotonin syndrome as both reuptake and metabolism of 5-HT are inhibited [20, 21].

Clinical Presentation and Life-Threatening Complications

The presentation of patients with an SS ranges from subtle changes in mental status to obtundation, neuromuscular rigidity, and hyperthermia [22]. Approximately 60% of patients with SS will present within 6 h of initial use of a serotonergic medication, an overdose, or change in medication [23]. These patients may present lucid and, as the drug is absorbed over the course of time and become somnolent, develop hyperreflexia, clonus, and tachycardia as they progress through the spectrum of SS.

Mild SS may present as a subtle change in mental status or mild confusion accompanied by hyperreflexia or tremor in patients receiving a

Fig. 2 Clinical manifestations of serotonin syndrome



serotonergic agent. Vital sign abnormalities in mild SS may include tachycardia. Patients with moderate poisoning may exhibit clonus, hyperreflexia, and tachycardia. Interestingly, hyperreflexia and clonus in moderate cases of SS tend to be greater in the lower extremities. Altered mental status can range from sedation to mild agitation or hypervigilance, and patients may exhibit pressured speech [22]. Patients with moderate SS may exhibit hypertension and tachycardia.

Altered mental status, inextinguishable clonus, diaphoresis, rigidity, and hyperthermia are hallmarks of severe SS [17]. While hypertension and tachycardia are common, patients may have striking changes in pulse and blood pressure accompanied by hyperthermia. Excessive neuromuscular activity leads to rigidity, which, in turn, culminates in hyperthermia. End-organ injury results from hyperthermia and can be detected as rhabdomyolysis, acute kidney injury, elevations in aminotransferases, and signs of disseminated intravascular coagulation [24]. The

presence of seizures in severe serotonin syndrome is uncommon but may arise in severely hyperthermic patients.

Diagnosis

No laboratory tests confirm the diagnosis of serotonin syndrome. Instead, physical examination findings (clonus, hyperreflexia, tremor, or akathisia without extrapyramidal signs) should compel the clinician to consider the diagnosis of serotonin syndrome. Several criteria have been proposed for the diagnosis of serotonin syndrome and can be applied in conjunction with a bedside clinical exam to confirm the diagnosis of SS (Table 2) [16, 22, 25]. Common among these criteria is a history of recent addition or dose escalation of a known serotonergic agent accompanied by clonus, tremor, hyperreflexia, or altered mental status.

Sternbach's original diagnostic criteria for SS were derived in 1991 from 38 reported human

Table 1 Xenobiotics that can contribute to serotonin syndrome

Increased serotonin synthesis
L-Tryptophan
Increased serotonin release
Amphetamines
Cocaine
Dextromethorphan
Reserpine
Decreased serotonin uptake
Selective serotonin reuptake inhibitors (SSRIs)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)
Tricyclic antidepressants (TCA)
Amphetamines
Cathinones
Cocaine
Dextromethorphan
Meperidine
Methadone
Sibutramine
Tramadol
Trazodone
Decreased serotonin metabolism
Monoamine oxidase inhibitors (MAO-I)
Linezolid
Harmine/Harmaline (Syrian rue)
Ritonavir
Serotonin agonists
Triptans
Ergotamines
Lysergic acid diethylamide (LSD)
Ondansetron
Metachlorophenylpiperazine
Other
Fentanyl
Lithium
Methylene blue
Electroconvulsive therapy (ECT)

cases in the medical literature [25]. The Sternbach criteria for SS include historical evidence of addition or increase in a known serotonergic agent, the absence of an alternative explanation, the lack of recent administration of a neuroleptic agent, and the presence of three of the ten most common clinical features in patients with SS in his review [25]. The most common findings in patients with SS were altered mental status (42%), restlessness (45%), and myoclonus (34%) [25]. The Sternbach criteria, although 75% sensitive and 96% specific, missed early, mild, or incomplete presentations of the disorder; possibly these early criteria were

Table 2 Decision criteria for serotonin syndrome

Sternbach's criteria ^a	Hunter criteria ^b
1. Recent addition or increase of a known serotonergic agent	In the presence of a serotonergic agent:
2. Absence of other possible etiologies	1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES
3. No recent addition or increase of a neuroleptic agent	2. ELSE IF (inducible clonus = yes) AND (agitation = yes) OR (diaphoresis = yes) THEN serotonin toxicity = YES
4. Three of the following symptoms:	3. ELSE IF (ocular clonus = yes) AND (agitation = yes) OR (diaphoresis = yes) THEN serotonin toxicity = YES
Altered mental status	4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
Agitation	5. ELSE IF (hypertonic = yes) AND (temperature > 38 °C) AND (ocular clonus = yes) OR (inducible clonus = yes) THEN serotonin toxicity = YES
Myoclonus	
Hyperreflexia	
Diaphoresis	
Shivering	
Tremor	
Diarrhea	
Incoordination	

^aAdapted from Sternbach [25]

^bAdapted from Dunkley et al. [16]

heavily weighted toward the presence of altered mental status [16, 26, 27].

The Hunter serotonin toxicity criteria was derived in 2003 from a case series of 2222 patient included in a medical toxicology registry [16]. Clinical features of patients diagnosed with SS by a medical toxicologist were recorded and a decision rule was derived and validated. Similar to initial studies, confusion, hyperreflexia, and myoclonus were the most common findings associated with SS. In addition, autonomic instability in the form of tachycardia, hyperthermia, mydriasis, and diaphoresis were identified as part of the spectrum of SS. Patients with progressive SS (defined as requiring endotracheal intubation for clinically worsening SS) exhibited high fever, truncal rigidity, and peripheral hypertonicity [16, 28]. When compared with the original Sternbach's criteria, the Hunter serotonin toxicity criteria are simpler, more sensitive (84% vs. 75%), and more specific (97% vs. 96%) in the diagnosis of SS [17].

Table 3 Differential toxidrome diagnosis for serotonin syndrome

	Serotonin syndrome	Anticholinergic toxidrome	Neuroleptic malignant syndrome
Agent	SSRI, SnRI, MAO-I	Antihistamines, anticholinergics	Antipsychotics, dopaminergic drugs
Pathophysiology	Blockade of 5-HT reuptake, increased synthesis, decreased metabolism	Inhibition of cholinergic transmission at muscarinic receptors	Modulation in dopamine receptor blockade
Physical exam	Mydriasis, altered mental status, hyperreflexia, clonus, diaphoresis	Mydriasis, altered mental status, hyperreflexia, flushed skin, ileus, urinary retention	Hyperthermia, altered mental status, hypertension, muscle rigidity
Typical lab findings	Elevated CPK	Unremarkable	Elevated CPK, leukocytosis
EKG	Sinus tachycardia, prolonged QTc	Sinus tachycardia, prolonged QRS	Sinus tachycardia
Antidote	Cyproheptadine	Physostigmine	Dantrolene

Laboratory Testing

The degree of laboratory abnormalities correlates broadly with the severity of illness. Mild cases of SS frequently have no laboratory abnormalities. Depending on the degree of neuromuscular activity, creatinine phosphokinase (CPK) may be elevated. Severe elevations of CPK, aminotransferases, and serum creatinine, as well as signs of disseminated intravascular coagulation, are due to hyperthermia [22]. Additional laboratory evaluation to screen for common coingestants in the suicidal patient can help exclude other evolving toxidromes in a polypharmacy ingestion. Quantitative measurement of drug concentrations has little if any impact on patient care; the concentration of many therapeutic agents cannot be measured in a timely manner and does not correlate with clinical presentation [29]. Clinicians should note that therapeutic dosing and drug concentration, however, do not exclude the diagnosis of SS.

The most common electrocardiographic finding in patients with SS is tachycardia [30]. Because of the presence of serotonin receptors in the myocardium, alterations in membrane depolarization can occur and may result in prolongation of the QT interval. Diagnostic imaging including computed tomography (CT) and magnetic resonance imaging (MRI) of the brain in

patients who present with alterations in mental status would be expected to be unremarkable in the patient with SS.

Differential Diagnosis

The differential diagnosis for SS includes anticholinergic toxicity, sympathomimetic toxicity, neuroleptic malignant syndrome (NMS), and malignant hyperthermia (MH), all of which can be distinguished from the serotonin syndrome on clinical grounds and a careful medication history (Table 3). The presence of clonus, muscle rigidity, and medication history containing a serotonergic agent distinguish the serotonin syndrome from the anticholinergic toxidrome, neuroleptic malignant syndrome, and malignant hyperthermia. Patients with anticholinergic poisoning will have mumbling speech and will be feebly picking at objects; on physical examination, these patients have normal reflexes along with mydriasis; agitation; dry oral mucosa; hot, erythematous skin; and an absence of bowel sounds. In contrast, patients with serotonin syndrome have moist oral mucosa, erythematous and diaphoretic skin, and hyperactive bowel sounds.

Patients with a pure sympathomimetic toxidrome may exhibit similar bedside clinical findings as patients with SS, but lack clonus and

a medication history consistent with SS. Neuroleptic malignant syndrome is defined by a slow onset of bradykinesia or akinesia, “lead-pipe” muscular rigidity, hyperthermia, fluctuating consciousness and autonomic instability in contrast to the rapid onset, hyperkinesia, and clonus of serotonin syndrome [31, 32]. Although not diagnostic, a chart review of 24 patients with NMS found marked leukocytosis, while patients who initially present with tremor and myoclonus invariably were diagnosed with SS [23]. Malignant hyperthermia is a pharmacogenetic disorder characterized by hypertonicity and hyperthermia [33]. The disorder occurs within minutes after exposure to inhalational anesthetic agents. On physical exam, patients with malignant hyperthermia have mottled skin, rigor mortis-like muscle rigidity, increasing concentrations of end-tidal carbon dioxide, and hyporeflexia distinguishing the disorder from hyperreflexia, clonus, and hyperthermia found in SS [33].

Treatment

The mainstay of treatment of SS is rapid recognition of the condition, supportive care, and removal of the inciting drug [30]. With the removal of the inciting agent, provision of supportive care, control of agitation, control of autonomic instability, and control of hyperthermia, the majority of cases will resolve within 12–24 h [23, 30, 34, 35]. The intensity of management correlates with the severity of SS.

Patients with mild SS (e.g., tremor, extinguishable clonus, mild tachycardia) typically require intravenous fluid support and benzodiazepines with resolution of symptoms within 24 h [35]. Diazepam, a long-acting benzodiazepine, has been shown to provide sedation while lowering fever in animal models of SS [36].

The interventions directed toward patients who progress to moderate or severe SS should correlate with severity of disease. Whereas supportive care followed by administration of benzodiazepines may be sufficient for mild cases of SS, hypertensive and tachycardic patients may require serotonin antagonists to help control serotonergic signs. In extreme cases, hyperthermic individuals

Table 4 Treatment of serotonin syndrome

Mild serotonin syndrome	
Tachycardia, inducible clonus, hypertension	Intravenous fluids, benzodiazepines
Moderate serotonin syndrome	
Tachycardia, clonus, altered mental status, hyperthermia	Intravenous fluids, benzodiazepines, cyproheptadine, dexmedetomidine
Severe serotonin syndrome	
Tachycardia unresponsive to benzodiazepines, coma, hyperthermia, rigidity, sustained clonus, seizures	Hemodynamic support, neuromuscular paralysis, cyproheptadine, benzodiazepines, vasopressors

require paralysis with ventilator support (Table 4). Patients with autonomic instability and hypotension may require vasopressor support [14, 17, 37]. The pharmacodynamics and pharmacokinetics of the inciting agents in overdose are difficult to predict because symptoms may persist longer than occur in therapeutic dosing.

In patients with moderate SS (e.g., tachycardia, inextinguishable clonus, hyperthermia, altered mental status) who do not improve with benzodiazepines, practitioners should initiate the serotonin antagonist cyproheptadine. Typically used as an antihistamine, cyproheptadine has muscarinic and 5-HT_{2A} antagonist properties that have been shown to improve the autonomic instability associated with SS [22, 38, 39] (level of evidence (LoE) II-3). Although no human trials have demonstrated a survival benefit from cyproheptadine therapy, murine studies suggest that treatment with cyproheptadine mitigates the tremor and clonus that are refractory to benzodiazepine therapy [40]. Initial dosing starts with a 12 mg oral loading dose followed by 2 mg every 2 h until the clinical condition improves [22, 30]. If improvement is seen, a maintenance dose of 8 mg every 6 h can be administered. In children, we recommend a 0.25 mg/kg/day oral dose divided over 6 h with a maximum of 12 mg/day (LoE II-3) [22, 40, 41]. A total dose of 12–32 mg of cyproheptadine, which binds 85–95% of serotonin receptors, may be required in the first 24 h of treatment [41]. Administration of cyproheptadine in the altered

patient may be challenging as the drug is only available as an oral formulation. In cases when cyproheptadine therapy is indicated, administration via a nasogastric tube may be warranted. The correct process in which clinicians should wean cyproheptadine is unknown. We recommend tapering the cyproheptadine dose over the course of 24–48 h with careful reexamination of the patient for the recurrence of serotonergic findings. Because of its anticholinergic properties, cyproheptadine may precipitate the anticholinergic toxidrome.

Dexmedetomidine, a centrally acting α -2 agonist, has been proposed as an agent for sedation in the context of the altered patient with moderate SS who remains refractive to benzodiazepines [42] (level of evidence [LoE] II-3). The α -2 effects of dexmedetomidine may decrease secretion of serotonin through a negative feedback loop in serotonergic neurons, thus decreasing the downstream effects of altered mental status and autonomic instability [43, 44]. Dosing of dexmedetomidine starts with a bolus infusion of 0.5–1 mcg/kg over 10 min followed by a continuous infusion of 0.2–0.7 mcg/kg/h [38, 45]. Few case studies have demonstrated the ability of dexmedetomidine to control agitation and confusion potentiated by serotonergic agents without producing decreased respiratory drive or the need for orotracheal intubation [38, 42].

Patients with progressively worsening tremor, hyperthermia, tachycardia, and rhabdomyolysis require aggressive supportive therapy with high-dose benzodiazepines, intravenous fluids, and cyproheptadine. Concomitant ingestion of a MAO inhibitor can produce dramatic fluctuations in blood pressure. We recommend direct-acting sympathomimetics such as norepinephrine, phenylephrine, and epinephrine instead of indirect agents such as dopamine [22]. Before it can act as a pressor, dopamine requires metabolism into vasogenic amines whose concentration is regulated by MAO. Patients on monoamine oxidase inhibitors (MAO-I) may experience varying concentrations of vasogenic amines in response to doses of dopamine and may experience profound fluctuations in blood pressure. Severe hypertension, whether due to SS or from an unanticipated

effect of vasopressor agents, can be treated with short-acting agents such as nitroprusside or an esmolol infusion that can be titrated to desired hemodynamic effect.

Hyperthermia (core temperature greater than 41 °C) is a sign of profound neuromuscular activity from sustained tremor culminating in muscle rigidity. Hyperthermia, because it heralds significant morbidity and mortality, must be aggressively corrected by reversing its cause, excessive muscle activity, with neuromuscular paralysis, orotracheal intubation, and mechanical ventilation [14, 17, 22, 37, 46]. Antipyretics such as acetaminophen and ibuprofen are not only ineffective in controlling hyperthermia in SS but also can paradoxically worsen outcomes because of the threat of hepatic injury. We recommend a nondepolarizing paralytic agent such as rocuronium or vecuronium. Paralysis should be discontinued upon resolution of hyperthermia in addition to clinical and laboratory signs of improvement – decreasing CPK, improved hepatic and renal injury, and resolution of extremity clonus. Succinylcholine should be avoided in patients with severe serotonin syndrome as its use could precipitate hyperkalemia from rhabdomyolysis. Premature termination of paralysis can be associated with return of hyperthermia and worsening rhabdomyolysis.

Prevention of SS can be accomplished by physician education, modification in prescribing patterns, and the use of pharmacologic programs that identify drug-drug interactions [2]. Application of pharmacogenomic principles may help predict patients at risk of developing SS when exposed to serotonergic agents [47, 48]. Once toxicity occurs, consultation with a medical toxicologist, a clinical pharmacology service, or a poison control center can identify proserotonergic agents, guide treatment, assist clinicians in anticipating adverse effects, and provide valuable clinical decision-making experience. We recommend inciting serotonergic agents be discontinued for at least 48 h after resolution of the serotonin syndrome; reinitiating these medications should be done in consultation with a medical toxicologist or psychiatrist to prevent future episodes of serotonin syndrome (LoE III).

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Sympathomimetics have been available as medicinal agents since antiquity. More than 5000 years ago, the ancient Chinese recognized ephedrine, the primary active ingredient from the ephedra plant *ma huang*, as an active ingredient to treat asthmatic conditions and to stanch bleeding. Pliny, in the first century AD, also used ephedrine to treat bleeding [1]. Caffeine made from brewing the seeds of the cocoa plant was used in South America and introduced to Europe in the Middle Ages. Amphetamine was introduced as a nasal decongestant, general stimulant, and anorexiant in the 1930s and its medical use continued through WWII. In the USA, the Controlled Substance Act of 1970 made amphetamine “Schedule II” substances, meaning they are deemed to have high abuse potential. Similar controls have been put in place in other countries. During the 1960s, home chemists experimented with merging various combinations of mescaline and amphetamine derivatives to yield the “alphabet soup” of hallucinogenic amphetamines. Now, in the twenty-first century, sympathomimetics are ubiquitous in daily life (Table 1). They are found in over-the-counter medications including cough and cold preparations, alternative medicinal agents, and illicit drugs. Caffeine can be found in beverages, in weight loss supplements, in coffee shops, in flavored waters; advertised to teenagers; and combined with alcoholic beverages (Table 2). Popular illicit sympathomimetics continue to include cocaine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA); and the most

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Table 1 Selected sympathomimetic agents

Albuterol
Amphetamine
Cocaine
Dextroamphetamine
Diethylpropion
Dopamine
Ephedrine
Epinephrine
Isoproterenol
Ketamine
MDEA
MDMA
Mephedrone
MDPV
Metaproterenol
Methamphetamine
Methylphenidate
Midodrine
Norepinephrine
Other hallucinogenic amphetamines
Pemoline
Phendimetrazine
Phenmetrazine
Phentermine
Phenylephrine
Phenylpropanolamine
Propylhexedrine
Pseudoephedrine
Ritodrine
Terbutaline
Tyramine

MDEA 3,4-methylenedioxyethamphetamine, *MDPV* methylenedioxypyrovalerone

recent wave of diversionary sympathomimetic agents include synthetic cathinones and other phenylethylamines including “2C” drugs, piperazines, and tryptamines [3].

Sympathomimetic Toxidrome

The sympathomimetic toxidrome comprises a broad constellation of signs and symptoms which reflect activation of components of the autonomic sympathetic nervous system. Although sympathomimetics are thought of as being interchangeable, there can be significant differences in

Table 2 Caffeine content of certain beverages and drugs

Source	Approximate amount of caffeine per unit (5 oz cup or tablet) (mg)
Beverages	
Brewed coffee	80–150
Instant coffee	85–100
Decaffeinated coffee	2–4
Tea (bag or leaf)	30–75
Cocoa	5–40
Cola drinks	35–60 ^a
Nonprescription (OTC) drugs	
Analgesics	
Anacin, Bromo-Seltzer, Cope	32
Empirin compound	
Excedrin	60
Stimulants	
NoDoz	100
Vivarin	200
Caffedrine	250
Many cold preparations	32

Modified from Oakley [2]
OTC over the counter

^a12 oz

physiologic effects. These effects depend upon whether the agent has predominant effects on dopaminergic, serotonergic, or adrenergic neurotransmission; whether the agent is a direct-acting or indirect-acting agent; and which receptor subtypes are involved. The effects of specific sympathomimetic agents are described in ► [Chap. 41, “Sympathomimetic Agents.”](#) In general, the classic picture of a sympathomimetic toxidrome is a patient who presents with signs of significant adrenergic excess. This can include dilated pupils, tachycardia, tachypnea, hypertension, hyperthermia, and psychomotor agitation – the classic “fight-or-flight response.” The patient may be agitated, confused, or seizing. If the patient has been on a prolonged “speed run,” he or she may show signs of “catecholamine depletion” with lethargy, unresponsiveness, and relatively normal vital signs. This is sometimes referred to as the “crash” or “washout” syndrome. Because few illicit sympathomimetic agents are pure agonists

at a single receptor, there may be signs of other neurotransmitter effects, such as dopamine and serotonin. These effects include tremor, myoclonus, lower extremity rigidity, hypotension, hallucinations, and psychosis. Dopamine and serotonin also may contribute to the confusion, mental status changes, and seizures that cannot be explained by adrenergic stimulation alone.

Pathophysiology

Sympathomimetics are defined as catecholamine-like substances that have physiologic actions similar to those engendered by activation of the autonomic sympathetic nervous system. These actions include an excitatory effect on some types of smooth muscle with an inhibitory effect on others, modulation of glycogenolysis in the liver and muscle, and alterations in free fatty acid metabolism in adipose tissues with muscle thermogenesis via β_3 receptors. In some cases, sympathomimetics alter the effects of insulin by affecting the islet α_2 receptors and β_2 receptors and pituitary hormone secretion (antidiuretic hormone) by stimulation of central β_1 receptors [4]. The most clinically salient effects are those that involve the heart and central nervous system (CNS). Sympathomimetics have an excitatory effect on the heart, enhancing both inotropy and chronotropy. Agents that cross the blood–brain barrier stimulate the CNS to increase wakefulness and psychomotor activity. Most have an anorexiant effect.

Structurally, many sympathomimetics are derived from a β -phenylethylamine (phenethylamine) parent compound (Fig. 1). Sympathomimetics with adjacent dihydroxy ($-\text{OH}$) substitutions on the benzene ring are called *catecholamines*. By altering the location of the hydroxyl groups on the phenyl ring and the size and location of the alkyl substitutions on the ethylamine moiety, the molecule can assume variable α and β selectivity [5, 6].

Normal biosynthesis of catecholamines (dopamine, norepinephrine, and epinephrine) occurs in the neuronal tuberosities. Tyrosine diffuses into the neuron and is taken up into storage granules containing tyrosine hydroxylase. This

enzyme converts the tyrosine to 3,4-dihydroxyphenylalanine. Further conversion by L-aromatic amino acid decarboxylase converts 3,4-dihydroxyphenylalanine to dopamine. Dopamine- β -hydroxylase converts dopamine to norepinephrine within synaptic storage vesicles. However, the enzyme dopamine- β -decarboxylase is not specific to dopamine and is also involved in the synthesis of serotonin from 5-hydroxytryptamine (5-HT) [7]. Epinephrine is created in the adrenal medulla by the same process except that norepinephrine diffuses out of the storage vesicle and is converted by phenylethanolamine-*N*-methyltransferase to epinephrine. It is then transported back into vesicles for release (see Fig. 2) [8, 9].

Norepinephrine is stored in the synaptic vesicles in high concentration along with ATP, chromogranin, and dopamine- β -hydroxylase. When norepinephrine is released, all of vesicle contents are released simultaneously. The effects of monoamine oxidase (MAO), which is an intracellular enzyme, and the high-affinity norepinephrine transporter protein keep the concentration of cytosolic norepinephrine low. On stimulation of a postganglionic sympathetic neuron, norepinephrine-containing vesicles are transported to the nerve membrane, where they fuse and release norepinephrine into the synaptic cleft. Neurotransmission is halted by reuptake of norepinephrine back into the presynaptic terminal or diffusion away from the synaptic cleft. Reuptake occurs by way of the norepinephrine transporter. This transporter has a high affinity for norepinephrine but also transports dopamine, tyramine, other monoamines, and other phenylethylamines such as amphetamine [10]. Although catechol *O*-methyltransferase (COMT) is present in the cleft, neurotransmission is halted mostly by reuptake and not by enzymatic degradation of the neurotransmitter (Fig. 3) [11, 12]. In addition to normal neurotransmission, the presence of other endogenous agents can alter neurotransmission by affecting prejunctional neuroreceptors (Fig. 4). These agents include adenosine triphosphate (ATP), opioids, and prostanoids. By altering ionic influx at the receptors, the nerve stimulation is affected (Table 3) [13].

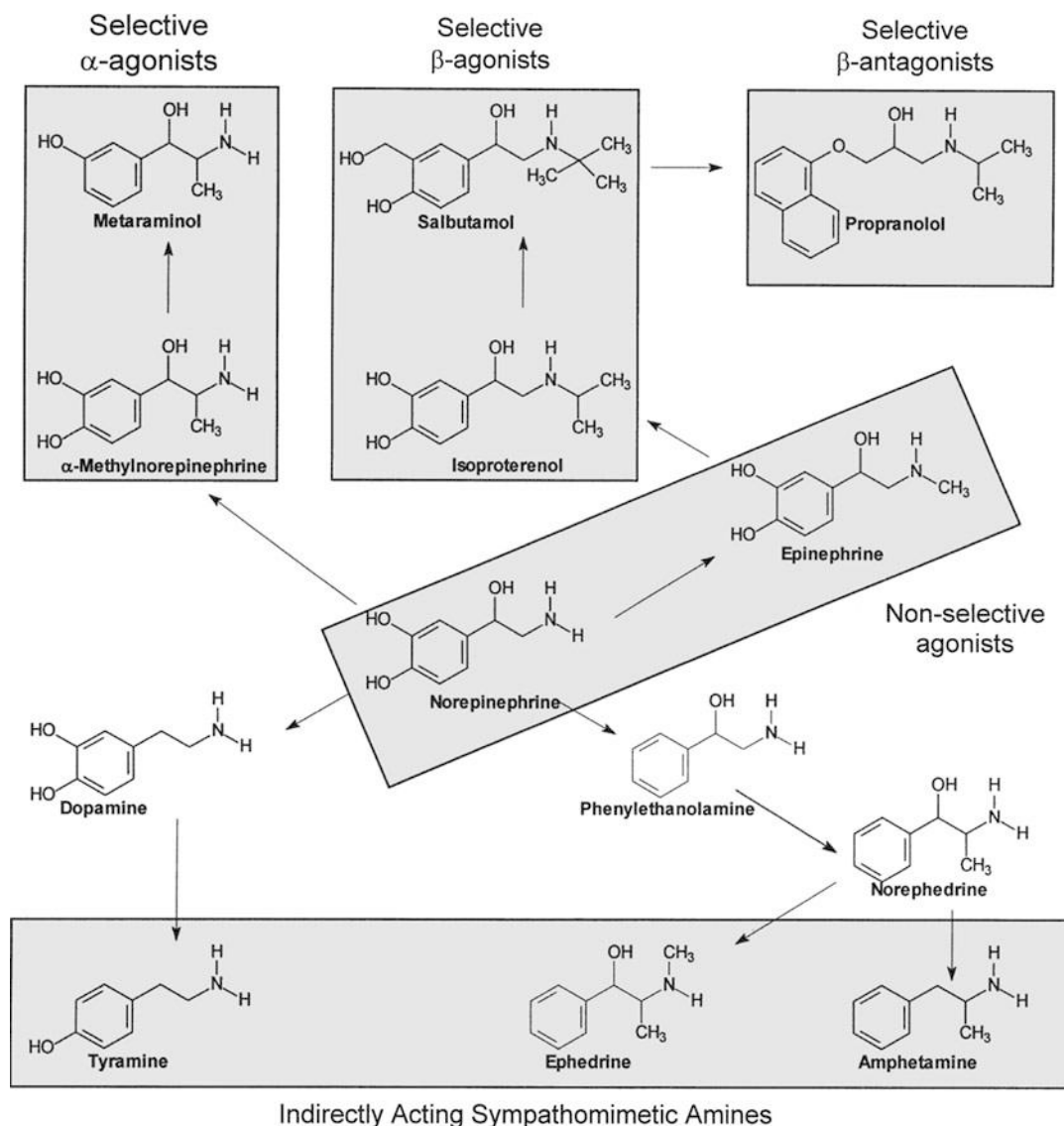


Fig. 1 Graphic depiction of the structure–activity relationships among the catecholamines and related phenylethylamines

The central sympathetic nervous system predominantly uses norepinephrine, epinephrine, and dopamine as communicating neurotransmitters. The main noradrenergic nucleus is located in the cortical locus coeruleus. Its axons radiate into the cortex, cerebellum, and other structures. Norepinephrine released from the locus coeruleus into the hippocampal projections increases cortical neurologic activity through β -adrenergic receptor stimulation. Norepinephrine release into

the outer cortical area has an inhibitory effect mediated by α -receptor agonism. If the locus coeruleus receives a nonspecific stimulus, there is widespread cortical activation with excitation. This activation may be part of the reason why nonspecific sympathomimetics can cause an increase in hyperattentiveness and reduction in fatigue [14]. Stimulation of the locus coeruleus also affects serotonin, endogenous opioid, and acetylcholine neurotransmission by way of the

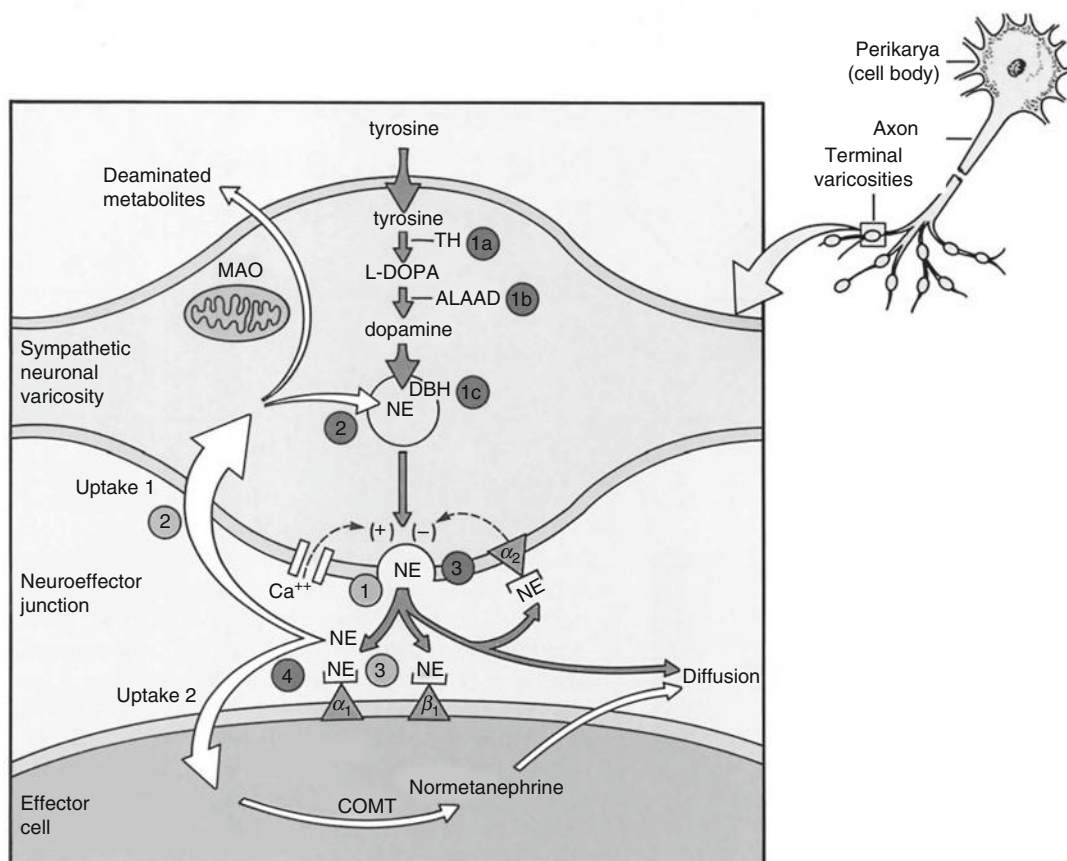


Fig. 2 Prejunctional and postjunctional sites of action of drugs that modify noradrenergic transmission at a sympathetic neuroeffector junction. L-Tyrosine is actively transported into the axoplasm of the neuron, where it is converted first to L-dopa by tyrosine hydroxylase (TH) and then to dopamine by aromatic L-amino acid decarboxylase (ALAAD). Dopamine is actively transported into synaptic vesicles, where it is converted by dopamine β-hydroxylase (DBH) to norepinephrine (NE). The arrival of a nerve action potential at the varicosity causes the influx of calcium ions, which promotes the exocytotic release of NE into the neuroeffector junction, where NE can activate receptors on postjunctional smooth muscle or glandular cells (α₁ or α₂) or cardiac cells (β₁) or on the prejunctional neuronal membrane (α₂). Activation of the α₂ receptor inhibits the further release of NE. The action of NE is terminated by transport back into the varicosity, uptake 1. In the varicosity, NE can

be stored in the synaptic vesicle or metabolized by monoamine oxidase (MAO) to inactive deaminated products. NE also is lost from the neuroeffector junction by diffusion and by transport into the postjunctional cell, uptake 2, where it is metabolized to normetanephrine by catechol O-methyltransferase (COMT). Drugs that enhance or mimic noradrenergic transmission (1) facilitate release (e.g., amphetamine), (2) block reuptake (e.g., cocaine), and (3) are receptor agonists (e.g., phenylephrine). Drugs that reduce noradrenergic transmission (1) inhibit synthesis (e.g., 1a, α-methyltyrosine; 1b, carbidopa; 1c, disulfiram), (2) disrupt vesicular storage (e.g., reserpine), (3) inhibit release (e.g., guanethidine), and (4) are receptor antagonists (e.g., phentolamine) (From Brody TM, Lamer J, Minneman KP [eds]: Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, with permission)

medullary cholinergic neurons, opioid peptide neurons, and central raphe serotonin neurons that all penetrate the locus coeruleus [14, 15]. Dopamine neurotransmission is likewise altered by

endogenous opioids at the μ and κ receptors in the mesolimbic system [16]. This interplay gives the varied presentation of patients with a sympathomimetic syndrome.

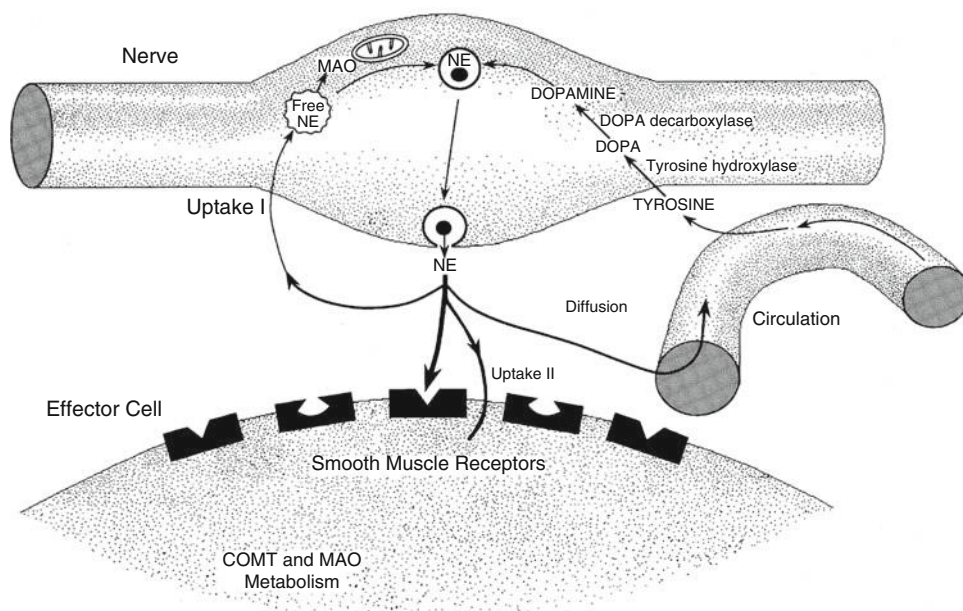


Fig. 3 Adrenergic neuroeffector transmission; the termination of norepinephrine (NE) neurotransmission. MAO monoamine oxidase, COMT catechol *O*-methyltransferase

(From Brown OM: Adrenergic drugs. In Smith CM, Reynard AM [eds]: Textbook of Human Pharmacology. Philadelphia, WB Saunders, 1992, p 144, with permission)

Adrenergic Receptors

Noradrenergic receptors (Table 4) act as the binding site for sympathomimetic agents. Receptors are divided into ligand-gated ion channel receptors and G protein receptors. When an agent binds to a ligand-gated ion channel, the pore undergoes a conformational change and allows entry of a specific ion, which triggers secondary effects. G-linked proteins are coupled to cyclic guanosine triphosphatase (GTPase). Activation of these receptors leads to phosphorylation of the cyclic GTPase and a cascade of activities eventually altering the ionic flow. A sympathomimetic agent may affect ligand-gated ion channels, G protein receptors, or both. All adrenergic receptors are of the G protein type. Adrenergic receptors generally have been classified as α_1 , α_2 , β_1 , β_2 , and β_3 [18], and their receptor distribution is variable throughout the various organ systems. The ocular radial muscle is α_1 , but the ciliary body is predominantly β_2 . The heart contains β_1 and β_2 receptors. Arteries vary in their concentration of α_1 , α_2 , and β_2 , whereas the CNS has α_1 . The venous system has α_1 , α_2 , and β_2 receptors

[18]. Bronchodilation occurs from stimulation of β_2 receptors in the bronchiole smooth muscle [19].

Sympathomimetic agents stimulate adrenergic receptors in a number of ways. Sympathomimetic agents classified as direct agents bind directly to α and β receptors. For the most part, these agents do not cross the blood–brain barrier. Indirect sympathomimetic agents cause the release of cytoplasmic norepinephrine or dopamine without vesicular exocytosis. The neuronal membrane bidirectional transporter facilitates the uptake of many indirect-acting sympathomimetics, such as amphetamine and ephedrine, which normally would have problems crossing the bilipid membrane (Fig. 5) [20]. When the indirect-acting sympathomimetic has entered the cell, the agent is transported into a storage vesicle. Normal vesicular pH is 5.5, but indirect-acting sympathomimetics buffer the storage vesicle pH, reducing the pH gradient across the membrane, which causes the release of stored norepinephrine and dopamine into the cytoplasm. Release of norepinephrine is accompanied by a small amount of dopamine. As the cytoplasmic concentration of catechol increases, norepinephrine and dopamine compete with these indirect-acting sympathomimetic agents for the

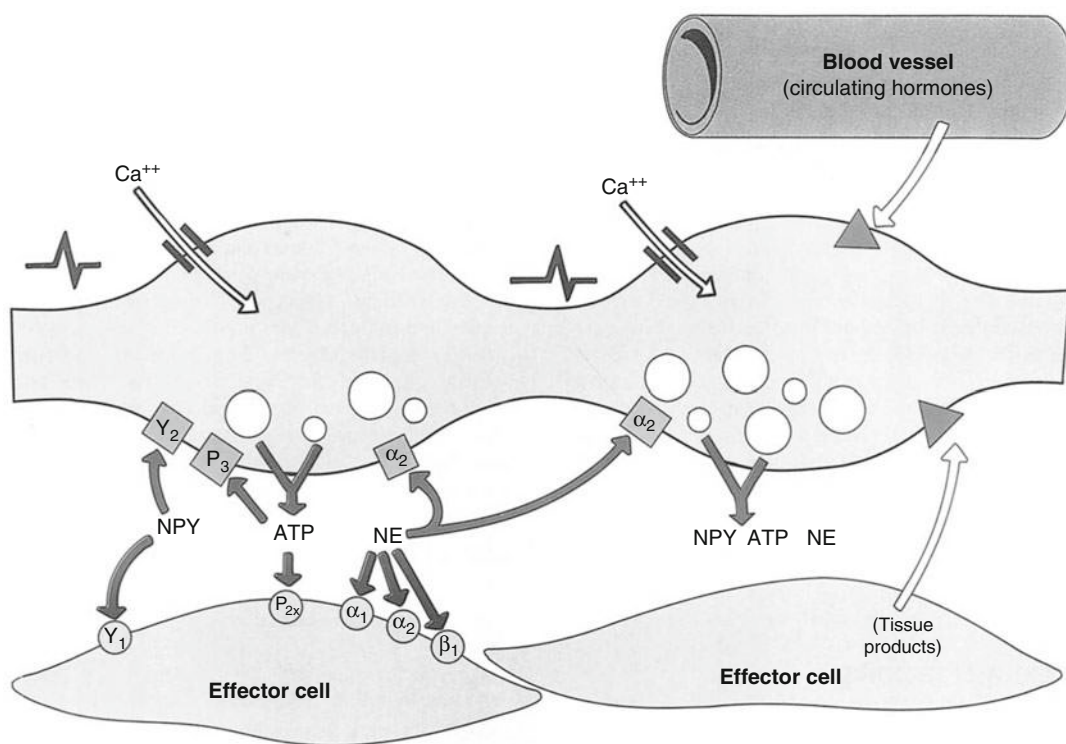


Fig. 4 Prejunctional regulation at the sympathetic neuroeffector junction. The *left* varicosity illustrates autoinhibition of neurotransmitter release, including possible “lateral” inhibition (i.e., transmitter from one varicosity inhibiting release from an adjacent varicosity). The *right* varicosity illustrates prejunctional regulation of transmitter release by tissue and blood-borne chemicals. See Table 3 for a list of involved substances. Postjunctional receptors are shown as circles; prejunctional inhibitory

autoreceptors are shown as squares; prejunctional heteroreceptors are shown as triangles. ATP adenosine triphosphate, NE norepinephrine, NPY neuropeptide Y (From Fink GD: Regulation of blood pressure by the autonomic nervous system. In Brody TM, Larner J, Minneman KP [eds]: Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, p 177, with permission)

transport back into the vesicle. The increased cytoplasmic catechol concentration facilitates reverse transport via the cytoplasmic norepinephrine transporter, to the extracellular synapse. The release of norepinephrine has an inhibitory effect on its own release through the presynaptic α_2 receptor; this occurs by inhibiting adenylate cyclase (Fig. 6 [21]). Inhibition of the transporter protein by tricyclic antidepressants abolishes amphetamine-induced norepinephrine release [6]. Nonpolar agents do not require the transporter to enter the cell but diffuse across the lipid bilayer [5]. Mixed-acting sympathomimetics can both indirectly cause norepinephrine release and directly stimulate adrenergic receptors. Neuronal uptake inhibitors can either competitively or noncompetitively inhibit biogenic amine uptake.

MAO and COMT inhibitors prevent catabolism of biogenic amines and increase cytosolic catechol concentrations. Finally, presynaptic α_2 antagonism interrupts normal feedback inhibition and increases sympathetic output.

Clinical Presentation

Central Nervous System (CNS)

The effects of sympathomimetics on the CNS are extensive, ranging from hyperpyrexia to mental status changes to seizures. Because projections from the locus coeruleus innervate most of the CNS, including the cerebral cortex, cerebellum,

Table 3 Prejunctional modulators of sympathetic neurotransmitter release

Chemical	Source	Receptor	Mechanism	Effect
Norepinephrine	SNT	α_2	$\downarrow \text{Ca}^{2+}$	\downarrow
Neuropeptide Y	SNT	Y_2	$\downarrow \text{Ca}^{2+}$	\downarrow
ATP	SNT	P_3, P_{2x}	$\downarrow \text{Ca}^{2+}$	\downarrow
Epinephrine	Blood	β_2	$\uparrow \text{cAMP}$	\uparrow
Angiotensin II	Blood/PJT	AT_1	$\uparrow \text{PLC}$	\uparrow
Prostanoids	PJT	?	$\downarrow \text{Ca}^{2+}$	\downarrow
Adenosine	PJT	P_1	$\downarrow \text{Ca}^{2+}$	\downarrow
Opioids	Blood	μ, κ, δ	$\downarrow \text{Ca}^{2+}$	\downarrow
Acetylcholine	Nerve	M_2	$\uparrow \text{cGMP}$	\downarrow
Dopamine	SNT	D_2	$\uparrow \text{K}^+$	\downarrow
Atrial natriuretic peptide	Blood	?	$\uparrow \text{cGMP}$	\downarrow
Nitric oxide	EC	?	$\uparrow \text{cGMP}$	\downarrow

cAMP cyclic adenosine monophosphate, *cGMP* cyclic guanosine monophosphate, *EC* endothelial cell, *PJT* postjunctional tissue, *PLC* phospholipase C, *SNT* sympathetic nerve terminal

From Fink [12]

and spinal cord, stimulation of this nucleus causes release of norepinephrine, leading to widespread cortical activation and excitation [22]. Indirect-acting sympathomimetics augment this excitation, increasing overall norepinephrine concentration; this explains the hyperattentiveness and lack of fatigue that accompanies the use of amphetamines, ecstasy (MDMA), and similar sympathomimetics [23]. Similarly many sympathomimetics cause concomitant dopamine release, which in turn activates the mesolimbic reward system and leads to euphoria, craving, addiction, and abuse potential. At the extreme end of the dopaminergic spectrum is the psychosis, repetitive/compulsive behaviors (“tweaking”), and marked agitation that can be seen with overdoses of these agents.

Additional behavioral effects attributed to sympathomimetic agent abuse can include CNS toxicity such as hemorrhagic strokes. Subarachnoid hemorrhage has been reported with the use of many agents including cocaine, methamphetamine, and MDMA [24–26]. This event is seen most frequently in individuals who have a preexisting cerebral aneurysm or arteriovenous malformation [27]. The transient but intense elevation in blood pressure that can be seen with cocaine use is enough to cause such defects to rupture [27]. The presence of methamphetamine predicts worse outcome in those who present with aneurysmal subarachnoid hemorrhages

[28]. Phenylpropanolamine (PPA) is an α -adrenergic sympathomimetic that formerly was available over the counter in the USA as a component of cold remedies and appetite suppressants [29]. In November 2000, the US Food and Drug Administration issued a public health advisory concerning the risk of hemorrhagic stroke in users of PPA and urged drug manufacturers to remove products containing PPA from the market. This advisory was prompted by the findings of the Hemorrhagic Stroke Project, which reported that use of PPA is an independent risk factor for hemorrhagic stroke in women [29] using these products as diet aids. Ephedra alkaloids, which were frequently sold over the counter as dietary supplements for weight loss or improved energy, have been linked only anecdotally to adverse cerebrovascular events [30]; the link has not been shown in a controlled trial. Regardless, the Federal Drug Administration banned the use of ephedra in dietary supplements in 2004 (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108242.htm>).

In addition to hemorrhagic strokes, thrombotic strokes have been reported in association with cocaine use. An increased risk of these ischemic strokes has not been shown in a controlled trial. If stroke does occur, it has been hypothesized that α stimulation may cause vasoconstriction of large cerebral arteries, leading to thrombosis as a result

Table 4 Noradrenergic receptors

Receptor type	Effector	Response to stimulation
α_1	Arterioles (resistance vessels)	Constriction
	Veins	Constriction
	Uterus	Contraction
α_2	Presynaptic nerve ending	Inhibit NE release
		Vasodilation
	Postsynaptic CNS	Decreased sympathetic tone
	Pancreatic islets	Vasodilation
		Decreased secretion
β_1	Heart	Increased inotropy
		Increased chronotropy
β_2	Bronchioles	Dilation
	Arterioles	Dilation
	Metabolic sites	Enhanced metabolism (glycogenolysis and gluconeogenesis)
	Uterine smooth muscle	Relaxation
	Pancreatic islets	Increased secretion
β_3	Adipose tissue	Lipolysis
	Muscle	Thermogenesis
Dopamine	Mesenteric arterioles	Dilation (low dose)
		Constriction (high dose)

Data from Refs. [12, 17]
CNS central nervous system, NE norepinephrine

of stasis and sympathomimetic-induced platelet activation [31]. This hypothesis is questionable because these vessels lack endothelial α receptors.

Seizures may complicate sympathomimetic overdose. Massive cocaine overdose, such as seen in packet rupture in body packers, can lead to generalized tonic-clonic activity and status epilepticus. Seizures are considered a major indicator of cocaine-related lethality in humans [32]. The long-term neurologic sequelae of cocaine-induced seizures have been documented [33]. Seizures have been seen in individuals using relatively small amounts of cocaine [34]. Cocaine-related seizures may be relatively refractory to many standard anticonvulsants

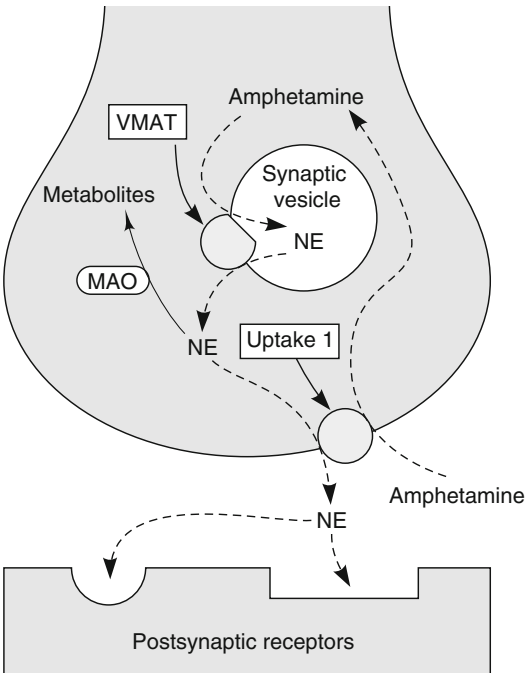


Fig. 5 The mode of action of amphetamine, an indirect-acting sympathomimetic amine. Amphetamine enters the nerve terminal via the norepinephrine (NE) carrier (uptake 1) and enters synaptic vesicles via the vesicular monoamine transporter, in exchange for NE, which accumulates in the cytosol. Some of the NE is degraded by monoamine oxidase (MAO) within the nerve terminal, and some escapes, in exchange for amphetamine via uptake 1, to act on postsynaptic receptors. Amphetamine also reduces NE reuptake via uptake 1, enhancing the action of the released NE. VMAT, vesicular monoamine transporter (From Rang HP, Dale MM, Ritter JM, Gardner P: Pharmacology, 4th ed. New York, Churchill-Livingstone, 2001, p 158, with permission)

[35]. The refractoriness is related in part to the lack of knowledge of the precise mechanism by which cocaine causes seizures but may reflect a decrease in gamma-aminobutyric acid (GABA) sensitivity and an increase of N-methyl D-aspartate sensitivity. Most standard anticonvulsants alter membrane sensitivity and prevent seizure propagation whereas sympathomimetic-toxic patients may need specific GABAergic medications such as benzodiazepines or barbiturates. Although seizures can result from a single high dose of cocaine, there is evidence that repetitive administration of subconvulsive doses of cocaine

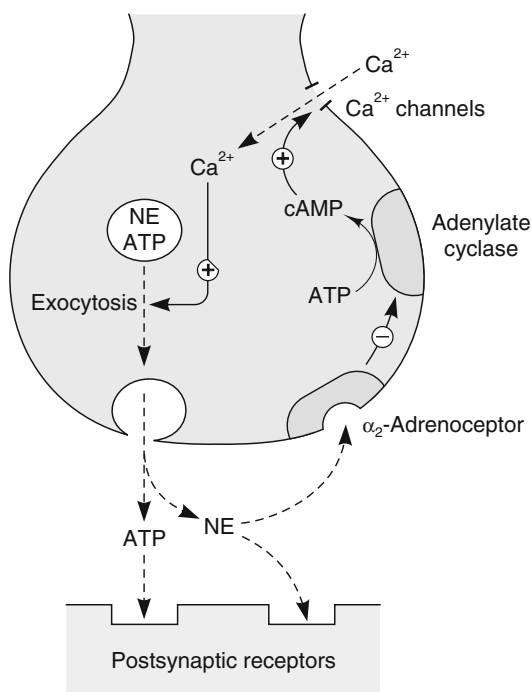


Fig. 6 Feedback control of norepinephrine (NE) release. The presynaptic α_2 adrenoceptor inhibits adenylate cyclase, reducing intracellular cyclic adenosine monophosphate (cAMP). cAMP acts to promote Ca^{2+} influx in response to membrane depolarization and to promote the release of norepinephrine and adenosine triphosphate (ATP) (From Rang HP, Dale MM, Ritter JM, Gardner P: Pharmacology, 4th ed. New York, Churchill-Livingstone, 2001, p 144, with permission)

can lead to a decreased seizure threshold, a phenomenon known as *pharmacologic kindling* [34, 36]. This feature, combined with the epileptogenic nature of cocaine, contributes to the significant neurologic impairment that can be associated with cocaine use.

In the CNS, cocaine causes an approximately threefold increase in D_3 binding sites in the locus accumbens and parts of the caudate and putamen, with upregulation of k_2 receptors in the amygdala. This activity can contribute to the hallucinations and aggressive and violent behavior seen in patients with cocaine overdoses [10, 16]. The pathophysiology of cocaine intoxication is described in ► **Chap. 75, "Cocaine."**

Psychiatric manifestations of sympathomimetic intoxication are common. Psychosis seems

to be more likely with amphetamines than cocaine, and once an amphetamine user experiences psychosis, it is likely to recur. These patients can be difficult to differentiate from a primary psychotic disorder based on presenting symptoms alone. Other neurological manifestations of sympathomimetic abuse include bruxism, euphoria, choreoathetosis, agitation, violence, and hallucinations.

Cardiovascular System

Cardiovascular manifestations are seen frequently with the sympathomimetic toxidrome. Because many of these agents have α -, β -, or mixed receptor agonism, the effects are varied. Agents with almost pure α effects, such as phenylpropanolamine, may cause isolated hypertension with reflex bradycardia. Hypertension from direct α agonism on the vasculature receptors results in significant vasoconstriction. Other agents, depending on the amount of β_1 or β_2 predominance, can cause hypotension from β_2 -induced vasodilation and β_1 -enhanced tachycardia. Generally, with the exception of patients intoxicated with the predominately α agents, patients present with tachycardia, dysrhythmias, and hypertension followed by, in the premonitory state, hypotension.

Sympathomimetics may cause coronary ischemia or infarction. Demand ischemia is the result of a mismatch between increased myocardial oxygen demand (hypertension and tachycardia) and supply (coronary blood flow). The significantly increased workload may be enough to cause ischemia in some sensitive individuals. Because cocaine is also a potent vasoconstrictor, it has the potential to exaggerate the mismatch between supply and demand. Cocaine has additional properties that promote intracoronary thrombosis by way of platelet activation and inhibition of clot dissolution, and long-term use may cause premature atherosclerosis [37, 38].

Dysrhythmias are a frequent and potentially lethal complication of sympathomimetic toxicity and occur through a number of mechanisms. β stimulation resulting in calcium entry into the myocytes and the subsequent elevation of the

resting potential enhances automaticity. Increased automaticity increases the potential for the generation of ectopic beats with the potential to degenerate into lethal dysrhythmias [39]. Some sympathomimetic agents, such as cocaine, can also affect cardiac ion channels and alter the duration of the action potential and the normal repolarization dispersion. Early after depolarizations in the setting of a prolonged action potential or prolonged JT interval from inhibition of I_{kr} can initiate ventricular tachycardia or torsades de pointes. For further discussion of dysrhythmogenesis caused by cocaine, see ► Chap. 75, “Cocaine.” Diseased areas of myocardium from contraction band necrosis serve as another potential nidus for arrhythmogenesis and loss of inotropy [40, 41].

Sympathomimetic-induced hyperthermia is multifactorial and a marker of significant toxicity. Amphetamines and MDMA activate the hypothalamic–pituitary axis and the sympathetic system and increase levels of circulating catecholamines, cortisol, and thyroid hormones. Endogenous heat production increases from a combination of increased psychomotor activity such as dancing and thermogenic brown fat activation via α_1 and β_3 stimulation. Concomitantly, norepinephrine-induced cutaneous vasoconstriction impairs heat dissipation. The resultant hyperthermia can lead to rhabdomyolysis, acidosis, and cerebral dysfunction. Mortality and severe outcomes are correlated with elevated temperatures in MDMA abusers and methamphetamine body stuffers [42, 43].

Renal System

The most significant renal-related side effect is acute kidney injury associated with rhabdomyolysis, which has been reported mostly for cocaine and the amphetamines. Renal injury can occur via several mechanisms. Prolonged seizures can lead to rhabdomyoglobinuric renal failure. Overdose-related coma with associated muscle compression also can cause rhabdomyolysis [44, 45]. Prolonged vasoconstriction of intramuscular arteries may contribute; it also is

hypothesized that cocaine has some direct toxic effects on skeletal muscle [44, 46, 47]. Rhabdomyolysis has been linked to sympathomimetic-induced hyperthermia resulting from a combination of centrally mediated processes, elevated ambient temperatures, peripheral vasoconstriction, indirect mitochondrial uncoupling, and prolonged dancing at ecstasy-driven rave parties [48]. Compartment syndrome is rare but has been reported in a case series of patients after ingestion of “bath salts” (cathinones) [49].

Renal failure has been reported without associated rhabdomyolysis [47]. This renal failure is believed to be secondary to renal vasculature vasoconstriction seen with cocaine abuse. Renal artery vasoconstriction can lead to ischemia and kidney infarction [45]. Additionally, chronic use of sympathomimetic drugs can lead to accelerated hypertension with associated renal failure [48].

Levamisole is a veterinary antihelminthic agent that had previously been used as an immunomodulatory therapy. Since 2003, levamisole has been increasingly identified as a “cutting” agent in cocaine due to its physical characteristics and the possibility that it adds to the euphoric effects of cocaine via multiple mechanisms. Reports of unintentional levamisole toxicity are increasing, and commonly one or more of the following have been associated with levamisole: leukopenia and agranulocytosis, thrombocytopenia, vasculitis, cutaneous necrotizing vasculitis (similar to warfarin induced), and multifocal inflammatory leukoencephalopathy [50].

Diagnostic Studies

The laboratory diagnosis is nonspecific. Patients may show secondary evidence of adrenergic excess with hypokalemia, hypomagnesemia, hyperglycemia, and leukocytosis without left shift. If the patient has a significant sympathomimetic syndrome, is hyperpyrexia, or shows evidence of prolonged muscle activity, there may be an associated lactic acidosis [51]. Ketonuria may be present if the patient has been using a sympathomimetic for a prolonged period without eating or if there is evidence of metabolic hyperactivity

and lipolysis. The electrocardiogram most often shows sinus tachycardia, but paroxysmal supra-ventricular tachycardia or other tachydysrhythmias may be present. Routine radiographic studies are not helpful unless there is suspicion of body packing or body stuffing.

Differential Diagnosis

It may be difficult to distinguish between a true sympathomimetic syndrome and many other overdoses and conditions (Tables 5 and 6). In particular, ethanol and sedative-hypnotic withdrawal may present with all of the same signs and symptoms, including mental status changes and seizures. In many respects, this could be considered an endogenous sympathomimetic syndrome because withdrawal causes a large release of catecholamines and creates the same physiologic state [51].

Anticholinergics tend to present with their own stereotypical syndrome that can be differentiated with careful observation and examination of the patient (see Table 6). In our experience, the anticholinergic toxidrome leads to mydriasis with cycloplegia, dry mucous membranes, tachycardia (but not usually as fast as seen with sympathomimetics), hypertension, hyperpyrexia, and tachypnea, usually in contrast to the extremes seen with sympathomimetics. Key differentiation points are loss of compensatory sweating, absence of bowel sounds, urinary retention, and red flushed skin in anticholinergic poisoning. The mental status change also is different. Patients with an anticholinergic toxidrome are nonfocally agitated, with picking motions of their hands. Their mouths appear cottony, and they answer with slurred, nearly incomprehensible speech. Many patients, when lying quietly, appear to be listening to internal voices. Treatment with antipsychotics that antagonize muscarinic receptors, such as many of the atypical second-generation agents, may enhance toxicity, and benzodiazepines may not be effective unless very large doses are used [52]. Physostigmine reorients the anticholinergic patient, restores vital signs toward normal, and confirms the diagnosis. The patient

Table 5 Differential diagnosis of sympathomimetic syndrome

Toxic
Anticholinergics (antihistamines, scopolamine, atropine, hyoscyamine, hydroxyzine)
Serotonin syndrome
Neuroleptic malignant syndrome
MAO inhibitor intoxication
Strychnine poisoning
Drug interactions (MAO inhibitor plus meperidine, lithium, or haloperidol)
Salicylates
Pentachlorophenol
Cyclic antidepressants
Lithium intoxication
Metabolic
Ethanol withdrawal
Sedative-hypnotic withdrawal
Thyrotoxicosis/thyroid storm
Status epilepticus
Heatstroke
Hypertensive encephalopathy
Hypoglycemia
Malignant hyperthermia
Infectious
Sepsis
Meningitis
Structural
Brain tumor
Pheochromocytoma

with a sympathomimetic syndrome may be nonfocally agitated and restless but constantly in motion, requiring significant restraint. Benzodiazepines in appropriate dosing can be useful [53, 54].

The neuroleptic malignant syndrome (NMS) and serotonin syndrome may present in what appears to be similar to a sympathomimetic toxidrome. In NMS, there is evidence of dopamine depletion or a central D₂ receptor block with decrease in dopaminergic activity in the CNS striatum and hypothalamus. This situation leads to disrupted core temperature regulation and hyperthermia, enhanced centrally mediated muscle activity with rigidity, increased sympathetic tone and autonomic instability, and a change in mental status. To be diagnosed with NMS, patients currently must be taking or recently

Table 6 Differential diagnostic features of stimulant syndromes

	BP	HR	Temperature	MS	Skin	Pupils	Special features
Sympathomimetic syndrome	↑	↑	↑	Altered	Diaphoretic	↑	Normal bowel sounds, reactive mydriasis
Alcohol/sedative-hypnotic withdrawal	↑	↑	Normal to ↑	Altered	Piloerection	↑	History of alcohol or sedative-hypnotic abuse, reactive mydriasis
Anticholinergic syndrome	↑↓	↑	↑	Altered	Dry	↑	Hypoactive bowel sounds, urinary retention, unreactive mydriasis
Complex status epilepticus	↓↑	Unreactive	Normal to ↑	Altered	Normal	Normal	Involuntary repetitive movements, unreactive pupils
Heatstroke	↓	↑	↑	Altered	Dry/hot	Normal	Core temperature >105 °F, history of exposure
Hypertensive encephalopathy	↑	↑ or ↓	Normal	Altered	Normal	Normal	Visual changes, papilledema, headache
Hypoglycemia	Normal	↑	Normal or ↓	Altered	Diaphoretic	Normal to ↑	Resolves with glucose
Meningitis	Normal or ↓	↑	↑	Altered	Normal to hot	Normal	Meningismus, headache
Neuroleptic malignant syndrome	Labile	Labile	↑	Altered	Normal to diaphoretic	Normal to ↑	Skeletal muscular rigidity, history of neuroleptic use
Serotonin syndrome	Labile	↑	Normal to ↑	Altered	Diaphoretic	↑	History of serotonin agent, myoclonus, shivering, hyperreflexia
MAO inhibitor	Labile	↑↓	↑	Altered	Diaphoretic	↑	History of MAO inhibitor agent, wide swings in vital signs with use of pressors, tremor, myoclonus
Cyclic antidepressants	↓	↑	Normal to ↑	Altered	Dry/flushed	↑	Widened QRS, R wave in aVR, and S wave in I, II
Pheochromocytoma	↑	↑	Normal	Normal to altered	Flushed	Normal	Paroxysms of hypertension and tachycardia
Sepsis	↓	↑	↑↓	Altered	Cool/clammy or hot/dry	Normal	Source of infection may be evident, low peripheral vascular resistance
Thyrotoxicosis	↑↓	↑	↑	Altered	Normal	Normal	Thyromegaly or tender thyroid, tachycardia disproportionate to fever

BP blood pressure, HR heart rate, MS mental status

have been taking a neuroleptic or another antidopaminergic medication and satisfy several additional criteria including increased core temperature, lead-pipe rigidity, autonomic instability, elevated creatine kinase, and change in mental status [55]. The chapter on NMS discusses this syndrome in more detail. By contrast, in the serotonin syndrome, there is primarily an excess of

5-HT_{2A} receptor stimulation, with a probable lesser contribution from effects at the 5HT_{1A} receptor. These patients have less remarkable extremity rigidity, but they should have the triad of altered mental status, autonomic dysfunction, and neuromuscular abnormalities. The neuromuscular findings are myoclonus, shivering, tremor, and hyperreflexia. In addition, patients may have

fever, incoordination, diaphoresis, and diarrhea. The patient may be on a single serotonin agent, on a series of agents, or overdosed on a serotonin agent [56, 57]. The serotonin syndrome is described in ► Chap. 24, “Serotonin Syndrome.”

Most serious MAO inhibitor overdoses involve agents that irreversibly inhibit MAO, the enzyme responsible for deaminating biogenic amines, leading to an increased availability of these amines in the cytosol. The patient may present with an initial asymptomatic phase, possibly with headache, and then develop neuromuscular excitation and evidence of enhanced sympathetic stimulation. The patient then becomes diaphoretic, agitated, hyperthermic, hyperreflexic, rigid, and tremulous and may develop myoclonus and seizures. Central nervous system depression, cardiac dysrhythmias, and cardiovascular collapse may follow. These patients are exquisitely sensitive to indirect-acting agents and may show wide autonomic instability if pressors are used [58]. The MAO inhibitor overdose may mimic serotonin syndrome but with rigidity, which may be lead pipe, particularly in the lower extremities; the patient also develops evidence of profound autonomic collapse [59, 60]. The reader is referred to ► Chap. 50, “Monoamine Oxidase Inhibitors” for a more complete discussion.

Patients with heatstroke may present with a high core temperature, tachycardia, altered mental status, tachypnea, and some muscular rigidity. Heatstroke is caused by loss of normal thermoregulation under some amount of heat stress. Patients may appear to be extremely toxic with a sympathomimetic syndrome, and differentiation may not be possible initially. The heatstroke patient initially may be diaphoretic and hypertensive but eventually becomes hypovolemic and hypotensive with dry skin. Multiple organ system failure then ensues. Treatment is the same as with the sympathomimetic syndrome, with supportive care and rapid cooling. The actual diagnosis may not be determined until after resolution of the acute event [61].

Malignant hyperthermia occurs in patients with abnormalities in their muscular excitation–contraction mechanisms. These

patients present with tachycardia and central hyperpyrexia. Differentiation from sympathomimetic syndrome is helped by a family history of similar events or temporally related exposure to general anesthesia or similar agents. The patients always have muscular rigidity and usually are sweating [61]. Additional discussion of this syndrome can be found in ► Chap. 29, “Malignant Hyperthermia.”

Diagnostic Studies

Certain studies may help in the differential diagnosis. Although leukocytosis is present in most sympathomimetic states, septic patients should show a left shift with other evidence of infection, such as toxic granules, Döhle’s bodies, or leukopenia. In thyrotoxicosis, thyroid-stimulating hormone is markedly depressed. In hypoglycemic patients, serum glucose is less than 70 mg/dL (3.89 mmol/L). Urinary collection of vanillylmandelic acid helps differentiate pheochromocytoma.

The electrocardiogram may be useful in differentiating neuroleptic agents and cyclic antidepressants from other causes. Most neuroleptics cause a nonspecific widening of the QT_c. Classic cyclic antidepressants frequently show a rightward deviation of the terminal 40 msec of the frontal plane QRS (an R wave in aVR and an S wave in I, II) and QT_c and QRS prolongation (Fig. 7).

A computed tomography scan of the head is useful to rule out CNS bleeding or mass. In the case of pheochromocytoma, computer tomography or magnetic resonance imaging of the abdomen and adrenals may identify the culprit lesions.

Toxicologic screening may identify some of these agents and help with differentiating toxic causes. Specific testing for lithium and salicylates is available. The most common immunoassay tests for sympathomimetic drugs of abuse such as amphetamine, methamphetamine, and cocaine. Since the immunoassay is a class assay and is predicated on the phenethylamine structure, these tests are fraught with many false-positive and false-negative results. For example, because

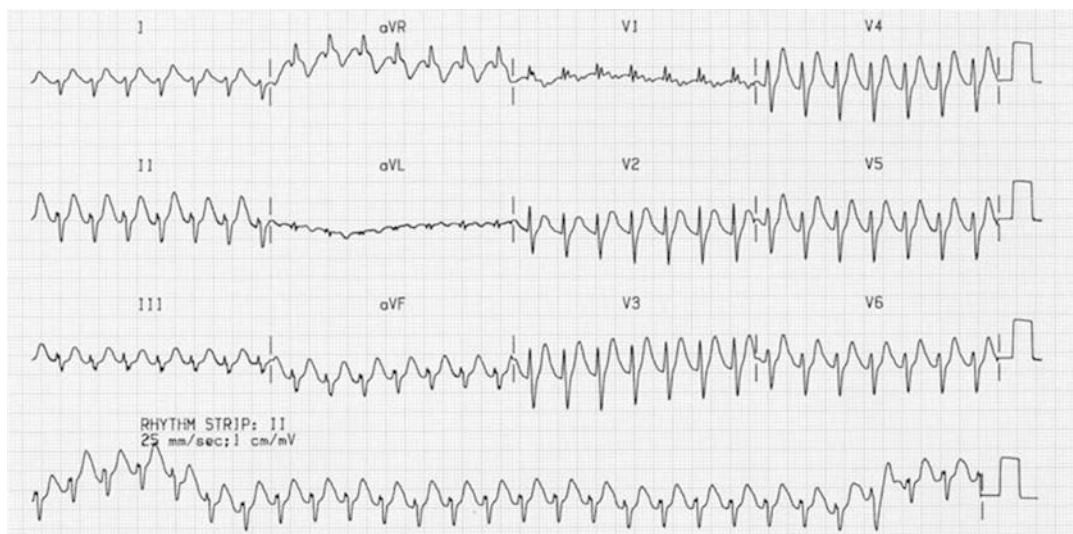


Fig. 7 A classic electrocardiogram from a tricyclic antidepressant-poisoned patient, showing sinus tachycardia, QTc and QRS prolongation, elevated R wave in aVR,

and S waves in I, II. This ECG would be highly suggestive of any fast inward sodium channel blocker toxicity

there is structural similarity to ephedrine and pseudoephedrine, the test may show a false-positive amphetamine result for these agents. Amphetamine derivatives, including cathinones and drugs such as MDMA, may not be detected when present and result in a false-negative result. These assays are not useful for anticholinergic agents and other serotonergic amphetamines or cathinone derivatives. Assays for tricyclic antidepressants identify a shared central seven-membered ring and will detect the classic cyclic antidepressants as well as agents sharing a similar structure, such as quetiapine. Beta-adrenergic agents, MAO inhibitors, and neuroleptics are not recognized by these immunoassays. Comprehensive thin-layer chromatography coupled with immunoassay, high-performance liquid chromatography, and gas chromatography–mass spectroscopy may identify many compounds. However, even with the high sensitivity and specificity of these diagnostics, newly synthesized xenobiotics may go undetected. A negative toxicologic screen does not exclude the presence of a particular xenobiotic and may represent poor assay selectivity or an insufficient quantity of the xenobiotic.

Treatment

Because sympathomimetic toxicity reflects a general increase in catechol effect, treatment is directed toward attenuating this pathway. The simplest and most efficient way is to depress the CNS release of catecholamines with benzodiazepine or barbiturate sedation [62, 63, 64] (Grade I recommendation) which decreases norepinephrine release. Administration of nitrates is beneficial in the management of some sympathomimetic effects such as cocaine-induced chest pain, coronary artery vasospasm, and hypertension [17, 65–67] (Grade I evidence). While the safe use of combined α and β -blockade with agents such as carvedilol or labetalol has been substantiated in small trials [68, 69] and is recommended by the American Heart Association as second-line agent considerations after nitroglycerin and calcium channel blockers for suspected ACS in cocaine and methamphetamine users [70], the use of beta-blockers without alpha antagonist activity, until further evidence emerges, should be avoided. Alpha antagonism may also help attenuate severe hyperthermia in MDMA toxicity (Grade 1)

[71, 72]. Tachydysrhythmias usually respond to sedation (Grade I evidence), but a calcium channel blocker may be required. Evidence demonstrating a consistent benefit of calcium channel blocker administration to patients with sympathomimetic toxicity is lacking but is a class I (Grade C) recommendation for cocaine and methamphetamine users with ischemic chest pain by the AHA (class I) [64, 70]. Peripheral alpha-adrenergic antagonists (phentolamine) and central alpha₂ agonists should also be considered to control severe hypertension either primarily (class I) or when benzodiazepines and nitroglycerin fail (class III). In general, most antidysrhythmics should be avoided since many sympathomimetic agents have sodium channel attenuating properties (e.g., cocaine) and may have additive toxicity. In the setting of QRS widening or wide complex tachycardias from cocaine, hypertonic sodium bicarbonate should be strongly considered (class I) [73]. Because sympathomimetics can induce platelet aggregation, aspirin therapy in the presence of cardiac-type chest pain is suggested [74] (Grade I evidence). Hyperpyrexia must be treated aggressively with rapid cooling and prevention of muscle hyperactivity since, at least with serotonin toxicity, mortality is directly correlated with core body temperature [43, 75]. Little evidence exists to suggest an optimum technique for cooling patients with drug-induced hyperthermia and this recommendation is derived from the benefits seen with aggressive cooling in exertional heatstroke (Grade III evidence) [76]. Sedation may be helpful, but if the patient has rigidity, marked myoclonus, or prolonged seizure activity, paralysis with a nondepolarizing agent, in addition to sedation, may be necessary to halt the continued lactic acidosis and heat production. Psychomotor agitation usually responds to sedation with a GABAergic agent such as a benzodiazepine or propofol (Grade III evidence), and seizures generally are brief and should also respond to benzodiazepines. If continued seizures develop, an anticonvulsant such as a barbiturate (e.g., phenobarbital 260 mg IV initial dose) is suggested [77, 78].

Special Populations

Patients who take β -blockers may not present with the tachycardia associated with the sympathomimetic syndrome. If there is a significant α component to the sympathomimetic agent, the patient may present with exaggerated hypertension from the unopposed α effect. Pediatric patients comprise a bimodal distribution of sympathomimetic toxicity. Younger patients tend to have accidental ingestions and usually present with smaller, self-limited sympathomimetic toxicity. Treatment is the same as adults except the medication doses are weight dependent. Adolescents tend to use larger doses or may “stack” the hallucinogenic amphetamines resulting in a more intense and prolonged toxicity. These patients can present extremely ill and markedly hyperthermic with multisystem organ failure. High doses of benzodiazepines, active external cooling, and aggressive attention to detail are all necessary for a good outcome.

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Drug reactions that lead to an intensive medical response represent a significant medical problem. These reactions can be due to known pharmacologic activities of a drug, activation of the immune system, or other mechanisms. Reactions that involve the immune system account for only 10% of cases but can be dramatic and life-threatening [1, 2]. The cost of drug reactions with an immunologic basis is approximately \$3 to \$13 billion/year, when extrapolated from estimates of the cost for all drug reactions in the United States [1, 3]. Reactions that involve immunologic mechanisms often are described as “allergic.” The word *allergic* is used to describe reactions that are mediated through the IgE class of antibodies. The term *immunologic drug reaction* includes any immune reaction that involves specific recognition by the immune system (via antibodies or the T-cell receptor) and thus includes IgE-mediated reactions [4]. The term *pseudoallergic* often is used to refer to drug reactions that mimic allergic reactions (e.g., release of proinflammatory mediators) but occur via activation of the immune system in a fashion that is independent of antibody or specific receptors [4–7]. The term *idiosyncratic* refers to an uncharacteristic response to a drug that is qualitatively different from its pharmacologic activity and that is not immunologic in mechanism. These reactions may be genetically based and related to metabolic or enzyme deficiencies [4, 5].

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History

At the end of the nineteenth century, there were dramatic advances in the use of inoculation of killed or attenuated organisms to prevent human infectious diseases, including smallpox, rabies, typhoid, cholera, and plague [8]. Two immunization strategies led to paradoxical reactions and inadvertently expanded our understanding of the immune system. In the first approach, animals were given injections of increasing doses of a toxin in an attempt to protect them from subsequent exposure. The second approach was to protect or treat humans with sera from animals that had been injected previously with infectious agents or toxins.

The importance of these unexpected reactions was first appreciated by Richet, who immunized dogs with sea anemone toxin with the objective of eventually treating Mediterranean Sea bathers stung by jellyfish [9–11]. Richet hypothesized that animals surviving a sublethal dose would be protected against subsequent stings. However, when given a subsequent dose of similar or smaller size, some of the dogs died within minutes. Reaction symptoms on rechallenge were considerably different from the subacute toxic reaction progressing over 4 or 5 days seen after the initial injections. Reactions to rechallenge were characterized by the rapid (within minutes) onset of breathing problems, lethargy, and diarrhea. Richet concluded that the first injections of toxin had not prophylaxed the dogs but rather had changed the animals into a state of anaphylaxis (without protection) [10, 12–14].

Reactions to heterologous (from another species) blood products were appreciated in 1667 after early attempts to use lamb's blood for transfusion [15]. The desire to treat human infectious diseases with sera from immune animals led to efforts to understand these reactions. In the early years of the twentieth century, antiserum developed in horses, particularly anti-diphtheria antitoxin, came into general use and was associated with 38 reported fatal reactions and many more nonfatal reactions between 1895 and 1923 [15]. Some of these reactions occurred

immediately and were similar to the reactions Richet observed in dogs, but most evolved more slowly with different manifestations. In 1905, Von Pirquet and Schick coined the term *serum sickness* to describe this latter reaction, characterized by fever, arthritis, and erythema multiforme occurring 7–10 days after exposure to heterologous serum [15]. During the next decade, the overlap between anaphylaxis and serum sickness became apparent, and the concept of different manifestations of “hypersensitivity” came to be appreciated. As medical care evolved during the twentieth century, therapy with heterologous serum gave way to the use of antibiotics and recognition of allergic reactions to these new agents. Immunologic reactions to antibiotics continue to be a substantial problem, and a plethora of drugs generated for a variety of illnesses have become important sensitizing substances. Most recently, the development of monoclonal antibodies has emerged as a novel source of sensitization.

Pathophysiology

Reactions to drugs vary widely. Some reactions are limited to the skin or to specific internal organs; others are systemic. Although some agents cause stereotypical reactions, almost any agent can cause any type of reaction. In the 1960s, Gel and Coombs characterized immunologic reactions by the major immunologic process operative in a reaction [4]. In this analysis, type 1 reactions are immediate hypersensitivity reactions involving cross-linkage of IgE bound to high-affinity receptors on mast cells or basophils. Type 2 reactions are due to cytotoxic antibodies. Type 3 reactions are due to immune complexes, and type 4 reactions are due to cell-mediated hypersensitivity. Adkinson described this concept for penicillin reactions (Table 1) [4]. Although this process is a useful method of discussing immunologic reactions to drugs, more recent data have shown that there is marked overlap among these arms of the immune system such that several of the Gel- and Coombs-type reactions can occur in a single reaction. A different approach that is more

Table 1 Immunopathologic penicillin reactions

Gel and Coombs classification	Mechanism	Examples of adverse penicillin reactions
I	Anaphylactic (IgE mediated)	Acute anaphylaxis Urticaria
II	Complement-dependent cytotoxicity (IgG/IgM)	Hemolytic anemias Thrombocytopenia
III	Immune complex damage	Serum sickness Drug fever Some cutaneous eruptions and vasculitis
IV	Delayed or cellular hypersensitivity	Contact dermatitis Morbilloform eruptions SJS/TEN Hepatitis

From Ref. [4]

functional is to classify reactions to drugs based on the timing and predominant clinical manifestation (Table 2) [2, 16].

Many drugs are small, immunologically inactive molecules, such as penicillin, that activate the immune system by virtue of their ability to “haptenate” naturally occurring plasma and cellular proteins. The process of forming haptens is fairly well understood for penicillin and probably is similar for other small molecules (Fig. 1). In this scenario, the drug itself is not recognized by the immune system because of its small size (molecular weight 100–1000 days). When the drug or its metabolic product is bound to a protein, it distorts the three-dimensional structure of the protein so that the drug, now presented as part of a protein, is recognized as a novel structure leading to clonal expansion of T cells. T cells interact with B cells and produce cytokines that also drive the maturation of B cells. These maturing B cells express surface immunoglobulin for the drug, then form plasma cells that secrete immunoglobulins that recognize the drug with high affinity [17]. Susceptible patients undergo class switching from an IgG response to produce IgE that binds to the high-affinity receptor for IgE (FcεRI) on mast cells and basophils, sensitizing these patients. Subsequent exposure to the “haptened” protein during a

Table 2 Classification of immunologic drug reactions based on their timing

Reaction type	Time of onset	Clinical manifestation
Immediate	<1 h	Anaphylaxis Angioedema Urticaria Bronchospasm
Delayed	>1 h, typically >6 h or several days	Morbilloform rash Interstitial nephritis Hemolytic anemia Thrombocytopenia Neutropenia Drug fever Stevens-Johnson syndrome Toxic epidermal necrolysis
	1–3 weeks	Serum sickness
	1–12 weeks	Drug reaction with eosinophilia and systemic symptoms (DRESS)

Modified from Refs. [2, 16]

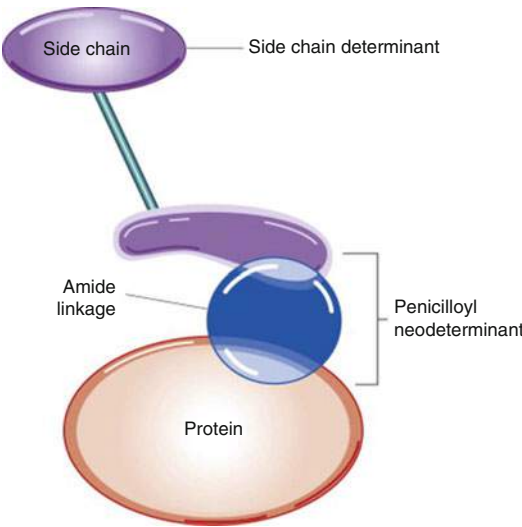


Fig. 1 Generation of haptens. SC side chain (From Ref. [4])

repeat course of therapy leads to cross-linking of the antigen-specific IgE bound to FcεRI, then to degranulation of mast cells and basophils [1, 4]. This process also can occur during a single course of drug therapy in which either the first

exposure was not appreciated or the initial sensitization and the effects of sensitization occur in rapid sequence [18].

The most limited reactions that are clearly IgE mediated manifest as diffuse urticaria (hives), but reactions can be generalized and include angioedema (of lips, tongue, and uvula), respiratory compromise (bronchospasm/wheezing, stridor, hypoxemia), gastrointestinal symptoms (abdominal cramping, vomiting), and vascular collapse [19]. It is unknown why only some patients produce IgE and why the reactions are to certain agents and not to others. Lack of a history of previous allergic reactions to drugs or to other allergens is not helpful. Some patients with a history of allergic reactions to drugs are prone to reactions with structurally unrelated medications [2]. This situation may be due to a genetic predisposition to recognize haptens; however, a history of allergic disease, such as allergic rhinitis, does not predispose to allergic drug reactions [1, 2]. Multiple drug hypersensitivity syndrome (MDH) may be due to derangements of T-cell function, as this is more common in delayed reactions, specifically severe cutaneous adverse reactions like drug reaction with eosinophilia and systemic symptoms (DRESS), also called drug-induced hypersensitivity syndrome (DiHS) [20].

Foreign molecules (antigens) can activate the immune system in a highly specific fashion. The molecules of the immune system that recognize antigens are either soluble proteins called *antibodies* or receptors on the surface of T cells (T-cell receptors) and B cells (B-cell receptors). Antibodies fall into five distinct molecular groups (in order of predominance in the circulation): IgG, IgM, IgA, IgD, and IgE. Antigens that lead to an IgE response are called *allergens*. Antibody molecules have two critical regions – the Fab region, which binds avidly to unique structures (antigens), and the Fc region, which binds to Fc receptors on effector cells. The IgG antibodies (normal range, approximately 700–1500 mg/dL [7–15 mg/mL]) account for the greatest portion of the humoral (soluble) immune response to foreign proteins. They participate in immune reactions by forming immune complexes with antigen or

by combining with Fc receptors on effector cells. IgE antibodies (normal range, approximately 0–250 ng/mL [0–0.25 mg/L]) are present at the lowest concentration, participate in host defense against parasites, and are responsible for immediate hypersensitivity reactions. IgE antibodies sensitize mast cells and basophils by binding with high affinity to FcεRI receptors. The process of antigen presentation by antigen-presenting cells (typically B cells, macrophages, and dendritic cells), immune recognition of T-cell epitopes (the component of an antigen recognized by the immune system) by T cells via the T-cell receptor, T-cell-mediated and antigen stimulation of B cells, maturation of B cells to become IgE-producing plasma cells, and sensitization of mast cells by IgE is illustrated in Fig. 2 [21]. IgE, bound to FcεRI and cross-linked by a specific antigen, causes degranulation of these cells with the rapid (0–30 min) release of potent vasoactive and proinflammatory mediators, such as histamine, leukotriene C₄, and prostaglandin D₂ [22]. T cells recognize a specific antigen by virtue of T-cell receptors (TCRs) that identify the unique specificity of a foreign peptide sequence in the context of the major histocompatibility loci [21]. A crucial precept of modern immunology is that the region of a foreign epitope recognized by the TCR is distinct from that recognized by the B-cell receptor and circulating antibodies [21].

Examples of IgE-mediated reactions are generalized anaphylaxis and more limited reactions, such as some cases of acute asthma, hives, and allergic rhinitis. IgG antibodies are responsible for more delayed adverse reactions, interacting with the immune system via Fcγ receptors (receptors for the Fc portion of IgG) and by forming soluble immune complexes. Immune complexes often activate the complement cascade, generating immunologically active complement fragments. Examples of IgG-mediated immunologic reactions include serum sickness and immune complex glomerulonephritis. Specific antigen receptors on T cells (T-cell receptors) have the ability to recognize foreign material in much the same way as antibodies do. This recognition leads to expansion and activation of clones of T cells.

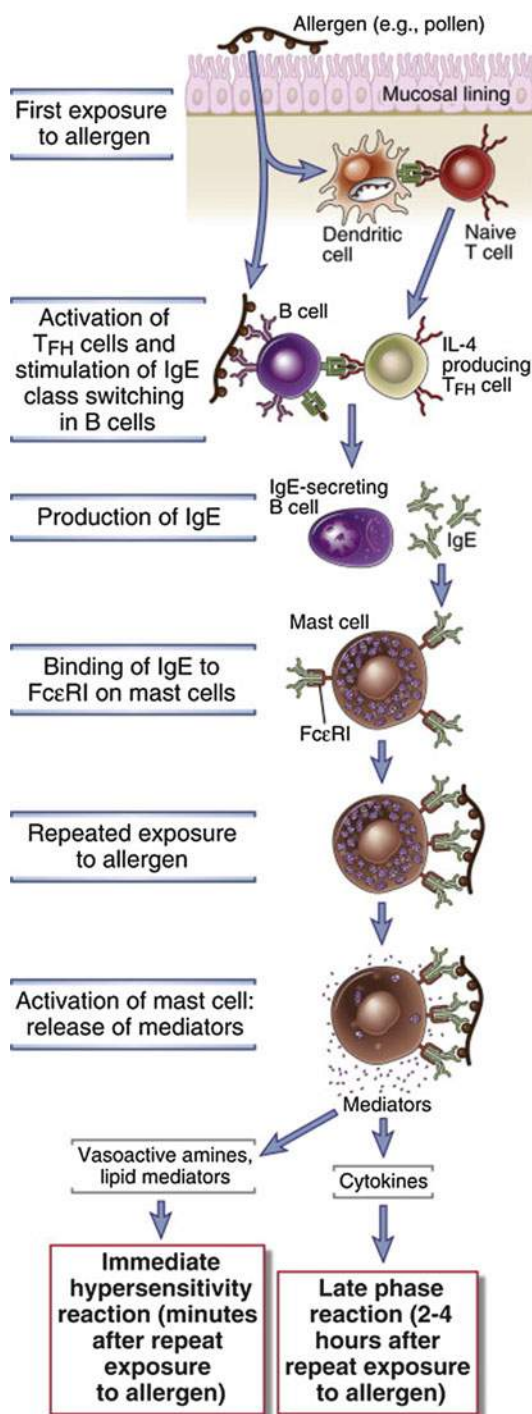


Fig. 2 Sequence of events in immediate hypersensitivity reactions. Immediate hypersensitivity diseases are initiated by the introduction of an allergen, which stimulates IL-4 producing helper T cell responses and IgE production. IgE sensitizes mast cells by binding to FcεRI, and subsequent

These reactions generally are referred to as *delayed-type hypersensitivity* reactions. The most familiar example is the dermatitis seen secondary to poison ivy, but delayed-type hypersensitivity reactions also are seen with topical medications, such as neomycin, and can be seen in dermatologic reactions to systemically administered drugs [1, 23].

Drug Reactions

Anaphylaxis

The most terrifying reaction to an exogenous agent is anaphylaxis. These reactions are typically observed within the first 30 min after parenteral administration of the offending agent but can occur minutes to hours after the ingestion of a food [14, 24]. Typically the patient has a brief prodrome of anxiety and a sense of impending doom followed by cutaneous reactivity (generalized urticaria, itching or flushing, swelling of lips/tongue/uvula), respiratory compromise (bronchospasm/wheezing, stridor, hypoxemia), gastrointestinal symptoms (abdominal cramping, vomiting), hypotension, or vascular collapse [19]. Not all of these signs and symptoms need be present. For example, approximately 15% of patients with cardiovascular collapse due to anaphylaxis do not have cutaneous signs. Specific criteria for the diagnosis of anaphylaxis have been determined (Table 3).

IgE-Dependent Anaphylaxis

Cross-linkage of IgE-FcεRI complexes on mast cells and basophils initiates the most common form of anaphylactic reaction – IgE-mediated anaphylaxis. For this reaction to occur, the patient generally has been exposed previously to the agent, and some time (weeks to months) has passed to allow for the production of sufficient

Fig. 2 (continued) exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic reactions of immediate hypersensitivity (From Ref. [21])

Table 3 Clinical criteria for diagnosing anaphylaxis (World Allergy Organization)

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen “lips-tongue-uvula”) AND AT LEAST ONE OF THE FOLLOWING: A. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) B. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse) syncope incontinence)
2. Two or more of the following that occur rapidly after exposure to a <i>likely</i> allergen ^a for that patient (minutes to several hrs) A. Involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch-flush, swollen lips-tongue-uvula) B. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) C. Reduced blood pressure or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence) D. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to <i>known</i> allergen ^b for that patient (minutes to several hours) A. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure ^c B. Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person’s baseline a) Or other trigger, for example, immunologic but IgE-independent or nonimmunologic (direct) mast cell activation b) For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, in a similar example, during allergen immunotherapy, after injection of a known allergen for that patient, generalized urticaria (only one body organ system affected) might be the only initial manifestation of anaphylaxis c) Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg, age 2) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80 to 140 beats/min at age 1–2 years, from 80 to 120 beats/min at age 3 years, and from 70 to 115 beats/min after age 3 years. Infants are more likely to have respiratory compromise than hypotension or shock, and in this age group, shock is more likely to be manifest initially by tachycardia than by hypotension

Modified from Ref. [19]

IgE to sensitize mast cells and basophils. Systemic anaphylaxis can be caused by a wide variety of agents. Many drugs are of such small molecular weight that they by themselves are not recognized by the immune system. Penicillins are the best-studied example of this type of drug. In this case, it is the drug bound to a large-molecular-weight protein (i.e., albumin) that becomes antigenic. In this situation, the drug is called a *haptén*.

In the hospital, a large array of drugs can precipitate IgE-dependent anaphylaxis, particularly antibiotics, neuromuscular blocking agents, and some reactions to nonsteroidal anti-inflammatory drugs (NSAIDs). Other substances may also trigger IgE-dependent anaphylaxis, including blood transfusions, foods, latex, and intravenous contrast material. In the operating room, some of the abovementioned warning signs may not be evident, and resistance to ventilation or vascular collapse may be the first sign of anaphylaxis. In the outpatient setting, patients can have IgE-dependent anaphylaxis as a result of food, insect stings, medications, or latex, as a

manifestation of systemic mastocytosis, and spontaneously idiopathic anaphylaxis.

IgE-Independent Anaphylaxis

Some agents cause a syndrome of anaphylaxis through an immunologic mechanism, but without involvement of IgE. These reactions were historically called *anaphylactoid reactions*, but more recently have been categorized as IgE-independent anaphylaxis. They are caused by direct mast cell activation, leading to symptoms that may be clinically indistinguishable from IgE-dependent anaphylaxis. Common causes of IgE-independent anaphylaxis include IV radio-contrast media, NSAIDs, opioids, dextrans (high molecular weight iron and colloids), and some monoclonal antibodies [19]. Intravenous radio-contrast material is thought to cause activation and degranulation of mast cells by virtue of its hyperosmolality. *N*-acetylcysteine can cause a similar syndrome, although the mechanism is even more obscure [25]. These can manifest just as severely as IgE-dependent anaphylaxis, and

treatment of both types of anaphylaxis is similar, with prompt use of epinephrine and removal of the offending agent.

Serum Sickness

The best-described non-anaphylactic systemic reaction is serum sickness. This reaction is characterized by fever, malaise, and a pruritic rash that is urticarial or maculopapular. Associated findings may include arthritis, proteinuria (rarely with frank glomerulonephritis), gastrointestinal symptoms, adenopathy, vasculitis, and peripheral neuropathy [26, 27]. Typically symptoms occur between 1 and 3 weeks from the initial exposure. However, if a prior exposure has occurred, symptoms can present more rapidly (within 12–36 h). This type of reaction is thought to be due to circulating immune complexes. Drugs commonly implicated in serum sickness include antibiotics (penicillin, sulfonamides, cefaclor in children), antiepileptics, NSAIDs, and thiazides. Some monoclonal antibodies and blood products can also cause serum sickness. Heterologous proteins commonly precipitate serum sickness, and these include antivenin (e.g., Crotalidae polyvalent and Crotalidae polyvalent immune Fab), digoxin immune Fab, and antithymocyte globulin [27, 28].

Drug Fever

The cause of drug fever is unknown, and it can be seen with many drugs, although β -lactam antibiotics are commonly implicated [29]. Drug fevers have a median onset of 7–10 days after initiation of the culprit medication, and this time interval is typical of antimicrobial-induced drug fever. However, intervals vary depending on the class of the culprit medication, with median onset of fever 0.5 days after initiation of antineoplastic drugs and 16 days with CNS agents [29]. It may be associated with eosinophilia, leukocytosis, and an elevated erythrocyte sedimentation rate, but it most frequently presents as an isolated symptom and poses a diagnostic dilemma. Because drug

fevers usually resolve within 48–72 h of stopping the drug, this forms a useful diagnostic test, although this is ultimately a diagnosis of exclusion [1].

Reactions with a Predominant Organ Involvement

Cutaneous reactions can occur with almost any drug taken systemically and vary from relatively benign to severe life-threatening lesions with morbidity similar to that seen with severe burns.

Urticaria and Angioedema

Diffuse urticaria or angioedema is due to degranulation of cutaneous mast cells. Although usually this is a self-limited process, urticaria and angioedema are severely distressing to the patient. This should be considered to be a systemic (not local) reaction and may be a harbinger of a more severe generalized reaction that is developing over time. If compromise of the airway is present, it must be treated aggressively. Angiotensin-converting enzyme inhibitors cause angioedema by virtue of their ability to inhibit important esterases, leading to excessive levels of vasoactive kinins (e.g., bradykinin). The localization of this swelling to the upper airway is not understood. Agents that can activate cutaneous mast cells by non-IgE-mediated mechanisms and cause symptoms of erythema, pruritus, dermatitis, or urticaria include radiocontrast media, vancomycin, *N*-acetylcysteine, opiates, amphotericin, tubocurarine, and physical stimuli, such as sunlight, pressure, vibration, heat, and cold. By virtue of location of the exposure or the presence of specific receptors, many of these agents most often activate only cutaneous mast cells, but more severe systemic reactions do occur [1, 4, 6].

Severe Cutaneous Adverse Reactions (SCAR)

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Erythema multiforme appears as raised erythematous lesions predominantly on the extremities with varied shapes, including target lesions, maculopapular rashes, urticaria, and vesicles. In most patients, infection or exposure to drugs or

both are thought to be responsible [1, 30]. Erythema multiforme minor is an acute, self-limited mucocutaneous syndrome [30]. Erythema multiforme major includes Stevens-Johnson syndrome and toxic epidermal necrolysis. These are severe blistering dermatoses characterized by mucocutaneous lesions, and differentiation between these disorders is based on the percentage of skin detachment. SJS is characterized by detachment of <10% of body surface area, and TEN is characterized by detachment of >30% of body surface area [31–33]. These disorders should be thought of as a systemic illness because of the extensive involvement of mucous membranes, and mortality rates as high as 50% for TEN have been reported [33]. The pathophysiology is not well understood but is likely mediated by drug-specific T cells.

Drug Reaction with Eosinophilia and Systemic Symptoms

The syndrome of drug reaction with eosinophilia and systemic symptoms is also called drug-induced hypersensitivity syndrome. It involves rash (typically erythematous and morbilliform, but presentations may vary), fever, eosinophilia, lymphadenopathy, and multiorgan dysfunction. Organs typically involved include the liver, kidneys, heart, and lungs, and while eosinophilia is common, it may not be present in up to 30% of cases. Onset is typically after 2–8 weeks but can be delayed up to 12 weeks from start of a medication [34, 35]. The pathogenesis is not well understood, but proposed mechanisms include abnormalities in drug detoxification enzymes with accumulation of reactive drug metabolites, reactivation of herpesviruses (EBV, CMV, HHV6, and HHV7), and genetic predisposition due to HLA alleles [34]. Unlike most other drug reactions, symptoms and organ involvement of DRESS may continue to progress for weeks after discontinuation of the drug and may persist for months after discontinuation [33]. Medications implicated include anticonvulsants (phenytoin), antibiotics (trimethoprim-sulfamethoxazole, minocycline, vancomycin), immunosuppressants (sulfasalazine, dapsone, cyclosporine), NSAIDs, D-penicillamine, hydrochlorothiazide, nevirapine,

and allopurinol [33]. Evidence that this syndrome has an immunologic basis includes the need for a sensitization period (reactions occur at least 7 days after the beginning of the drug therapy or after repeated exposure), no clear relationship to dose, the presence of blood and tissue eosinophilia, the presence of fever, positive rechallenges, and the presence of drug or drug-specific antibodies or drug-reactive T cells [36].

Vasculitis

Henoch-Schönlein purpura is predominantly a disease of children characterized by cutaneous vasculitis with the deposition of IgA. Although most often associated with an antecedent infection, particularly group A β -hemolytic streptococcus, it occasionally is associated with the recent intake of carbidopa/levodopa [33]. Henoch-Schönlein purpura also can present as a systemic vasculitis and can be seen in adults [37]. Drug-induced vasculitis can also be associated with hydralazine, antithyroid medications, minocycline, and penicillamine [33].

Hepatitis

Drug-induced liver injury most often is hepatotoxicity due to toxic effects of drugs (e.g., acetaminophen) but infrequently is hepatitis due to immunologic activation. Immunologic reactivity within the liver can manifest as cholestasis, hepatocellular damage, and granulomatous reactions. Although many drugs can cause allergic hepatitis, halothane and anticonvulsants (phenobarbital, carbamazepine, phenytoin) are most prominent [1].

Renal Failure

Drug-induced nephropathies include interstitial nephritis and membranous glomerulonephritis. Interstitial nephritis may result from high dose of β -lactam antibiotics or sulfonamides and is characterized by eosinophils in the urinary sediment (a positive Hansel stain) [33]. It may also be accompanied by fever, rash, peripheral eosinophilia, and high IgE [33]. Eosinophiluria is not always found in drug-induced renal damage, and gold, penicillamine, and allopurinol can induce a nephrotic syndrome, characterized by membranous glomerulonephritis [33, 38].

Hematologic Disorders

Immune-mediated hematologic disorders, such as thrombocytopenia and hemolytic anemia, are well described. Patients can present with thrombocytopenia, hemolytic anemia, or leukopenia. In most occurrences, drugs (e.g., penicillins) or their metabolic by-products bind to cellular membranes and initiate an immunologic reaction via the hapten mechanism by forming new antigenic determinants. IgG antibodies thus formed react with the blood elements, leading to sequestration by splenic macrophages. Cell lysis may occur if complement is activated. A less common mechanism has been documented with α -methyl dopa, levodopa, and procainamide, in which autoantibodies against red blood cells are formed, generating a clinical picture that looks like autoimmune hemolytic anemia [33].

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis can be seen with many drugs, including antimicrobial agents (nitrofurantoin, sulfonamides), anticonvulsants (phenytoin, carbamazepine), diuretics (hydrochlorothiazide), antiarrhythmics (amiodarone), narcotics (heroin, methadone, propoxyphene, cocaine), antirheumatics (gold, methotrexate, penicillamine, naproxen), and chemotherapeutics (bleomycin). The clinical picture is similar to that seen after inhalation of organic dusts from multiple sources, such as moldy hay (farmer's lung), bird proteins (pigeon breeder's disease), or contaminated humidifiers [39]. This syndrome is characterized by fever, nonproductive cough, and dyspnea associated with bilateral patchy infiltrates suggestive of a pulmonary infection.

Immunologic Reactions Due To Specific Agents

Antibiotics

Antibiotics are associated most commonly with immunologic drug reactions, probably due to their widespread and intermittent usage. Fatality from penicillin has been estimated to occur in 0.0001% of treatments, resulting in 400–800 deaths per

year during the 1970s [2]. Parenteral administration is associated with more allergic reactions, but it is unclear whether this is related to the route of administration or to the dose administered.

Penicillins and Other β -Lactams

Penicillins and other β -lactam antibiotics (cephalosporins, carbapenems, and monobactams) are small molecules, but they present a range of antigenic determinants to the immune system [40, 41]. Penicillins bind covalently to proteins by an amide linkage to the side chain ϵ -amino group on lysine residues, generating the “penicilloyl” residue (the major determinant), commercially available as penicilloyl polylysine and less well-characterized “minor” determinants, of which only penicillin G is commercially available [42]. Antibodies to the penicilloyl group constitute up to 95% of the responses to penicillin and penicillin allergy is not due to reactions to the β -lactam ring [17, 43]. Although up to 10% of the population may self-report allergy to penicillin, when evaluated with skin testing or other assays, the true incidence of penicillin allergy is <10% of those who self-report they are allergic, and rates may be as low as 0.3–3% (Grade II-2) [43]. IgE-mediated drug reactions require sufficient time for development of an antibody response, but allergic reactions can develop during the course of a single treatment or even manifest 2 weeks after termination of the treatment [18].

While IgE mediated, immediate hypersensitivity reactions to penicillin are the best studied, they can also cause delayed reactions, including serum sickness and delayed maculopapular eruptions. The delayed maculopapular or morbilliform rash commonly seen with ampicillin or amoxicillin in patients with infectious mononucleosis, other viral illnesses, chronic lymphocytic leukemia, or concomitant allopurinol therapy is not IgE mediated [1].

Cross-Reactivity of β -Lactams

Early studies with first-generation cephalosporins suggested strong but incomplete cross-reactivity with penicillin. However, more recent observations suggest that only about 2% of penicillin

skin test positive patients will react to cephalosporins. It is recommended that those with a reported history of penicillin allergy be skin tested prior to administration of a cephalosporin (Grade III); however, if penicillin-allergic patients are NOT skin tested, extrapolating from the approximation that, at most, only 10% of people with self-reported histories of penicillin allergy will have positive skin tests, the risk of reaction with cephalosporins is likely <1% (Grade III) [33]. Patients with a delayed, maculopapular (not urticarial) rash associated with intake of a penicillin (most often amoxicillin), especially in the context of a viral infection (Epstein-Barr virus or cytomegalovirus), are unlikely to have systemic reactions to penicillin or cephalosporins. Some guidelines recommend the use of cephalosporins without further evaluation in those with penicillin allergy by history who did not experience urticaria, angioedema, respiratory distress, or anaphylaxis (Grade III) [44].

About 25% of cephalosporin allergic patients will react to penicillin, and so penicillin skin testing is recommended prior to penicillin administration in those with cephalosporin allergy (Grade II-2) [45]. The major cross-reactivity between penicillin and cephalosporins is directed toward side chains, and not the β -lactam ring, and so for those with penicillin allergy, cephalosporins with similar side chains should be avoided (Grade III) [43]. For those allergic to ampicillin or amoxicillin, this includes cephalosporins with identical R1 side chains including cefaclor, cephalexin, cefprozil, cefadroxil, cefatrizine, cephaloglycin, and loracarbef, as well as those with similar R1 components, cefamandole and cefonicid [43]. Cephalosporin allergy does not cross all generations of the antibiotic class, and cross-reactivity is based on the similarity of R1 and/or R2 side chains (i.e., cefepime and ceftriaxone, cefoxitin and cephalothin) [43].

Carbapenems have very low cross-reactivity with penicillins. In one study only 1% of penicillin skin test positive patients were positive to imipenem, and all those with a negative skin test to imipenem passed challenges (Grade II-2) [46]. Aztreonam does not cross-react with any β -lactam antibiotics except for ceftazidime, due

to a common side chain, and penicillin- and cephalosporin-allergic patients may safely receive aztreonam, unless they specifically are allergic to ceftazidime (Grade III) [33]. There were no positive skin tests and no reactions to challenge with aztreonam in those with a history of penicillin allergy and positive penicillin skin testing (Grade II-2) [47].

Other Antibiotics

Reactions to sulfa drugs may be immunologically mediated and manifest as hives or anaphylaxis or both. The major concern for sulfa drugs is development of SJS/TEN, and it is crucial to consider these severe cutaneous adverse reactions in any patient with a rash in the context of sulfa drug administration. Vancomycin can cause mast cell degranulation directly, leading to the “red man syndrome.” The pseudoallergic activation of mast cells with vancomycin is functionally similar to the nonspecific degranulation of mast cells seen with radiocontrast material, although the red man syndrome is limited to the skin. It is unknown why this activation manifests as a diffuse erythema rather than hives and why is it limited to the skin.

Antiepileptics

Similar to other drugs, antiepileptic drugs can cause a maculopapular or morbilliform rash as well as severe cutaneous adverse reactions, including SJS/TEN and DRESS/DiHS [33, 48]. The concomitant administration of valproate and lamotrigine seems to increase the risk. Valproate is known to increase the half-life of lamotrigine, and the dose should be adjusted accordingly (Grade II-2) [49]. In some cases, these reactions clearly have an immunologic basis, with histocompatibility locus HLA-B*15:02 associated with severe cutaneous adverse reactions with both phenytoin and carbamazepine in Asian populations (Grade II-2) [50]. Genetic variants in hepatic enzyme CYP2C, including CYP2C9*3, have also been associated with severe cutaneous adverse reactions. These variants decrease clearance of plasma

phenytoin and higher levels of phenytoin were associated with development of these reactions (Grade II-2) [51].

Local Anesthetics

Bona fide reactions to local anesthetics are extremely rare, although there are many patients who profess that they have had reactions, mostly during dental procedures. The most generally accepted alternative explanations for these histories are that these either are vasovagal reactions or are due to the inadvertent intravenous injection of the local anesthetic agent with epinephrine. Some of these patients may be allergic to latex. A simple approach to these patients is to perform skin testing to reassure the patient and to switch to the alternate class of local anesthetic agent (benzoic acid esters versus amide-type local anesthetics) (Grade III) [2, 52].

General Anesthesia

The incidence of life-threatening immunologic reactions to drugs used in general anesthesia has been estimated to be 1 in 3500 to 1 in 6000 [53]. These reactions typically occur in the context of administration of multiple drugs. This situation obscures temporal relationships and complicates determination of the specific offending agent. The patient typically is unconscious and covered, delaying awareness that a systemic reaction is taking place. Increased ventilatory resistance or loss of blood pressure may be the earliest signs of anaphylaxis. Based on the demonstration of drug-specific IgE, 50% of these reactions may be IgE mediated, and the remainder are thought to be pseudoallergic. Muscle relaxants, such as suxamethonium, are the cause in approximately 60% of the IgE-mediated reactions. Quaternary ammonium ions, which are present in many drugs and cosmetics, may be the active epitope [54]. Other agents, such as hypnotics and morphine derivatives, occasionally are identified as causal. Some agents, such as tubocurarine, may be able to release

histamine from mast cells on a non-IgE-mediated basis, but the clinical importance of this is controversial [2, 53]. Latex sensitivity may also explain some episodes of intraoperative anaphylaxis [14].

Latex

Latex allergy is included in this chapter because sensitivity to latex proteins is an important consideration in patients presenting with immediate hypersensitivity reactions in the hospital. The early reports of anaphylaxis after exposure to latex were in patients undergoing barium enemas and in children with spina bifida. In the 1990s, it became apparent that many individuals were sensitized to latex, and individuals at highest risk are patients who have undergone multiple surgeries or invasive procedures, health-care professionals, and latex workers. Prevalence of anti-latex IgE in health-care workers is 9–18% compared with about 6% in unselected blood donors [55]. This higher rate of sensitization has been attributed to the institution of universal precautions in 1987 with the concomitant increased use of poorly manufactured rubber gloves coated with cornstarch [56]. Although many patients present with dermatitis, conjunctivitis, rhinitis, or asthma, life-threatening allergic reactions can be the initial presentation for latex allergy. Powdered gloves are the most allergenic because the powder acts as a vehicle for the latex proteins. Procedures performed on latex-sensitive persons are conducted in a latex-free environment. Latex is a natural product manufactured from the sap of the rubber tree and contains many proteins, several of which are allergenic in susceptible individuals. An important corollary is that fruit of other plants, particularly those of tropical origin, such as kiwi, banana, and avocado, contains similar proteins and can be cross-reactive. Cross-reactivity between latex and chestnuts, grass pollen, and ragweed pollen also has been reported. Seasonal rhinitis and food allergies are often present in latex-sensitive patients, and inadvertent exposure to specific foods can cause anaphylactic reactions [56].

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs can activate the immune system in both an IgE-dependent and an IgE-independent fashion. Typically IgE-dependent reactions to NSAIDs are to a specific drug, while the IgE-independent, or pseudoallergic, reactions are typically to all NSAIDs as a class. Urticarial and anaphylactic reactions to aspirin and NSAIDs tend to occur within minutes of oral ingestion [57]. Clinical manifestations of pseudoallergic reactions include bronchospasm and exacerbations of rhinosinusitis and occasionally urticaria or angioedema. Vascular collapse is not typically part of this picture, but bronchospasm can be profound [57]. Aspirin-induced bronchospasm occurs in 30–40% of asthmatics who have concomitant nasal polyps. The clinical syndrome of aspirin-exacerbated respiratory disease, or triad asthma, refers to patients with asthma, sinusitis with nasal polyposis, and sensitivity to aspirin and other NSAIDs. These reactions to NSAIDs manifest by upper and/or lower respiratory symptoms and can include rhinorrhea, conjunctivitis, periorbital edema, laryngospasm, and prolonged bronchospasm [57]. Since the type of reaction is typically to NSAIDs as a class, it suggests a central role for COX-1 inhibition, and although specifics of the pathophysiology are unknown, it seems to involve activation of macrophages, mast cells, and endothelial cells, leading to excessive production of vasoactive lipid-derived molecules (e.g., leukotrienes and prostaglandins) [57]. Increased production of leukotriene E₄, the terminal metabolic product of cystinyl leukotriene production, has been shown in the urine of these patients. Increased levels of a key enzyme, leukotriene synthase, have been shown in lung tissue from some of these patients. This finding suggests that when the cyclooxygenase pathway is inhibited, these patients may overproduce proinflammatory leukotrienes [58].

Radiographic Contrast Material

Reactions to radiographic contrast material have been discussed previously as the best example of a

non-IgE-mediated anaphylactic drug reaction. The most important approach to these reactions is to be prepared for them, to identify patients who have had previous reactions, and to premedicate or use low-ionic-strength contrast material in susceptible patients. One must be prepared because even without a history of previous reactions, 1–2% of patients have a systemic reaction, which can include cutaneous hives, angioedema, wheezing, and anaphylaxis. Severe reactions were rare in a large-scale Japanese study, occurring in 0.04–0.22% of the reactions and resulted in 1 death per 169,000 procedures [59]. History of a previous reaction to radiocontrast material is the best historical clue to predict a reaction. Of patients with a generalized reaction to a previous exposure, 17–35% react on a subsequent exposure at an increased risk of 8–35 times that of patients without a prior reaction [60]. Other less important risk factors that have been recognized include a history of asthma, a history of skin test positivity to common allergens, and a history of allergy to penicillin [59]. Factors that are NOT predictive of a reaction include a history of allergic reactions to seafood, history of cutaneous reactivity to iodine-containing skin disinfectants, parotid swelling after radiocontrast material administration, and a positive cutaneous reaction to radiocontrast material [1].

Pretreatment with diphenhydramine and prednisone (Table 4) reduces the frequency of repeat reactions to approximately 10% and reduces their severity. The combination of premedication and the use of low osmolar radiocontrast material in patients with a history of severe reactivity reduces the risk of systemic reaction to approximately 0.7% (Grade III) [61]. The use of β -blockers

Table 4 Management of patients at risk for reactions to radiographic contrast media

- | |
|--|
| 1. Remove any β -blockers if possible |
| 2. Have emergency therapy available |
| 3. Pretreat with prednisone 50 mg PO 13, 7, and 1 h prior to the procedure and diphenhydramine 50 mg IM or PO 1 h prior to the procedure |
| 4. For patients with a history of generalized anaphylaxis, pretreat and use a lower osmolar radiographic contrast medium |

interferes with the action of epinephrine and complicates resuscitation of patients from anaphylaxis. These agents should be stopped, if clinically possible, before radiocontrast material is administered. Table 4 lists recommendations for administration of radiocontrast material in susceptible patients [59].

Biologics

As mentioned at the beginning of the chapter, horse serum was used extensively in the first half of the twentieth century to treat a variety of infectious diseases and was associated with frequent immunologic reactions. More recently, purified polyclonal IgG, purified Fab fragments of polyclonal IgG, monoclonal IgG, and humanized monoclonal IgG have provided safer, biologically derived therapeutic agents. An example of a therapeutic material containing unfractionated horse globulins (not purified IgG) is black widow spider antivenin [62]. An example of a material containing predominantly polyclonal horse IgG currently in use is antithymocyte globulin [62]. Crotalidae polyvalent immune Fab and digoxin immune Fab antibody (sheep IgG) are produced from sheep by papain digestion of serum from immunized sheep and the subsequent isolation of the less immunogenic Fab portion of the antibody [28]. This preparation has replaced polyclonal horse IgG antivenin (Crotalidae) polyvalent for the treatment of crotaline snake bites.

Antithymocyte globulin is an effective treatment for severe, resistant aplastic anemia. Because this is purified equine IgG, there is ample opportunity for immune activation even in patients who have severely dysfunctional bone marrow and are leukopenic. In a prospective study of 35 patients treated for aplastic anemia, 86% developed serum sickness. Urticaria and anaphylaxis were rare, but one patient died [63, 64]. In a study of 43 patients receiving multiple courses of treatment, serum sickness occurred in 66% of the patients [65].

Antivenin Crotalidae polyvalent also has been associated with numerous case reports of acute allergic reactions and a reported incidence rate

ranging from 23% to 56% [28]. In a prospective study, the incidence of acute reactions to the potentially less immunogenic Crotalidae polyvalent immune Fab was 14%, and most of the events were of mild to moderate severity. Crotalidae polyvalent immune Fab has not been used as extensively as antivenin (Crotalidae) polyvalent, however, and these differences should be considered preliminary. Serum sickness also is seen with each of these agents, with reported rates between 15% and 86% of patients receiving antivenin Crotalidae polyvalent and 16% of patients receiving Crotalidae polyvalent immune Fab [28].

A postmarketing survey of the efficacy and safety of digoxin immune Fab included 717 patients with life-threatening digitalis intoxication treated in 487 hospitals. Six subjects had adverse reactions that probably or possibly were due to the Fab fragments. These reactions included pruritic rashes, angioedema, chills, and thrombocytopenia and occurred more frequently in patients with a history of allergic reactions. None of the reactions were life-threatening, and all resolved with cessation of the infusion and appropriate medical treatment [66].

Monoclonal antibodies have been useful clinically, although the first ones developed were murine monoclonal antibodies, which were associated with anaphylaxis in some patients [33]. To decrease the immune response against the murine monoclonal antibodies, chimeric and humanized monoclonal antibodies were engineered. Chimeric monoclonal antibodies are composed of murine variable regions fused onto human constant region, and humanized monoclonal antibodies are composed almost entirely of human antibodies, except for the hypervariable regions necessary to retain immunologic activity and bind antigen. Examples of chimeric monoclonal antibodies include infliximab (Remicade[®], antitumor necrosis factor- α) and rituximab (Rituxan[®], anti-CD20). Infusion reactions to the first infusion of rituximab including flushing, rash, and shortness of breath are common, and the mechanism is not well understood, although it is not thought to be IgE mediated [67]. One chimeric monoclonal antibody, cetuximab (Erbix[®], anti-epidermal

growth factor receptor), caused anaphylaxis with a geographical variation in the United States, with national rates of 6% or less but rates of over 20% in the southeastern United States [68]. The basis for this was determined to be an IgE-mediated anaphylaxis, with IgE directed against a specific carbohydrate, galactose- α -1,3-galactose (α -gal), on the Fab portion of the antibody [68]. This IgE directed against α -gal was present in serum even prior to the administration of cetuximab, and it was later determined that IgE specific for α -gal may have developed due to prior tick bites from the tick *Amblyomma americanum*, which has a geographic distribution that overlaps with areas of increased anaphylaxis to cetuximab [68, 69].

An example of a humanized monoclonal antibody is omalizumab (Xolair[®], anti-IgE), which is >95% human antibody. Despite this, there have been rare reports of anaphylaxis with omalizumab (0.09%) with some anaphylactic episodes that were delayed over 2 h after injection of omalizumab [70]. There have been reports of other types of immunologic reactions with other humanized monoclonal antibodies, including serum sickness with natalizumab (Tysabri[®], anti- α -4 subunit of integrin molecules).

Another approach has been to engineer novel proteins consisting of sequences for soluble human receptors and the Fc region of human IgG. The Fc region of IgG imparts a long half-life to these agents. An example is etanercept (US trade name Enbrel[®]), a fusion protein containing the extracellular ligand-binding portion of the human tumor necrosis factor receptor linked to the Fc portion of human IgG₁ [62]. Immune-mediated reactions to etanercept have been described and can include urticaria and vasculitis [33]. Finally, there are fully human monoclonal antibodies, produced in transgenic mice or via phage display library in bacteria, which allows for production of antibody without nonhuman components [71]. An example of human monoclonal antibody adalimumab (US trade name Humira[®], anti-TNF), which despite the fact that it is fully human, has still been associated with immediate infusion reactions

similar to etanercept and infliximab, which are not likely IgE mediated [72].

Differential Diagnosis

In a hospitalized patient who has had a severe systemic reaction, the main considerations are allergic reactions to drugs, blood products, foods, or latex, distinguishing these anaphylactic reactions from shock. Cutaneous eruptions, such as hives (with or without angioedema) or angioedema, are typical manifestations of an acute allergic reaction. In the acute setting, the presence of hives is the best predictor that a reaction is allergic although the absence of hives is not helpful [73].

Angioedema (with or without hives, localized or diffuse) may be due to an allergic reaction or to a known pharmacologic activity of a drug in a sensitive patient (NSAIDs or angiotensin-converting enzyme inhibitors). Other causes of angioedema need to be considered, however, including hereditary angioedema and acquired angioedema. These latter diseases are caused by deficiencies in the quantity or function of a protein called *C1 esterase inhibitor* and should not be accompanied by urticaria. C1 esterase inhibitor exerts regulatory control on complement activation and activation of vasoactive peptides called *kinins*.

Severe cutaneous eruptions may be due to drugs, infections, or intercurrent disease. Infections associated with severe dermatitis include upper respiratory viruses, cytomegalovirus, human immunodeficiency virus, Epstein-Barr virus, viral hepatitis, staphylococcal scalded skin syndrome, and *Staphylococcus aureus*-induced toxic shock syndrome. Concomitant collagen vascular diseases, lymphoma, porphyria, and syphilis also can be the cause of severe cutaneous eruptions (Table 5) [19, 48].

Crucial diagnostic concerns are distinguishing anaphylaxis from shock from other causes and recognizing pseudoallergic reactions when they occur. The possibility of a pseudoallergic reaction should be considered if a patient becomes symptomatic in the context of

Table 5 Differential diagnosis of immunologic reactions

Angioedema without urticaria
Hereditary angioedema
Urticaria with or without angioedema
Acute urticaria
Severe cutaneous eruptions
Upper respiratory viruses
Cytomegalovirus
Human immunodeficiency virus
Epstein-Barr virus
Viral hepatitis
Scalded skin syndrome
Toxic shock syndrome
Collagen vascular diseases
Lymphoma
Porphyria
Syphilis
Shock
Septic
Hypovolemic
Cardiogenic
Distributive, due to spinal cord injury
Flushing syndromes
Menopause
Carcinoid
Medullary thyroid carcinoma
Scombroid
Niacin ingestion
Others
Anxiety/panic attack
Vasovagal syncope
Neurologic event: seizure, stroke
Vocal cord dysfunction

administration of an agent known to cause this type of a reaction.

When one has determined that a specific reaction is an allergic or a pseudoallergic reaction, the work to determine the cause of the reaction begins. A decision regarding which of many suspects is the etiologic agent is not straightforward and often cannot be determined absolutely. As in all aspects of medicine, a detailed history is the beginning step. The history as it relates to a possible drug allergy must include a detailed analysis of all medications that have been used, including prescribed medications, over-the-counter medications, dietary supplements, and herbals. If the

reactions occurred in the operating room, exposure to latex may be important. In the emergency department, inadvertent exposure to foods in a patient with food allergy is a possible cause of a systemic reaction. The temporal relationship between administration of a suspected agent and the onset of the reaction is crucial. A history of a previous reaction to a suspected or chemically similar drug is useful, whereas a history of other allergies or a family history of a reaction to a given drug is not useful. For reactions with later onset, such as maculopapular rashes, other rashes, or serum sickness, temporal relationships may be much less clear.

The physical examination is useful because some manifestations are more typically “allergic” than others. In the acute setting, a patient with rapid onset of vascular collapse often can be recognized easily to be having an anaphylactic reaction because of associated urticaria. Other cutaneous presentations, such as maculopapular rashes, diffuse erythema, or the symptom of pruritus, are less specific, however, and there may be no cutaneous changes at all. Wheezing can be a prominent sign of anaphylaxis, although in the operating room, this may be manifest only as increased resistance to ventilation. Fever typically is not part of an acute allergic reaction (but it can be a manifestation of more delayed reactions, such as a drug fever or serum sickness), and its presence should raise the likelihood of sepsis.

Testing

In Vitro Tests

Results from general laboratory testing can be helpful. Elevated numbers of eosinophils generally indicate an allergic process. Antigen-specific IgE measurements are helpful if positive but have poor negative predictive value. Products from mast cells can be measured. Plasma levels of histamine increase rapidly (approximately 5–10 min) after an allergic reaction and return to baseline within 30 min. Plasma samples must be handled carefully and processed promptly. Determination of urinary *N*-methylhistamine in a 24-h collection beginning immediately after the onset

of a reaction can be helpful if the values are quite elevated. Levels of β -tryptase increase more slowly than serum histamine (peak at about 1 h) and stay elevated longer (3–4 h) [14]. These laboratory tests are complementary, but normal values do not rule out an allergic reaction. There is no value in ordering a total IgE level.

The syndromes of hereditary angioedema and acquired angioedema are due to abnormal complement pathway activation and need to be considered in patients with angioedema without urticaria. Typically, these syndromes have low levels of C4 between attacks and nearly absent C4 during attacks. The C4 level may help to differentiate these conditions from other causes of angioedema; however, by itself a low C4 is not diagnostic of hereditary angioedema. Complement activation occurs in a variety of conditions seen in the hospital, and the most appropriate diagnostic test for hereditary angioedema is to measure level and function of C1 esterase inhibitor.

In Vivo Tests

Skin tests can be useful diagnostic tools to distinguish among various possible etiologic agents that may have precipitated an allergic reaction; however, they have many limitations. One limitation is that for many drugs, the reactive species may be a metabolic product or a haptenated protein and not the original drug itself. The best-characterized skin tests are those for penicillins, but they are suboptimal because the minor determinant mix is not commercially available.

To perform skin prick tests, one first must determine if the patient can react appropriately to skin tests by placing a positive (histamine) and negative (saline) control. The main cause of lack of reactivity to the positive control is recent administration of an antihistamine, but conditions such as uremia also give a false-negative reaction to histamine. The most common cause of unexpected reactivity to the negative control is inappropriate activation of dermal mast cells by the physical stimulus of pricking the skin. This activation occurs in patients who have dermatographism. One cannot interpret skin tests in patients when the positive control is negative or the negative control is positive. For penicillin testing, it first should be established that

the patient can mount a skin response to histamine that is substantially (>3 mm wheal with erythema) more than the saline control. Then skin tests should be performed to the drug in question. Skin tests for other drugs are useful if positive, but if negative they do not exclude the possibility of an allergy to the tested drug, and the gold standard is to perform a challenge to the drug after negative skin testing. Tests for IgE-mediated processes have no predictive value for non-IgE-mediated immunologic reactions, including serum sickness, and dermatologic reactions, including morbilliform rashes and severe cutaneous adverse reactions.

Treatment

Anaphylaxis

Treatment of anaphylaxis requires the immediate intramuscular administration of epinephrine, in the mid-anterolateral thigh to maximize absorption. Typically the dose is 0.3 mg of a 1:1000 (1 mg/mL) solution, and epinephrine may be readministered 5–15 min later if needed. Another important measure is ensuring the patient is supine and not sitting or standing (Grade II-2) [19]. Intravenous access should be established with large-bore intravenous catheter(s) for infusion of intravenous fluids if needed, and high-flow supplemental oxygen should be given [19, 24]. Vital signs should be monitored regularly, and, if needed at any time, cardiopulmonary resuscitation according to current advanced cardiac life-support guidelines should be followed (Fig. 3). Adjunctive treatments include antihistamines and corticosteroids, which may be useful but should not be used instead of epinephrine (Grade III). Diphenhydramine (US trade name Benadryl[®]), 0.5 to 1 mg/kg up to 50 mg intravenously or intramuscularly, and methylprednisolone (US trade name Solu-Medrol[®]), 1 mg/kg intravenously, may also be given. Other treatments that may be helpful include nebulized albuterol for bronchospasm, as well as racemic epinephrine via nebulizer, especially in the cases for treatment of laryngeal edema or severe bronchospasm. The ameliorative effect of epinephrine



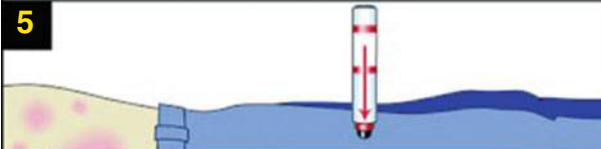

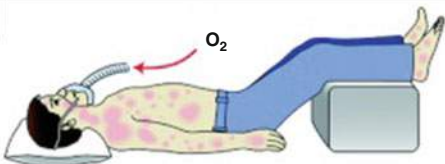
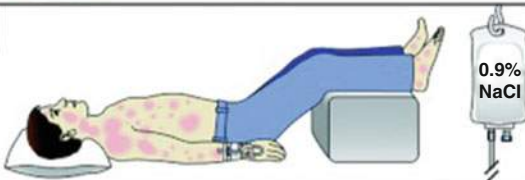

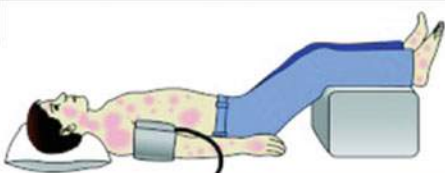
1	Have a written emergency protocol for recognition and treatment of anaphylaxis and rehearse it regularly.
2	Remove exposure to the trigger if possible, eg. discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.
3	 <p>Assess the patient's circulation, airway, breathing, mental status, skin, and body weight (mass).</p>
4	 <p>Promptly and simultaneously, perform steps 4, 5 and 6.</p>
5	 <p>Inject epinephrine (adrenaline) intramuscularly in the mid-anterolateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution, maximum of 0.5 mg (adult) or 0.3 mg (child); record the time of the dose and repeat it in 5–15 minutes, if needed. Most patients respond to 1 or 2 doses.</p>
6	 <p>Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; fatality can occur within seconds if patient stands or sits suddenly.</p>
7	 <p>When indicated, give high-flow supplemental oxygen (6–8 L/minute), by face mask or oropharyngeal airway.</p>
8	 <p>Establish intravenous access using needles or catheters with wide-bore cannulae (14–16 gauge). When indicated, give 1–2 litres of 0.9% (isotonic) saline rapidly (e.g. 5–10 mL/kg in the first 5–10 minutes to an adult; 10 mL/kg to a child).</p>
9	 <p>When indicated at any time, perform cardiopulmonary resuscitation with continuous chest compressions.</p>
10	 <p>In addition,</p> <p>At frequent, regular intervals, monitor patient's blood pressure, cardiac rate and function, respiratory status, and oxygenation (monitor continuously, if possible).</p>

Fig. 3 Treatment of anaphylaxis (From Ref. [19])

in anaphylaxis is mediated predominantly through β_2 -receptors, and the concurrent treatment of a patient with nonselective and selective β -blockers can interfere with its effect. Patients who have anaphylaxis while on a β -blocker are notoriously difficult to treat. In this setting, glucagon is given, 1 to 5 mg intravenously as a bolus followed by an infusion of 5–15 $\mu\text{g}/\text{min}$ titrated to the clinical response (Grade III) [14]. The effects of epinephrine may give a false sense of security; close monitoring and support are necessary after the initiation of a reaction since protracted and biphasic patterns of anaphylaxis occur.

Angioedema

Compromise of the airway constitutes a medical emergency. A patient with angioedema due to either an allergic reaction or lack of C1 esterase inhibitor activity may experience closure of the larynx. Intubation in this situation is difficult and may be unsuccessful, and the local trauma of an unsuccessful intubation may make angioedema worse. In this situation, it is essential to act as soon as the problem is recognized and to be ready to perform an emergency cricothyrotomy. Specific treatments that target the pathway of bradykinin-mediated angioedema have been developed and are useful in treatment of hereditary and ACE-inhibitor-induced angioedema. Treatment with the bradykinin B2 receptor antagonist icatibant (US trade name Firazyr[®]) significantly shortens the time for improvement in those with ACE-inhibitor angioedema from 11.7 h to 2.0 h, when compared with steroid and antihistamine treatment. Icatibant also reduced the median time to complete symptom resolution from 27.1 h to 8.0 h (Grade I) [74].

Severe Cutaneous Adverse Reactions

The most important treatment for severe cutaneous adverse reactions is identification and removal of the offending agent. Supportive care including transfer to a burn unit in the case of TEN may be necessary. Corticosteroid use in SJS is controversial and is contraindicated in TEN.

Intravenous immune globulin, or IVIG (dosed at 0.5 g to 1 g/kg/day for 3–4 days), has been studied for treatment of TEN, and results have been mixed, without clear evidence of benefit (Grade III) [33, 75]. Anti-TNF agents have some limited evidence of potential benefit in treatment of TEN (Grade III) [33]. For DRESS/DiHS, if there is not severe organ involvement, management with supportive care and topical steroids alone may be adequate (Grade II-2) [76]. If there is evidence of severe organ involvement, administration of prednisone 0.5 mg to 2.0 mg/kg/day has been used (Grade III). Once clinical improvement occurs, a very gradual tapering of steroids may help reduce the risk of rebound symptoms (Grade III) [77].

Readministration of the Drug via Desensitization

Avoidance of the offending agent is the simplest approach, but there are clinical settings in which administration of the offending drug is clearly indicated. An example is treatment of a pregnant woman who is allergic to penicillin and has syphilis. In this case, there is no acceptable alternative and desensitization is necessary.

Desensitization is a potentially life-threatening procedure that should be performed only by physicians with substantial experience, such as allergy/immunology specialists, and should be done in carefully controlled settings. The most extensive experience in desensitization to drugs is with β -lactam antibiotics, although this approach has been generalized to include many other agents. In general, patients with acute systemic reactions (urticaria or anaphylaxis) are good candidates for desensitization because there is good reason to think that their reactions are mediated by IgE. Patients with positive skin tests to the suspect drug are likely at greater risk than patients with negative skin tests. The presence of a negative skin test is not a guarantee, however, that the patient can tolerate the drug.

To perform desensitizations, the patient is placed in a setting that allows careful monitoring. After informed consent is obtained, an initial dose

of the drug that is approximately 10,000-fold less than the therapeutic dose is administered, and the patient is observed for a period of time. Incremental doses are administered until the therapeutic dose is achieved. Desensitization is maintained only as long as the drug is administered on a frequent basis. Patients with atypical reactions (e.g., morbilliform rashes) to agents known to cause IgE-mediated reactions and negative skin tests often are not desensitized but rather are given test doses (1/10 of a full dose) in a controlled setting because the index of suspicion of an IgE-mediated allergic reaction is not high. Drugs which caused severe cutaneous adverse reactions are not good candidates for desensitization. Examples of agents for which desensitization is not used are antiepileptic drugs in patients who have had severe cutaneous reactions. There is a strong relative contraindication to desensitizing patients to sulfa drugs especially in patients who are not immunosuppressed. Although the cutaneous reactions to sulfa drugs may either be T-cell mediated or not immune mediated, patients who are immunosuppressed may have successful desensitization to sulfa drugs. Trimethoprim-sulfamethoxazole has been administered successfully (using a desensitization protocol) to patients with human immunodeficiency virus and to patients who are status post-lung transplantation (Grade III) [78, 79].

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The use of mind-altering substances predates written history. As a consequence, so do the withdrawal syndromes associated with the abrupt cessation of these substances. The discussion of withdrawal requires defining the following terms: *narcotic*, *tolerance*, *dependence*, *addiction*, *withdrawal*, and *cross-tolerance*. Defining these words not only allows for better understanding but also enables the appropriate application of these terms (Fig. 1). *Narcotic* literally means any drug that induces sleep, although it also has the socio-legal implication of an illegal substance. For the purpose of maintaining clarity, drugs should be referred to by their clinical class (i.e., opioids, sedative-hypnotics, and stimulants [e.g., cocaine and amphetamines]). *Tolerance* is the process by which increasing drug dosages are required to obtain a desired effect and can be represented graphically by a shift in the dose-response curve to the right. This effect is exemplified by heroin tolerance, in which a tolerant person's routine dose would be lethal to a naïve user. Tolerance can be mediated via receptor modulation (opioids), induced metabolism (barbiturates), or both (ethanol). *Dependence* implies that cessation of the drug leads to withdrawal symptoms. *Withdrawal* can be physical (i.e., autonomic instability, nausea, vomiting, diarrhea, hyperactivity, or altered mentation), psychological (i.e., emotional symptoms and craving), or both. Withdrawal is a response to lowered drug concentrations resulting in a predictable constellation of symptoms (e.g., tremor,

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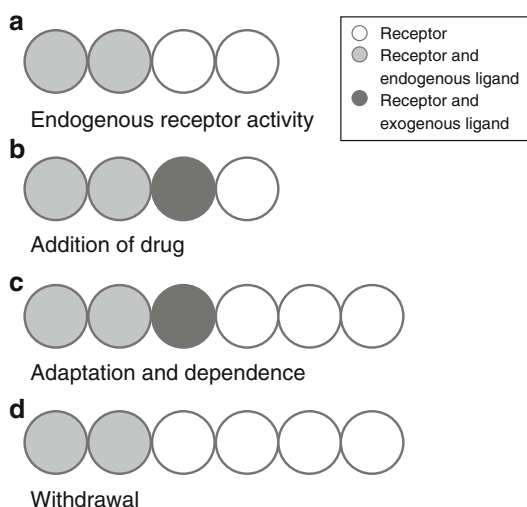


Fig. 1 Schematic representation of receptor activity

hypertension, nausea, vomiting, and diarrhea). These symptoms are reversible if the drug in question is reintroduced. Not all withdrawal symptoms are negative or unpleasant. Piloerection, yawning, and lacrimation are associated with opioid withdrawal, but most patients do not perceive these symptoms as negative compared with their drug craving, nausea, and vomiting. When continued use of a drug induces socially unacceptable behavior (theft) or results in unacceptable outcomes (a driving-while-intoxicated conviction), the user of the drug is considered *addicted*.

Understanding *cross-tolerance* is the key to treating most withdrawal syndromes. The concept is that two different drugs share enough common receptor or metabolic activity such that one drug can be substituted for the other to prevent or treat withdrawal. This principle is most important for treatment of withdrawal from heroin/other opiates/opioids, alcohol, benzodiazepines, barbiturates, baclofen, and more recently γ -hydroxybutyrate (GHB) or its analogues γ -butyrolactone (GBL) and 1,4-butanediol.

The nature of withdrawal and self-treatment behavior makes it impossible to describe its actual incidence. It would be expected that most dependent users go through mild withdrawal every day. The alcoholic who awakens in the morning and

drinks an “eye-opener” may best exemplify this concept. Current estimates state that almost 17 million adult Americans are alcoholics, with a 2:1 male-to-female ratio [1]. It is estimated that 2,000,000 Americans are either opioid dependent or opioid abusers, only 15% of whom are in methadone maintenance programs [2]. More recently, GHB and GBL abuse and dependence have been described, but this remains unquantified. Benzodiazepines are some of the most commonly prescribed drugs worldwide. Tolerance to any of these drugs can lead to withdrawal, and in the case of alcohol and the sedative-hypnotics (including GHB/GBL), withdrawal can be life-threatening.

History

Spanish physicians described symptoms consistent with delirium tremens (DTs) in the first half of the nineteenth century [3]. Seven clinical cases were reported in the 1840s and were referred to as *alcoholic chorea* or *ataxis fever*. These patients received various treatments ranging from bleeding with leeches to tincture of opium. The differential diagnosis at that time included epilepsy and meningitis.

In North America, Osler [4] reportedly recognized DTs as a complication of alcoholism in the early part of the twentieth century. His recommended treatment consisted of chloral hydrate, potassium bromide, hyoscine, opium, cessation of alcohol, and bed rest. Around 1919, Victor and Adams [5] credited Mellanby as being “among the first to become cognizant of the immediate adjustments of the nervous system to alcoholic intoxication.” Alterations to Osler’s treatment included the addition of restraints, paraldehyde, and strychnine or ergots to control tremor. Despite these innovations, mortality remained around 14%. It was not until the early 1950s with the work of Victor and Adams [5] and Isbell and colleagues [6] that DTs was uniformly accepted as a manifestation of alcohol abstinence. At the same time, treatment regimens began to focus on rehydration, substrate supplementation, and supportive care. By the early 1960s, mortality

approached 5.4% at Philadelphia General Hospital [7]. Studies in the 1960s comparing paraldehyde and antipsychotics showed a 35% mortality rate with promazine versus a 4.5% mortality rate with paraldehyde [8]. In 1975, benzodiazepines were compared with paraldehyde, and a demonstrable benefit was recognized for this new class of drug in the treatment of alcohol withdrawal. Since 1976, the mortality of alcohol withdrawal has been expected to approach zero, unless insufficient therapy is provided [9]. Mortality still results from common medical conditions that force alcohol abstinence. Pancreatitis, pneumonia, head trauma, and peptic ulcers commonly precede alcohol withdrawal [10]. A delay in diagnosis and treatment of these entities because of a focus on the highly visible manifestations of withdrawal can result in significant morbidity and mortality.

Mind-altering agents can occur naturally and can also be synthesized. As new agents are developed, the potential for abuse, dependency, and withdrawal exists. GHB use has increased since the 1980s [2]. Meanwhile, the use of cocaine in the United States has declined from its peak of 5.7 million users in 1985 to 1.7 million in 2012 [2]. By contrast, heroin use has been on the rise. Based on the 2012 US National Survey on Drug Use and Health, 467,000 Americans are addicted to heroin. In addition, the survey estimated that there are 2.1 million Americans with substance use disorders related to prescription opioids. Globally, it is estimated that there are 27 million people that use drugs on a regular basis (dependence), of which 12.7 million use the injectable route for administration [11]. International opioid use has also grown significantly, especially in Eastern and Southeastern Europe, South Asia, and Oceania [11]. A basic understanding of the pathophysiology of withdrawal and its treatment has general applicability to any withdrawal syndrome, new or well known.

Pathophysiology

Withdrawal is a phenomenon of altered neurochemistry with the central nervous system (CNS) as the most consequential target. Under normal

conditions, the CNS maintains a balance between excitation and inhibition. Although there are several ways to achieve this balance, excitation is usually constant, and actions occur through removal of inhibitory tone [11–13]. Two major neurotransmitters in the CNS are glutamate and γ -aminobutyric acid (GABA). Glutamate's effects at the *N*-methyl-D-aspartate (NMDA) receptors increase intracellular calcium, resulting in excitation [14]. Stimulation of GABA-A receptors increases inhibitory tone via chloride (Cl^-) channel opening. This Cl^- channel is surrounded by receptors, which when activated exert various effects on the channel. In the presence of GABA, stimulation of the benzodiazepine receptor increases the frequency of Cl^- channel opening, depolarizing, and thus inhibiting the cell (Fig. 2) [15]. The barbiturate receptor increases the duration of Cl^- channel opening, resulting in a similar effect [15]. Although this action is facilitated by the presence of GABA, the anesthetic barbiturates can depolarize the cell even in the relative absence of GABA. GHB appears to exert its effect via the GABA-B receptor, but there is evidence of a G protein-mediated GHB receptor as well [16]. Although it previously was unclear how certain agents (alcohol, propofol, and inhaled anesthetics) interacted with the GABA-A receptor, there is now mounting evidence that these drugs work via binding specific amino acid residues on ligand-gated ion channels to enhance receptor function [17, 18]. Most notable, chronic alcoholism causes a shift in GABA-A receptor subunits such that the α_1 subunit is under-expressed and the α_4 and γ_1 subunits are over-expressed [19]. This conformational change defines dependence and cross-tolerance to benzodiazepines [19].

The most studied excitatory receptor in the CNS is the NMDA receptor. This receptor controls a voltage-gated and ligand-dependent Ca^{2+} channel. Calcium and sodium influx result in cell depolarization, causing CNS stimulation. Many drugs act as NMDA receptor antagonists, including ethanol, ketamine, phencyclidine, and dextrophan, the metabolite of dextromethorphan [20–23].

Finally, opioids stimulate the opioid receptor subtypes μ , κ , and δ to varying extents. Although

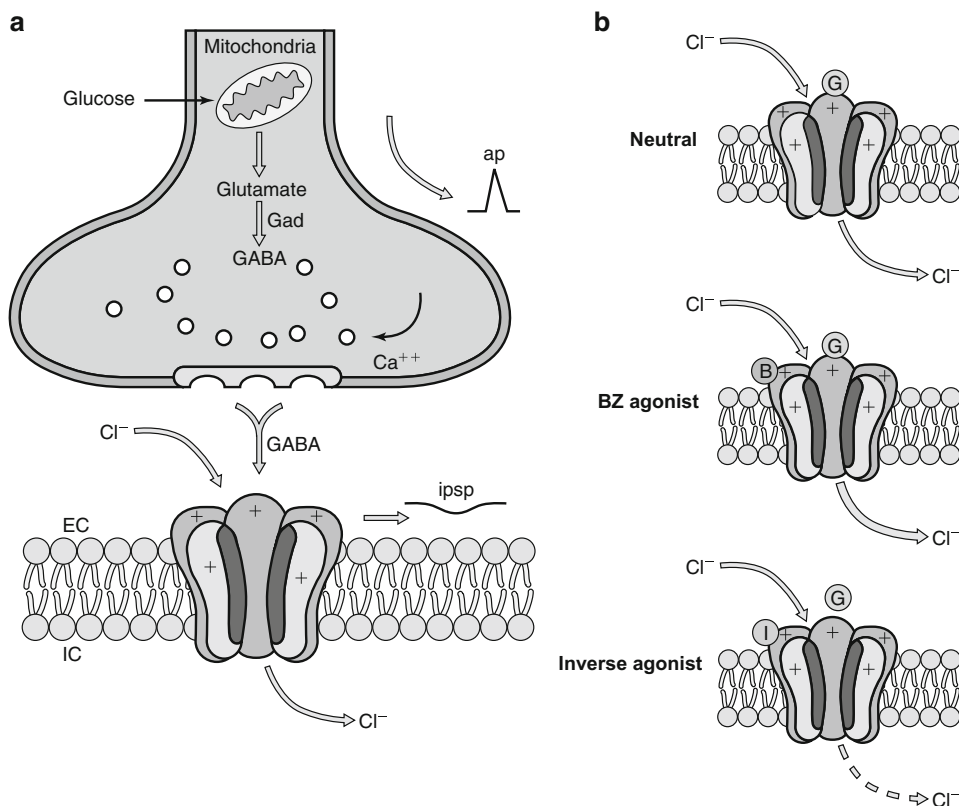


Fig. 2 Idealized model of γ -aminobutyric acid (GABA)-benzodiazepine (BZ)-chloride (Cl^-) channel at axosomatic (postsynaptic) inhibitory synapses. (a) Presynaptic and postsynaptic elements; *ap* action potential, *Gad* glutamic acid decarboxylase, *EC* extracellular, *IC* intracellular, *ipsp* inhibitory postsynaptic potential. (b) GABA-BZ receptor interactions influencing permeability of chloride channels. Neutral: GABA receptor binds GABA (G) with moderate affinity in the absence of BZ ligand. BZ agonist:

direct BZ agonist (B) enhances GABA affinity for its receptor, resulting in maximal chloride permeability. Inverse agonist: inverse agonists bound to BZ receptor result in poor GABA affinity and markedly reduced chloride permeability (From Rech RH: *Drugs to treat anxieties and related disorders*. In Brody TM, Larner J, Minneman KP: *Human Pharmacology: Molecular to Clinical*, 3rd ed. St. Louis, Mosby, 1998, p 367, with permission)

there are many different opioids available, the common pathway for the development of dependence is stimulation of the μ receptor. Stimulation of opioid receptors by opioids begins a cascade of events, mediated via G proteins, that alter the cell's conductance and decrease intracellular adenylyl cyclase [24]. Outward potassium channels are activated, decreasing intracellular potassium, hyperpolarizing the cell, and inhibiting its activation [25, 26]. The decrease in adenylyl cyclase results in less cyclic adenosine monophosphate (cAMP), preventing protein kinase-mediated activation of Ca^{2+} influx

(Fig. 3) [27]. The net result is to hyperpolarize the cell and prevent neurotransmission of glutamate and substance P, which manifests clinically as CNS depression and analgesia.

Chronic receptor alteration by a drug results in changes in the receptors such that a constant concentration of that drug is needed to maintain normal baseline neuronal activity. When the drug is stopped abruptly, or as the serum concentration drops below threshold, the patient manifests withdrawal symptoms specific to the class of drug used. For sedatives, the result is noradrenergic hyperactivity in the locus caeruleus. This

hyperactivity may be produced by enhanced NMDA activity or decreased GABA-A tone. CNS excitation is the end result and leads to altered mental status, hyperactive muscular activity with resultant hyperthermia, and rhabdomyolysis [28].

Chronic opioid use leads to cellular and synaptic adaptations. These adaptations include

desensitization and internalization, or down-regulation, of receptors (removal of surface receptors), leading to tolerance [29, 30]. In addition to these processes, counteradaptation occurs. Activation of the nuclear transcription factor CREB (cAMP-responsive element-binding protein) increases the expression of adenylyl cyclase in the locus caeruleus, which may explain the autonomic hyperactivity that occurs in opioid withdrawal [31]. These compensatory changes also are a form of tolerance, increasing cellular excitability and requiring the presence of the drug to maintain basal activity. The best-studied adaptation is the CREB-mediated increase in adenylyl cyclase, which results in Ca^{2+} influx and cellular depolarization. In this excitable state, the user experiences withdrawal when opioid use is discontinued or when an opioid antagonist, such as naloxone, is administered.

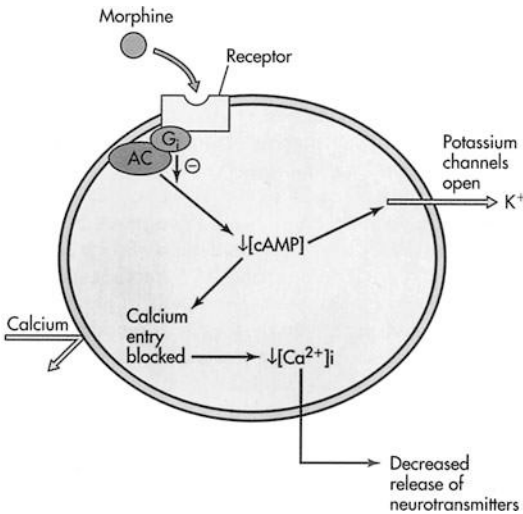


Fig. 3 Mechanism of action of opioids on neurons. Opioid receptors μ , δ , and κ are coupled negatively to adenylyl cyclase by G proteins (G_i). Activation of an opioid receptor by an agonist decreases activity of adenylyl cyclase, resulting in a decrease in the production of cyclic adenosine monophosphate (*cAMP*). This leads to an increase in the efflux of K^+ (primarily with μ and δ opioid receptors), cellular hyperpolarization, a decrease in the influx of Ca^{2+} (primarily with κ opioid receptors), and lower intracellular concentrations of free calcium. The overall consequence is a decrease in the neuronal release of neurotransmitters. Opioid receptors also may be coupled by G proteins to intracellular second messengers other than cAMP (From Brody TM, Larner J, Minneman KP: Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, with permission)

Toxic Effects: Withdrawal Syndrome

Although there is a great deal of overlap between different substances and their associated withdrawal syndromes, several drugs are discussed individually. These syndromes are alcohol, sedative-hypnotics (including GHB/GBL), opioids, and cocaine (Table 1). Finally, the unique aspects of neonatal withdrawal syndromes are discussed.

Alcohol Withdrawal

Alcohol withdrawal is one of the most common withdrawal syndromes, after those of nicotine and caffeine. The alcohol withdrawal syndrome is multifaceted and should be considered a spectrum. The discrete aspects of alcohol withdrawal

Table 1 Vital signs and mental status changes in withdrawal

	Opioids	Sedative-hypnotics ^a	Alcohol	Cocaine
Heart rate	↑	↑↑	↑↑	↓
Blood pressure	↑	↑↑	↑↑	↓
Respiratory rate	↑	↑↑	↑↑	↓
Hyperthermia	—	+	+	—
Altered mental status	—	±	±	—

^aIncludes benzodiazepines, barbiturates, and γ -hydroxybutyrate/ γ -butyrolactone

can follow a progression or occur independently. These aspects include alcoholic tremulousness, withdrawal seizures, hallucinosis, and DTs. These terms are preferred to the original terms described in the works of Victor and Adams [5] because they are less confusing. It may be more clinically relevant, however, to describe withdrawal as mild, moderate, or severe (life-threatening). Each aspect of alcohol withdrawal is discussed separately, with the understanding that they all are part of a single syndrome.

Alcohol withdrawal (previously called “alcoholic tremulousness”) typically begins within a few hours after cessation of drinking, when serum ethanol concentrations fall below a threshold level. This level varies with the degree of tolerance the patient has developed. The initial features are usually mild, and tremor is a common symptom. Other accompanying features variably include tachycardia, hypertension, diaphoresis, and anxiety [5, 6]. Intervention at this point may halt the progression or development of more significant symptoms and complications.

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures (previously called “rum fits”) usually occur within 6–48 h after cessation of drinking, although they may occur later. The syndrome is typified by a single brief, generalized seizure with a short postictal period. Occasionally the patient has multiple short seizures over a brief period, but true status epilepticus occurs in less than 3% of cases [5]. Alcohol withdrawal seizures may be the initial manifestation of withdrawal and the sentinel event in approximately one-third of untreated patients who develop DTs [5].

Alcoholic Hallucinosis

In alcoholic hallucinosis, the hallucinations are typically visual or auditory and may be persecutory in nature. Onset is often within a few hours of abstinence. Alcoholic hallucinosis can occur independently of other signs or symptoms of withdrawal [5]. Although patients experience hallucinations, their mentation is otherwise clear. As such, the hallucinations often are disturbing in the otherwise functional and oriented patient.

Delirium Tremens

DTs is the best studied of all the withdrawal syndromes. The term *delirium tremens* not only applies to alcohol withdrawal but also serves as a model for all forms of sedative-hypnotic withdrawal (including GHB/GBL). Symptoms develop 24 h or more after the last drink and usually last 3–5 days [5]. As the name implies, *delirium* is an important aspect of DTs. During mild withdrawal, or shortly after a “rum fit,” the patient’s mental status generally is intact. An altered sensorium is one of the key distinguishing features of DTs. Patients may hallucinate, have seizures, and display extreme psychomotor agitation (tremens). Hallucinations can be visual or tactile (formication). Autonomic instability may manifest as hypertension, tachycardia, diaphoresis, miosis, and hyperthermia. Psychomotor agitation and autonomic instability associated with DTs represent the life-threatening aspects of alcohol withdrawal and should prompt aggressive therapy.

Sedative-Hypnotic Withdrawal

Sedative-hypnotic withdrawal (benzodiazepines, barbiturates, and GHB/GBL) may be clinically indistinguishable from alcohol withdrawal. The chronology may offer a clue, however, as to the etiology of the withdrawal. Because of rapid metabolism and the lack of active metabolites, GHB/GBL withdrawal generally occurs within 2–3 h of cessation of drug usage [32]. Seizures do not seem to be a common manifestation of GHB withdrawal. In a series of eight cases of presumed GHB withdrawal, only one patient had seizure-like activity, which was a preterminal event [32]. In this same series, patients had notable neuropsychiatric effects including paranoia and delirium, also the withdrawal syndrome was often protracted, and patients were given antipsychotics in addition to benzodiazepines (Grade III evidence). In contrast to the rapid onset of GHB withdrawal, diazepam has active metabolites, and withdrawal symptoms may not manifest for 1 week after cessation. Seizures are a common sign of benzodiazepine withdrawal.

Benzodiazepine withdrawal responds promptly to treatment with benzodiazepines (Grade II evidence), and GHB withdrawal may respond variable to this treatment. Other treatment options for GHB withdrawal include propofol and baclofen (Grade III evidence) [32].

Opioid Withdrawal

Opioid withdrawal can be divided into physical signs and symptoms and psychological symptoms. Piloerection, yawning, and lacrimation are some of the physical signs; nausea, vomiting, and diarrhea are common symptoms. These patients also have intense opioid craving associated with the feeling of being unwell. In contrast to sedative-hypnotic withdrawal, opioid withdrawal is associated with minimal autonomic instability. Patients may be slightly tachycardic and have minimal elevation in blood pressure, but this is partly in response to their physical and emotional symptoms. Opioid withdrawal is almost always associated with a normal mental status. Needle use in heroin abusers predisposes them to many infections, including CNS infections. Attributing fever and an altered mental status to opioid withdrawal could have catastrophic results. Opioid withdrawal, although thoroughly unpleasant, is unlikely to be life-threatening unless complicated by aspiration pneumonitis or complications of vomiting and diarrhea such as fluid and electrolyte abnormalities. The onset and duration of withdrawal secondary to opioid discontinuation depend on the agent in question. Heroin withdrawal can begin within 6 h of the last dose, peak by 48 h, and last 4–5 days. Although methadone withdrawal begins 2–3 days after the last dose and may last 2 weeks [33], iatrogenic opioid withdrawal can occur immediately after administration of an antagonist (such as naloxone or naltrexone) or a partial agonist (such as buprenorphine). This type of opioid withdrawal is most commonly associated with naloxone use and is short-lived as the duration of action of naloxone is limited (approximately 40–60 min) and usually requires no intervention. With withdrawal induced by longer-acting antagonists or

partial agonists, altered mental status may occur because of the abrupt, severe, and prolonged nature of the withdrawal.

Cocaine Withdrawal

Cocaine withdrawal is associated with an emotional component, whereas the existence of a physical component is debatable. The emotional component is associated with intense craving. This craving is the significant component of cocaine addiction and is the reason why detoxification from cocaine is more rehabilitation oriented. The “washed-out” syndrome that can occur after prolonged cocaine use may be interpreted as physical withdrawal symptoms. [34] Because this phenomenon is not prevented by continued cocaine use, defining it as withdrawal is debatable [35]. The chronic use of cocaine depletes presynaptic neurotransmitter stores, especially dopamine, leaving the user catecholamine depleted [36, 37]. As a result, baseline adrenergic activity is diminished, and patients may appear lethargic or adynamic with depressed vital signs. This effect usually is self-limiting and requires minimal if any supportive care.

Neonatal Withdrawal

Maternal addiction can lead to neonatal withdrawal. Time to clinical signs after birth varies with the agent in question. Neonatal alcohol withdrawal typically begins within 3 days of parturition and is manifested by opisthotonos, tremor, nystagmus, clonus, seizures, hypertonia, crying, hyperactive or asymmetric reflexes, excessive rooting (an oromotor reflex), diarrhea, vomiting, startle, and inability to thermoregulate [38, 39]. Opisthotonos and abdominal distention rarely occur in opioid withdrawal and can help differentiate the two when the mother is dependent on multiple substances. Although initially thought to occur only as a complication of fetal alcohol syndrome, neonatal alcohol withdrawal can occur independent of the fetal alcohol syndrome [39]. The presentation of neonates withdrawing from sedative-hypnotics would be indistinguishable. Regardless of the etiology, treatment remains the same.

The development of neonatal opioid withdrawal symptoms depends on the agent used by the mother. Heroin withdrawal typically begins in the first few days, whereas methadone withdrawal may not be evident for 10–14 days [40]. Neonatal and adult opioid withdrawal are similar. In addition to vomiting, diarrhea, irritability, yawning, sleeplessness, diaphoresis, lacrimation, tremor, and hypertonicity, neonates can have seizures, a high-pitched cry, skin mottling, and excoriation. These latter signs and symptoms are more typical of opioid withdrawal and rarely occur with neonatal alcohol withdrawal [38].

Differential Diagnosis

Most dependent users are skilled at treating their own withdrawal. While constructing a differential diagnosis for substance withdrawal, the clinician should try to elucidate the circumstances surrounding the patient’s withdrawal. Although lack of finances and lack of availability are common reasons to develop withdrawal, patients often have an underlying illness that prevents “self-medication.” An alcoholic patient may have pancreatitis, pneumonia, head trauma, CNS infections, or gastrointestinal hemorrhage [10]. Undiagnosed medical disorders may contribute significantly to mortality despite adequate therapy. Additionally, complications of alcohol withdrawal can be catastrophic. Besides hyperthermia and a myriad of metabolic complications, myocardial infarction may occur secondary to the physical stress associated with withdrawal.

Many disorders may be mistaken for alcohol withdrawal. Among them are thyroid storm, hypoglycemia, encephalitis, and to a lesser extent serotonin toxicity and neuroleptic malignant syndrome (Table 2). Also, certain toxins can mimic withdrawal symptoms. Sympathomimetic toxicity can present in a manner similar to sedative-hypnotic withdrawal, creating the same diagnostic dilemma. The anticholinergic patient may present with hallucinations, tachycardia, and hyperthermia. Symptomatic overdose of certain drugs may mimic substance withdrawal; these agents

Table 2 Nontoxic differential diagnosis of alcohol and sedative-hypnotic withdrawal

Encephalitis
Hypomagnesemia
Hypoglycemia
Meningitis
Pneumonia
Thyrotoxicosis

Table 3 Toxins that may mimic alcohol and sedative-hypnotic withdrawal

Agents causing neuroleptic malignant syndrome
Amphetamines
Anticholinergics
Caffeine
Carbamates
Cathinones
Clenbuterol
Cocaine
Lithium
Organophosphates
Salicylates
Serotonergic drugs (serotonin toxicity)
Theophylline

include lithium, aspirin, and caffeine or theophylline (Table 3).

Diagnostic Studies

The diagnosis of withdrawal cannot be established without first excluding the other life-threatening disorders in the differential diagnosis. All patients in withdrawal should have serum analysis performed for standard chemistries, including glucose, magnesium, and calcium. Patients may have underlying metabolic derangements stemming from poor nutritional status or from vomiting and diarrhea. A complete blood count should be performed to assess the status of all cell lines because bone marrow suppression and occult hemorrhage are common afflictions in alcoholic patients. An elevated white blood cell count does not necessarily indicate infection, as it may be a marker of a stress response. Liver

function tests and coagulation assays are important in alcoholic patients, the latter to determine their synthetic function. A serum ethanol concentration may be a helpful prognostic tool because patients in alcohol withdrawal with elevated ethanol concentrations tend to have more severe withdrawal and are less likely to be compliant with outpatient detoxification programs [41].

A chest radiograph and computed tomography (CT) scan of the head are essential in the evaluation of the withdrawal patient with altered consciousness or seizures. A chest radiograph can help exclude pneumonia, whereas a CT scan of the brain can show subdural hematomas, cerebral edema, and other intracranial pathology that may be mistaken for delirium [42]. When symptoms are consistent with central nervous system (CNS) infection, a lumbar puncture is necessary to exclude the diagnosis. A CT scan of the brain also should be part of the evaluation of anyone presenting with new-onset seizure before the diagnosis of an alcohol withdrawal seizure is established [43]. An abdominal CT scan can help identify other disorders in the differential diagnosis of withdrawal, including pancreatitis, cholecystitis, and intestinal obstruction.

Treatment

In the past, numerous regimens were used to treat withdrawal. Mild withdrawal can be remedied by self-administration of the offending agent. When a patient is admitted for withdrawal or develops withdrawal as an inpatient, physicians must be aware of all treatment options. Logically, withdrawal responds best to reinstitution of the particular agent in question. Heroin and alcohol withdrawal present ethical dilemmas, however. Although some institutions may accept treatment of alcohol withdrawal with alcohol, most clinicians would find this treatment as enabling the underlying disorder, alcoholism [44]. Treatment with alcohol not only does not promote rehabilitation but also contributes to all the health risks associated with chronic alcohol use, including cirrhosis, pancreatitis, hepatitis, gastritis, and bone marrow suppression. The principle of cross-tolerance may be

applied in this instance. Benzodiazepines show therapeutic effect to varying extents for sedative-hypnotics, alcohol, and GHB/GBL. The safety and efficacy of benzodiazepine-based withdrawal therapy were borne out in studies performed in the mid-1970s [45]. Benzodiazepines are excellent anticonvulsants. Current practice guidelines for the treatment of alcohol withdrawal use benzodiazepines as first-line therapy (Grade I) [46].

Ethanol Withdrawal

Mild-to-moderate ethanol withdrawal usually responds well to low-dose oral benzodiazepines. Treatment regimens vary, and fixed-schedule treatments are common. Studies demonstrate, however, that “front-loading” benzodiazepines relieves withdrawal symptoms faster [47, 48]. In these studies, oral diazepam was given to patients in either a 10- or 20-mg dose at 1–2-h intervals until patients were asymptomatic. In one study, patients used one-third the amount of diazepam used with fixed-schedule therapy. More recently, as-needed chlordiazepoxide was compared with fixed-schedule dosing in a double-blind, placebo-controlled study [49]. Not only did the as-needed group require less chlordiazepoxide (100 Vs. 425 mg), but also total treatment time was reduced to 9 h from 68 h.

Moderate-to-severe withdrawal can be life-threatening and requires parenteral sedative-hypnotics or anesthetic agents. The use of the latter often necessitates endotracheal intubation. Dosing regimens are not well established and are highly variable. Most patients respond to conventional doses of benzodiazepines. Occasionally, larger doses are required to treat the withdrawal symptoms. If initial doses greater than 200 mg of diazepam or its equivalent are given to a patient without satisfactory effect, an alternative agent is often necessary (Grade III). Historically the barbiturates have been the second-line agent of choice [50]. Physician familiarity and established history are the major benefits of barbiturate therapy. Phenobarbital has a lag time to response that can make titration difficult, and the kinetics of

short-acting barbiturates may result in prolonged sedation when extended therapy is required (e.g., thiopental) [51]. However, a recent study demonstrated reduced ICU admissions for ethanol withdrawal patients who received a single dose of phenobarbital at the initiation of standard lorazepam treatment with no increase in adverse events [52]. Optimal therapy results in the patients being sedated and arousable but not obtunded or comatose. Whether regimens use benzodiazepines or barbiturates, prolonged therapy often leads to tolerance of the agent used. Tapering is required to prevent withdrawal from the therapeutic agent. Agents with longer half-lives or active metabolites, such as diazepam or chlordiazepoxide, may facilitate tapering.

In Europe, GHB has been studied for the treatment of alcohol withdrawal [53–55]. The investigators concluded that although effective, the use of GHB could not be recommended for all alcohol withdrawal patients. In the United States, GHB is restricted at this time. Similarly, carbamazepine has also been used in Europe for decades to treat alcohol withdrawal [56]. However, a systematic review of the use of carbamazepine and other anticonvulsants for alcohol withdrawal failed to show a significant benefit to this treatment modality over benzodiazepines [57].

Propofol has an increasing role in sedative-hypnotic withdrawal. It has been used for barbiturate and GHB withdrawal and has been studied for alcohol withdrawal (Grade II-3 evidence) [58, 59]. The benefits of propofol include rapid onset of sedation, rapid emergence when discontinued, and anticonvulsant properties. In addition to being a GABA agonist, propofol has NMDA antagonist properties [60]. This dual activity is similar to that of alcohol and may explain why propofol works well for patients refractory to benzodiazepines. Propofol withdrawal is not well described. However, propofol is a costlier agent than the other options discussed and has a narrow therapeutic index requiring close monitoring for respiratory depression. While propofol has great utility in intubated patients, benzodiazepines remain the mainstay of therapy. Ketamine is another anesthetic agent that has recently been evaluated as an

adjunctive treatment for alcohol withdrawal when combined with benzodiazepines (Grade III evidence) [61]. However, while an initial study suggests lower overall dosage requirements of benzodiazepine, the results have not been reproduced. Similarly, dexmedetomidine has also been studied as an adjunct to benzodiazepine treatment for alcohol withdrawal (Grade III evidence) [62]. Again, more research is needed on the adjuvant agents before formal recommendations can be made.

Other agents that have been used include antipsychotics, β -blockers, and clonidine [63, 64]. These agents are able to treat psychosis and autonomic instability but fail to treat the underlying disorder and as such are not recommended. These agents also may mask some of the symptoms associated with withdrawal, resulting in suboptimal treatment. Finally, although the use of neuroleptics in patients with psychotic symptoms seems logical, they are not cross-tolerant with sedative-hypnotics, lower the seizure threshold, exacerbate tachycardia, and impair heat dissipation. In animal models and case reports, neuroleptics, such as haloperidol, exacerbate sedative-hypnotic withdrawal [65, 66].

Sedative-Hypnotic (and γ -Hydroxybutyrate) Withdrawal

The principles of treatment for sedative-hypnotic and GHB withdrawal are based on alcohol withdrawal treatment. Although specific regimens for GHB withdrawal have not been developed, the goal of therapy is the same: restoration of autonomic stability, reduction of psychomotor agitation, and mild-to-moderate sedation. Duration of withdrawal varies with the specific agent involved (Table 4).

Opioid Withdrawal

Heroin (and other opioid) withdrawal is often treated with a medically acceptable opioid, such as morphine or methadone (Grade 1 evidence). Although methadone is available orally for

Table 4 Expected onset and duration of withdrawal symptoms by agent

Agent	Symptom onset	Duration
Alcohol	6–12 h	5–7 days
Alprazolam	24–48 h	4–5 days
Diazepam	5–7 days	Weeks
Lorazepam	2–4 days	Weeks
Heroin/morphine	4–6 h	3–5 days
Methadone	1–2 days	5–7 days
Butalbital	4–6 days	3–5 days
Phenobarbital	7–10 days	3–5 days
GHB/GBL	1–4 h	3–5 days

GHB/GBL, γ -hydroxybutyrate/ γ -butyrolactone

maintenance therapy, acute withdrawal should be treated parenterally (10 mg of methadone intramuscularly). The intramuscular route is preferable because these patients may be vomiting, and this route guarantees delivery of methadone. When methadone is unavailable or unacceptable, morphine provides a suitable alternative in the acute setting. An initial dose of 0.1 mg/kg intravenously followed by titration to response can provide symptomatic relief. Many oral opioids are available and can be dosed similarly using morphine equivalents. Iatrogenic withdrawal induced by naloxone is treated best by supportive measures only. Although unpleasant, the withdrawal is not life-threatening in an awake patient and is self-limited, often lasting less than 1 h. Other agents that have been used to treat opioid withdrawal include clonidine, benzodiazepines, and antiemetics [67–70]. A recent review of the literature related to clonidine use in the management of withdrawal syndromes (including opioid and alcohol withdrawal) suggests that while clonidine may be used as adjuvant therapy, further formal trials are needed to define best practice and dosing recommendations [71]. These agents treat some of the physiologic symptoms associated with heroin withdrawal; however, they do not relieve the intense craving, which may lead some patients to self-discharge. This may be a factor when deciding whether to use these agents alone or as adjuncts to opioid therapy. Long-term therapy in this subgroup of patients has developed into methadone and buprenorphine maintenance programs. These programs often combine counseling with high-dose

oral methadone (>100 mg) or buccal buprenorphine to prevent heroin use in these patients.

Summary

Familiarity with the terms *dependence*, *tolerance*, *cross-tolerance*, *addiction*, and *withdrawal*, coupled with an understanding of the pharmacology of the agents in question, not only facilitates the evaluation of patients in withdrawal but also enables appropriate management, decreasing morbidity and mortality in these patients. Substance abuse, which precedes withdrawal, is a multifaceted problem requiring a multidisciplinary approach. Although medical management of withdrawal may be sufficient initially, ultimately patients benefit from additional psychiatric and social counseling and support.

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Background/Introduction and Possible Scenarios of Acute Radiation Injuries

Acute exposure to ionizing radiation can cause acute injuries in a variety of settings or during a number of scenarios (Table 1). Because these incidents are infrequent, health-care providers may not be familiar with the evaluation and management of the resulting potentially life-threatening illnesses. This chapter will discuss the evaluation and management of acute radiation syndrome (ARS) and will include a concise discussion of internal contamination with radioactive materials and its clinical consequences.

Definition and Types of Ionizing Radiation

Ionizing radiation is a form of energy that travels in space and that is able to remove an electron (i.e., ionize) from an atom upon interacting with it. Ionizing radiation emanates from the nucleus of “unstable” or radioactive atoms that decay to reach a more stable state. Radiation emission from the nucleus is termed disintegration. The number of disintegrations per second (termed activity of the source) is measured using the S.I. (Le Systeme International d’ Unités) unit Becquerel (Bq). The physical half-life of a radio-nuclide is the time it takes for the activity of a specific source to decrease by half through

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Table 1 Examples of radiological/nuclear scenarios

Scenarios	Circumstances	Settings	Clinical impacts
Nuclear power plant accident	Accidental Intentional (less likely)	Occupational	Workers Public
Nuclear detonation (nuclear weapon or improvised nuclear device)	Intentional	Nonoccupational	Public
Radioactive dispersal device	Intentional Unintentional (less likely)	Nonoccupational	Public
Radiological exposure device	Unintentional (more commonly reported) Intentional	Occupational Nonoccupational	Workers Public
Transportation-related accident	Unintentional Intentional	Occupational Nonoccupational	Workers Public

Table 2 Physical, biological, and effective half-life of important radionuclides

Radionuclide	Physical half-life	Biological half-life	Effective half-life
Iodine-131	8 days	120–138 days	7 days
Cesium-137	30 years	110 days	108
Strontium-90	28 years	50 years	18 years
Polonium-210	138 days	~50 days	~37 days
Uranium-238	4.5 billion years	4 days	4 days

radioactive decay. Table 2 lists the physical half-life of a number of radionuclides.

The ionizing radiation that is emitted can be in the form of electromagnetic waves (i.e., gamma rays or X-rays) or particles (i.e., alpha and beta). Neutrons are a form of ionizing radiation that have wavelike and particle-like properties. Because of differences in electrical charge and mass, these different types of ionizing radiation vary in the distance they can travel in space, the ability to penetrate the body and irradiate internal organs, and the amount of energy they deposit on their path, which is termed linear energy transfer or LET. For example, alpha particles are positively charged, have a high LET, and will deposit the energy they carry over a short distance compared to gamma rays that are uncharged and have a low LET. Alpha particles are unable to penetrate the outer layer of the skin and therefore do not pose a radiation hazard when they are released from a radioactive source located outside the body. Gamma rays and neutrons are uncharged and therefore can penetrate the body

Table 3 Different types of ionizing radiation

Type of ionizing radiation	Travel in air	Ability to penetrate the body
Gamma ray	Several meters	Yes
X-ray	Several meters	Yes
Alpha particle	1 cm	No
Beta particle	1 cm	No
Neutron	Several meters	Yes

when they are emitted from a radioactive source located outside the body and can, therefore, irradiate internal organs and cells. Table 3 lists different types of ionizing radiation and their respective physical properties.

Radioactive atoms occur either naturally (i.e., uranium or radon) or are man-made in a reactor (e.g., cesium). People are continuously exposed to ionizing radiation emitted from natural sources such as radon or cosmic rays or man-made sources like nuclear power plants or medical diagnostic and therapeutic procedures (e.g., computed tomography scans or nuclear medicine procedures). On average, in the USA, one is exposed to 6.2 millisievert (mSv) of ionizing radiation annually [1].

Biological Effects of Ionizing Radiation

The biological effects of ionizing radiation result directly from interaction of the alpha or beta particles with DNA or indirectly from the production

of free radicals through gamma ray-induced hydrolysis of intracellular water. The clinical outcome of these biological interactions is divided into deterministic and stochastic categories. Deterministic clinical manifestations do not occur below a certain threshold radiation exposure dose. The higher the dose received, the more severe the clinical manifestations and the earlier they occur. Stochastic (derived from Greek – random) clinical manifestations can occur after exposure to any dose of radiation (i.e., there is no threshold). The higher the dose received, the greater the likelihood of the clinical manifestations, but the clinical effects are not necessarily more severe and they do not occur more rapidly. Acute radiation syndrome is an example of a deterministic clinical manifestation, whereas cancer is an example of a stochastic one. Different cells and tissues vary in their sensitivity to radiation: the Bergonie–Tribondeau law states that cells that are active mitotically or are undifferentiated are radiosensitive [2]. Lymphocytes are an exception because they are radiosensitive without being mitotically active [3]. Their sensitivity to the effects of radiation is not completely understood, but may be due to their high nucleus to cytoplasm ratio.

Lastly, the biological effect that results from a certain dose of radiation is greater when that dose is delivered more rapidly (i.e., higher dose rate). This is evident in radiotherapy where the patient tolerates very large (otherwise lethal) doses of radiation fractionated over several weeks [4].

Routes of Exposure to Ionizing Radiation

People exposed to ionizing radiation emitted from a source located outside their body are not contaminated with radioactive material and do not pose any hazard of secondary contamination or exposure to others. In contrast, patients can be externally contaminated with radioactive material that has deposited on their clothes, skin, or hair. These patients can transfer the material to others and cause secondary contamination. They can also secondarily expose people in their

proximity to ionizing radiation (i.e., gamma rays) emitted from the radioactive materials. It is important to highlight that people who are externally contaminated with a radioactive material that decays by emitting only alpha and or beta particles will not expose others in their proximity to ionizing radiation because the emitted particles are unable to travel a sufficient distance to deposit on another person. Radioactive material can also deposit inside the body and lead to internal contamination. This can occur by ingestion, by inhalation, or through wounds. Patients who are internally contaminated with radioactive material are exposed to the ionizing radiation emitted from these materials as long as they are inside the body (termed residence time) and as long as the material is radioactive (emitting radiation during the natural process of radioactive decay) [5].

The behavior of a radioactive element inside the body is governed by its chemical and not physical properties. In simple terms, the body does not know if the element is radioactive or not. Therefore, absorption, distribution, and elimination are not related to the radioactive properties of the element. Consequently, a radioactive element is subject to biological elimination and its corresponding biological half-life (Table 2) in addition to its radioactive decay and corresponding physical half-life. The effective half-life, which represents the combination of both processes, should be used when assessing radiation dose exposures received from an internalized radioactive element (Table 2) [6].

Radiation Units of Measurements

The amount of energy of ionizing radiation that is absorbed by the body or an organ is measured in the S.I. unit gray (Gy). Different types of ionizing radiation have a different health impact for the same dose of radiation absorbed by the body or an organ. This is referred to the dose equivalent and is measured using the S.I. unit sievert (Sv). A radiation weighting factor (K) is used to convert a radiation-absorbed dose to a dose equivalent. The K factor is 1 for gamma rays, X-rays,

and beta particles. For alpha particles the K factor is 20 and for neutrons it varies from 5–20 depending on the energy of the specific neutron [5]. In other terms, from the same dose of radiation absorbed by the body or an organ, an alpha particle is more “potent” than a gamma ray in terms of biological effects. Therefore, if a patient receives a dose of 1 Gy in the form of a gamma ray, then the dose equivalent is 1 Sv. On the other hand, if the dose received was in the form of alpha particles, the dose equivalent is 20 Sv [5].

Personal Protection Principles of Health-Care Providers at the Hospital

The following discussion assumes that patients have been screened for external contamination with radioactive materials and satisfactorily decontaminated at the scene by emergency medical services or upon arrival to the emergency department.

Professionals who care for patients who have been exposed to, or contaminated with, radioactive material inside the emergency department or in inpatient areas should follow universal or standard precautions. Protection from secondary contamination with radioactive material can be achieved by protecting the eyes, mouth, and respiratory system from dustlike materials. A surgical or N-95 mask is adequate, especially in the post-decontamination, hospital setting. Higher levels of respiratory protection, such as an air-purifying respirator or a powered air-purifying respirator, may be necessary on the scene or prior to the decontamination of a patient in the emergency department triage who is externally contaminated with radioactive materials [7].

Gamma rays that are potentially emitted from radioactive materials located inside or over the surface of a patient’s body will penetrate various protective suits including the ones used in Level A personal protective equipment. Providers can effectively decrease the radiation dose that they receive by minimizing the time they spend in proximity to the patient, maximizing the distance

and following standard precautions. These include hand hygiene measures and wearing goggles, a protective suit, and gloves. Distance is particularly protective because the dose of radiation is inversely proportional to the square of the distance from the source [8].

The use of lead aprons is not practical and may not be sufficiently protective from high-energy gamma rays [9].

Health-care providers should use personal dosimeters when caring for patients who are contaminated with radioactive materials. These could be in the form of passive detectors that need to be sent to a laboratory for analysis or digital detectors that are able to provide a real-time estimate of the dose received by the provider. Hospital radiology technologists and staff who are occupationally exposed to radiation (e.g., interventional cardiologists) routinely use these dosimeters to monitor their occupational exposure. The results of their monitoring are assessed and managed by the hospital radiation safety department and the radiation safety officer. For example, the US Occupational Safety and Health Administration annual dose limit for occupational exposure to the whole body is 50 mSv (Fig. 1).

There are no reported cases or incidents in which health-care providers have developed acute radiation illnesses after caring for patients contaminated with radioactive materials. In Goiania, Brazil, patients contaminated with radioactive cesium were cared for by providers for several days before the discovery of the incident (personal communication with Dr. Luiz Bertelli from the Los Alamos National Laboratory). None of these providers developed any radiation illness. Similarly, the monitoring of 37 health-care workers who cared for Alexander Litvinenko in London for 3 weeks prior to the discovery of his poisoning with polonium-201 did not reveal any significant secondary contamination [10].

Although biological samples of patient who are internally contaminated with radionuclides will be radioactive, the amount of radioactivity is minute, and the hazard to health-care workers is not significant as long as standard precautions are followed [10].



Fig. 1 Photo of personal dosimeter (thermoluminescent detector)

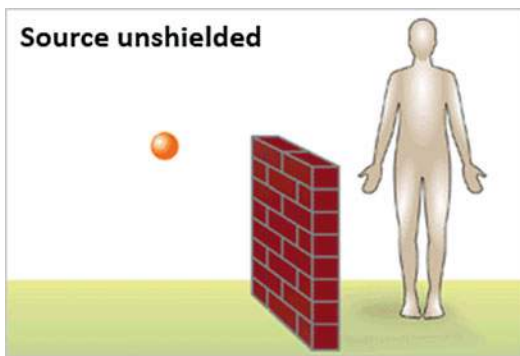


Fig. 2 Partial body exposure (Source: REMM)

Acute Radiation Syndrome

Acute radiation syndrome (ARS) is a complex disease that can be life threatening. It occurs in patients whose whole body (or a large part of the body) has received a dose of penetrating ionizing radiation that is greater than a threshold of approximately 0.5–1 Gy, over a short period of time (i.e., minutes to hours). Although some abnormalities can be detected in blood cells after exposure to whole body doses between 0.7 Gy and 2 Gy, ARS is not clinically apparent until the dose received is greater or equal to 2 gray.

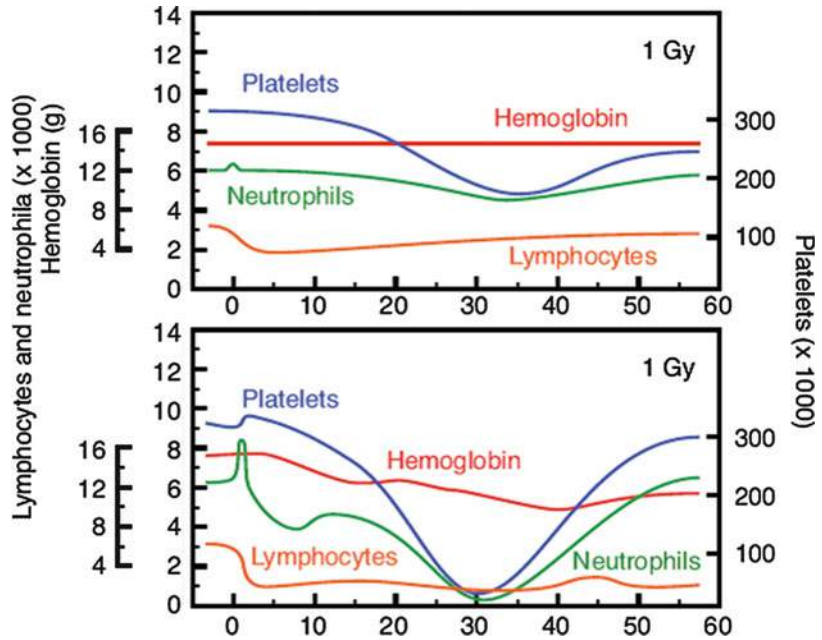
When only part of the body is exposed, the patient is said to have received partial body exposure: unaffected cells can assist in the recovery of irradiated areas (Fig. 2 below from Radiation Emergency Medical Management website https://www.remm.nlm.gov/exposureimage_1.htm).

Additionally, when the dose rate is low and the dose is received over greater than 6 h, the normal physiological processes may repair the damage and the person can recover. When a patient is externally contaminated with a radioactive material that decays by emitting alpha or beta particles, and not by emitting gamma rays, the radiation is unable to penetrate the body and irradiate internal organs. In these cases, ARS will not occur. On the other hand, when the material is internalized and the dose is therefore delivered internally and is high enough (i.e., greater than 1 Gy), multiple organ dysfunction and ARS can occur. This occurred in Mr. Litvinenko, who was internally contaminated with polonium that decays by emitting primarily alpha particles [11].

The acute radiation syndrome has four phases: prodrome, latent, manifest, and recovery or death. As discussed above, ARS is a deterministic disease. The higher the dose received above the threshold, the more severe and the shorter the time course of the clinical illness. The dose of radiation that is expected to kill 50% of an exposed population within 30 days (LD50/30) without treatment is approximately 3.5–4.5 Gy. The LD100/60 is approximately 10 Gy [12]. With intensive medical therapy, the LD50/60 could increase. Similarly, the LD50/60 will be smaller when the patient has suffered combined injuries (e.g., trauma or burns) or has comorbid illnesses [13].

During the prodromal phase, the patient will develop nonspecific signs and symptoms due to the inflammatory response caused by the radiation

Fig. 3 Cellular kinetics for the hematopoietic syndrome as a function of days following exposure (Acute Radiation Syndrome in Humans from the Textbook of Military Medicine: Medical Consequences of Radiological and Nuclear Weapons, Borden Institute Publisher. Chapter 2, Page 20)



exposure. When the inflammation subsides, the patient enters the latent phase and feels better. During this time, rapidly dividing cells would have already died and new cells would have not been produced to replace them. Affected cell line will decrease in number and clinical effects become apparent in the manifest illness phase. For example, myeloid stem cells die after exposure to radiation and can no longer produce neutrophils. This will lead to neutropenia and its secondary complications such as infection. Cell lines with longer life spans like red blood cells (120 days) will need longer to manifest the secondary illness (i.e., anemia) (Fig. 3).

It is important to note that these phases are not discrete and some overlap will occur. Additionally, the higher the exposure dose, the more compressed the clinical timeline. For example, patients who are exposed to 30 Gy of radiation may go through the four phases and die within 24–48 h. In comparison, a patient who receives a dose of 4 Gy may develop ARS and recover after 4–8 weeks of therapy [14].

The clinical manifestations of ARS will therefore depend on several factors such as radiation dose and dose rate, the individual patient characteristics (e.g., age, comorbid illnesses, combined

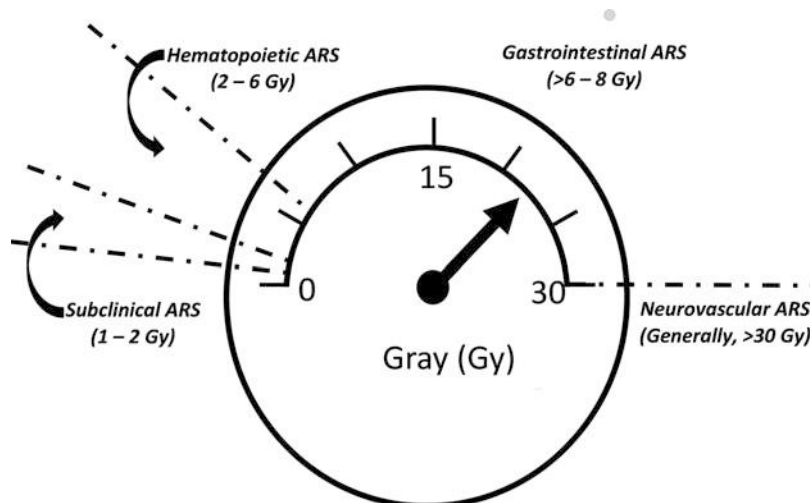
injuries), the body area that was irradiated (e.g., whole body irradiation, partial body irradiation, shielding), and the time elapsed since exposure. In general, ARS consists of four sub-syndromes: the hematopoietic, gastrointestinal, neurovascular, and cutaneous sub-syndromes (Fig. 4).

When the dose received is between 2 and 6 Gy, the hematopoietic system is primarily affected and the patient develops the hematopoietic sub-syndrome. The neutrophil and lymphocyte counts will decrease and patients will develop bone marrow aplasia in subsequent days to weeks. The resulting pancytopenia predisposes the patient to infections, sepsis, bleeding, poor wound healing, and death [15].

When the dose of radiation received is greater than 6 Gy, the intestinal crypt cells are affected, which leads to denuding of the intestinal lining because of the inability to replace dying cells. Patients will develop the gastrointestinal sub-syndrome which manifests in vomiting, diarrhea, gastrointestinal bleeding, sepsis, electrolyte abnormalities, circulatory collapse, and death [15].

When the dose received is greater than 30 Gy, the patient can develop the neurovascular sub-syndrome. This sub-syndrome is not very

Fig. 4 Dose–response relationship of classic ARS sub-syndromes



well understood or characterized due to a paucity of clinical experience. Based on previous reports, affected patients develop altered mental status, seizures, coma, and cardiovascular collapse within minutes to hours after their radiation exposure and die 1–2 days later [15, 16]. The cutaneous sub-syndrome occurs when a dose of radiation greater than 2 Gray is deposited in the skin. The effects range with increasing radiation dose between early transient erythema, epilation, main erythema, dry desquamation, wet desquamation, late erythema, necrosis and ulceration. With the exception of the early transient erythema that occurs within the initial 24 hours after exposure, the cutaneous effects do not manifest until 10 days to several after the exposure [15].

It is particularly important to note that the clinical manifestations overlap and the duration of illness will vary greatly depending on the dose received and the individual clinical characteristics of the patient.

Recently, a different perspective on the pathophysiology of acute radiation syndrome has developed to include systemic effects that include, in addition to the classical four sub-syndromes, involvement of the lung, kidney, liver, and other organs and that occur at the higher dose ranges. Additionally, inflammation is thought to take a prominent feature of early radiation injury and prodromal manifestations which may serve as target of future therapies [17].

The assessment of the dose of radiation received by the patient has clinical and prognostic value. Initially, this assessment will be based on the exposure history, which includes the geographic location relative to the source of radiation, the signs and symptoms developed, and biological markers [15].

The time to onset of vomiting is commonly used as an initial rapid, albeit crude, method to assess the dose received. The higher the dose, the greater the likelihood of vomiting and the shorter the time to its onset. In general, patients who start to vomit within 4–5 h of their radiation exposure are likely to have received a dose greater than 1–2 gray and may develop clinical ARS. Patients who vomit or develop diarrhea within 1 h of exposure are expected to have received a dose greater than 6 Gy (Fig. 5).

Additionally, the rate of decline of the absolute lymphocyte count (ALC) can be used in dose assessment (Image Legend: Andrew's Lymphocyte Nomogram) (Fig. 6).

Resources permitting, an ALC should be obtained as soon as possible after the exposure and repeated every 8 h for 2–3 days then twice per day for the following 3–6 days [15]. A 50% decrease in the ALC during the first 24 h after exposure followed by a further steeper decline in the count over the subsequent 48 h is associated with a potentially lethal radiation exposure [15]. On the other hand, an exposure dose of 2–4 Gy,

Fig. 5 Relationship between time to onset of vomiting and dose over a range of 2–10 Gy (Reproduced with permission from the TMT Handbook Graph F30.b)

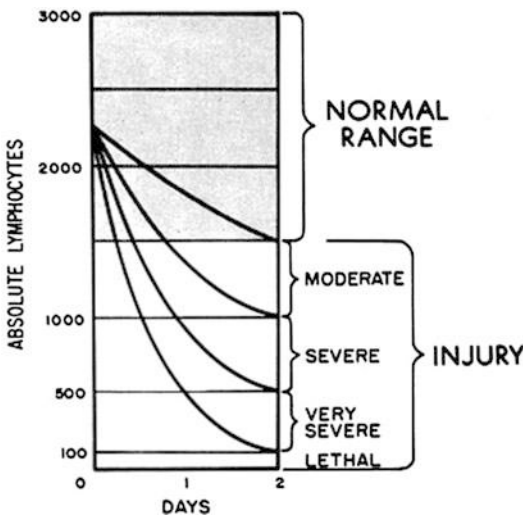
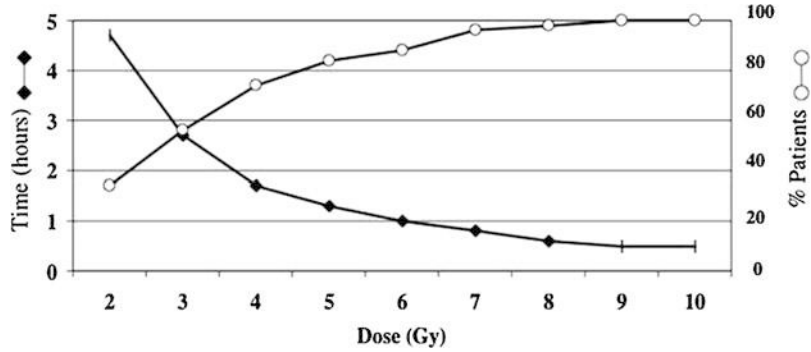


Fig. 6 Andrew's Lymphocyte Nomogram. From Andrews GA, Auxier JA, Lushbaugh CC. *The Importance of Dosimetry to the Medical Management of Persons Exposed to High Levels of Radiation*. In *Personal Dosimetry for Radiation Accidents*. Vienna: International Atomic Energy Agency; 1965. Extracted from the Centers for Disease Control and Prevention Website <http://emergency.cdc.gov/radiation/arsphysicianfactsheet.asp> Accessed on February 6, 2016)

which is below the LD50/60, will cause the ALC to decline over approximately 4–6 days [18]. The Radiation Emergency Medical Management website provides an online dose estimator [18] that can be used for time to onset of vomiting and serial ALC measurements. It is based on the Armed Forces Radiobiology Research Institute Biodosimetry Assessment Tool [19] and is available at http://www.remm.nlm.gov/ars_wbd.htm.

Additionally, the medical treatment protocol for radiation accident victims ("METREPOL") tool was developed in Europe to be used for the diagnosis and triage of people exposed to radiation in small and medium size incidents but not very large mass casualty incidents like an improvised nuclear device. This tool assigns patients to various response categories (RCs) using the severity of clinical manifestations in the critical target organs (hematopoietic, gastrointestinal, neurovascular, and cutaneous systems). This classification is repeated at regular time intervals that depend on the case severity. The RC is in turn utilized to guide medical management into one of several options that range from supportive care to stem cell transplantation [20].

The gold standard for assessing the dose of radiation received by a patient is the chromosome-aberration cytogenetic bioassay that uses the dicentric assay. This test can be performed at cytogenetic biodosimetry laboratories such as the one located at the Radiation Emergency Assistance Center/Training Site in Oak Ridge, Tennessee, USA [21]. Unfortunately, the assay is labor intensive and can require several days to complete. Some efforts have been made to increase test throughput by utilizing cytogeneticists who view the chromosomes remotely [22]. Additional biodosimetry tools and assays that utilize serum protein markers and gene expression are being studied. Electron paramagnetic resonance of nails or teeth is also being evaluated for its ability to estimate exposure

dose after a mass casualty incident. In general, several authorities have recognized the importance of combining a number of data sources (e.g., protein and genetic markers) when estimating radiation exposure dose in a patient. The use of electronic software to assist in data analysis has also been proposed [23].

Management of the Acute Radiation Syndrome

The management of acute radiation syndrome consists of supportive care, antiemetics, antidiarrheals, prevention and treatment of infections, blood products, colony-stimulating factors, and stem cell transplants in select cases. In addition, patients should be provided with neutropenic precautions similar to those who receive chemotherapy or transplantation.

Antiemetics are necessary to treat the nausea and vomiting that occur in patients with ARS. Serotonergic receptor antagonists such as ondansetron and granisetron are appropriate therapeutic options and are believed to be more efficacious and safer than prochlorperazine (Grade I evidence) [24–27]. Antidiarrheals like loperamide or diphenoxylate may also be necessary in patients with diarrhea (Grade III evidence) [28].

Antimicrobials should be administered to patients who have received a whole body dose of radiation greater or equal to 2 Gy and are at risk of becoming neutropenic. Oral fluoroquinolones are a reasonable initial choice in low-risk cases that are clinically stable and afebrile. Broad-spectrum antibacterials including parenteral agents are necessary in patients who develop fever, who are clinically unstable, or who develop severe neutropenia (absolute neutrophil count [ANC] < 500 cells/mm³). The therapeutic regimen should also include prophylaxis against herpes infections using acyclovir and antifungals in severe cases that do not respond to initial broad-spectrum bacterial coverage. Clinicians should consult with infectious disease specialists or refer to clinical guidelines for the management of neutropenia in cancer patients undergoing chemotherapy and published by professional societies such

as the Infectious Disease Society of America or the American Society of Clinical Oncology (Grade III evidence) [29, 30].

Blood products may be needed during the initial trauma resuscitation or during the following 2–4 weeks in patients who develop bone marrow aplasia and pancytopenia. Blood products should be irradiated to 25 Gy in order to prevent the occurrence of a transfusion-related graft versus host disease reaction. Blood products should also be leukoreduced to prevent febrile nonhemolytic reactions, lessen immunosuppressive effects of transfusions, decrease the risk of alloimmunization toward platelets, and lower the risk of transmission of cytomegalovirus infection [15].

Colony-stimulating factors are cytokines that stimulate surviving myeloid stem cells in the irradiated bone marrow. They are used for the hematopoietic sub-syndrome to decrease the severity and duration of neutropenia with the hope of decreasing mortality. These drugs have been shown to be beneficial and are used routinely in cancer patients receiving chemotherapy, in patients undergoing stem cell transplants, and in donors undergoing peripheral stem cell collection. The evidence supporting the use of these drugs in the hematopoietic sub-syndrome is limited to animal studies because of the inability to conduct randomized clinical trials in humans with ARS for both practical and ethical reasons. These drugs have been shown in animal models (e.g., rhesus macaques) to decrease the severity and duration of neutropenia and to increase survival after exposure to ionizing radiation (Grade III evidence) [31–33]. In 2015, the US Food and Drug Administration approved filgrastim (Neupogen[®]) and pegylated filgrastim (Neulasta[®]) for the treatment of radiation-induced myelosuppression and the hematopoietic sub-syndrome of ARS (Grade III evidence) (Table 4).

Other drugs with similar mechanisms of action are available and could potentially be used in an emergency (e.g., sargramostim, Leukine[®]; TBO-filgrastim, Granix[®]; and filgrastim, Zarxio[®]) (GRADE III). In the USA, the Food and Drug Administration could authorize these drugs under an emergency use authorization mechanism.

Table 4 Colony-stimulating factors approved by the US Food and Drug Administration for the hematopoietic sub-syndrome

Drug	US FDA indication	Dosage	Side effects and precautions
Filgrastim (Neupogen®) Grade III	Radiation dose ≥ 2 Gy, as soon as possible, preferably within 24 h of exposure	10 mcg/Kg s/c every 24 h until ANC > 1000 cells/mm ³ for three consecutive CBC or ANC > 10,000 cells/mm ³ after a radiation-induced nadir	Bone pain Sickle cell crisis in patients with sickle cell disease or trait Splenic rupture
Pegfilgrastim (Neulasta) Grade III	Radiation dose ≥ 2 Gy, as soon as possible, preferably within 24 h of exposure and a second dose 1 week after	Two doses, 6 mg each, administered S/C 1 week apart Dose is weight based in children weighing less than 45 Kg (refer to drug label)	Bone pain Sickle cell crisis in patients with sickle cell disease or trait Splenic rupture

A World Health Organization expert panel reviewed relevant literature and experiences [34–38] and made a weak recommendation for the use of allogenic matched stem cell transplant in specific patients who do not recover their hematopoietic function after 2–3 weeks of standard therapies, including colony-stimulating factors and who do not have limiting comorbid conditions or combined injuries (Grade III evidence) [39]. Therefore, stem cell transplant can be considered in specific situations and in consultation with experts in the field. The US Radiation Injury Treatment Network (“RITN”) is composed of approximately 64 transplant centers that are poised to assist in the management of patients with acute radiation syndrome, including those who require a transplant [40].

Depending on the specific emergency and the number of victims, resources can be scarce and standards of care may need to be altered. Medical providers may need to prioritize resources and medical countermeasures to patients with survivable injuries and provide palliative care measures to those who are moribund or have a poor prognosis for survival or recovery.

Delayed Effects of Acute Radiation Exposure

Patients who survive the acute radiation syndrome may develop delayed effects months to years later. This is due to the delay in manifestations that are

expected in slowly dividing cells. For example, cataract development is the most common delayed complication and has a variable latency period and severity (6 months to 35 years depending on the dose of radiation received and its dose rate). The current US annual occupational exposure limit to the eye is 150 mSv. Treatment is usually surgical replacement of the opaque lens [41].

Pulmonary disease that progresses from pneumonitis to pulmonary fibrosis may manifest month to years later in patients who have received a dose greater than 8 Gy to their thorax. Treatment of this potentially fatal disease is supportive [42].

Male and female sterility can also occur after exposure to ionizing radiation. The threshold for the development of temporary sterility in males is 1 Gy. The effect is usually temporary, and recovery occurs at variable times depending on the dose of radiation, age of the person, and gender (i.e., testes are more radiosensitive than ovaries) [43].

Internal Contamination

After externally contaminated patients are decontaminated to a satisfactory level, patients need to be assessed for internal contamination. This section will provide a brief description of the assessment and treatment paradigm for internal contamination. A comprehensive discussion is outside the scope of this chapter. In 2008, the

Table 5 Drugs approved by the United States Food and Drug Administration for the management of internal contamination with certain radionuclides

Radionuclides	Therapy and dose	Notes
Cesium or thallium	Prussian blue insoluble (Radiogardase®) Adults: 3 g PO every 8 h Children > 2 year: 1 g PO every 8 h	Can cause constipation, hypokalemia, and bluish discoloration of stools
Plutonium, americium, or curium	Calcium or zinc DTPA Adults: 1 g IV every 24 h Children: 14 mg/kg IV per day not to exceed 1 g per day	Calcium DTPA preferred during the first 24 h after internal contamination Zinc DTPA preferred in children and pregnant females
Tritium (H3)	Saline diuresis or water	Increasing glomerular filtration rate

National Council on Radiation Protection and Measurements published Report Number 161 (Management of Persons Contaminated with Radionuclides: Handbook) which is a valuable reference for this topic.

Internal contamination can be diagnosed by direct bioassay using a radiation detector placed outside the body if the radionuclide that has been taken up inside the body decays by emitting gamma rays [5]. This method cannot be used if the radionuclide decays by emitting only alpha particles or beta particles because these forms of ionizing radiation are not able to travel far enough in space to reach the detector. As an example, Alexander Litvinenko had a negative radiation detection survey because he was internally contaminated with polonium-210 that decays primarily by emitting alpha particles.

On the other hand, analysis of urine or fecal samples can detect radionuclides that decay by emitting gamma rays, alpha particles, or beta particles. This analysis is best performed on a 24-h urine sample to account for any diurnal variations in excretion. The US Centers for Disease Control and Prevention has developed assays that can utilize a spot urine sample to rapidly screen for internal contamination with a gamma, alpha, or beta emitter. This rapid screen can be followed with additional tests to identify the specific radionuclide and quantify the level of activity per unit volume of sample analyzed [44].

The quantification of the activity of a radionuclide present inside the body is important in order to estimate the dose of radiation that it will deliver

to target organs or the entire body over its biological and radiological life span, which is represented by the specific radionuclide effective half-life. If the dose delivered is greater than 250 mSv, the National Council on Radiation Protection and Measurements (NCRP) recommends long-term monitoring and decorporation therapy, if possible and available. To aid clinicians in making these determinations, the NCRP has created the clinical decision guide (CDG) which defines “the maximum once-in-a-lifetime intake (in Bq) of a radionuclide that represents a stochastic risk and avoidance of deterministic effects” [5].

The clinical manifestations of internal contamination depend on the physical and chemical properties of the radionuclides and the dose of radiation that would be delivered to specific organs, or the whole body, over the residence time of the radionuclide inside the body. For example, children or adolescents who were internally contaminated with radioactive iodine in the aftermath of the Chernobyl nuclear power plant accident had an increased risk of developing thyroid cancer [45]. Similarly, Alexander Litvinenko developed gastrointestinal distress followed by hair loss, bone marrow failure, and death within 3 weeks from his polonium-210 incorporation [11].

The management of internal contamination is primarily supportive. In the USA, a few drug therapies have been approved by the Food and Drug Administration to hasten the excretion and elimination of certain radionuclides from the body and therefore decrease the dose delivered to organs and the whole body over the duration of

their residence inside the person. These drugs are listed in Table 5.

Additionally, internal contamination with uranium salts can lead to renal toxicity that may be mitigated by alkalinizing the urine to a pH of 8 with intravenous or oral sodium bicarbonate for 3 days [1, 46] (Grade III evidence).

Patients who have received an internal dose that is greater than 250 mSv (i.e., have an activity greater than the corresponding CDG) need to be registered with the health department and undergo long-term follow-up and monitoring for delayed onset complications and illnesses like cancer.

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Henry Rosenberg, Dorothea Hall, and Harvey Rosenbaum

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Malignant hyperthermia (MH) syndrome is an unusual disorder. Much like an individual who has an allergy, the MH-susceptible patient is often unaware of his or her problem unless there is a family history of anesthesia-related problems that suggest MH or until exposed to the “triggering” agent. MH syndrome may not develop on all exposures. The resemblance to an allergy breaks down, however, on further analysis. MH is an inherited disorder [1]. Patients develop a hypermetabolic condition on exposure to drugs that are generally used to produce general anesthesia such as isoflurane, halothane, desflurane, and sevoflurane or skeletal muscle paralysis, namely, succinylcholine [2]. The pathophysiologic change in MH relates to an uncontrolled increase of intracellular calcium in skeletal muscle that leads to hypermetabolism, depletion of energy sources, acidosis, and membrane breakdown [1–3]. Untreated, MH syndrome is fatal in most cases. With prompt discontinuation of trigger agents and administration of the drug dantrolene [4], mortality may be close to zero [5]. This chapter discusses clinical presentation, pathophysiology, molecular genetics, diagnosis, treatment, and sources of information for this unusual cause of anesthetic morbidity and mortality.

History

MH was recognized in the early 1960s by clinical anesthesiologists and a clinical geneticist in Melbourne, Australia [6]. The event that attracted

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their attention related to surgery for a young man who sustained a motor vehicle injury. The patient expressed great concern because many members of his family had died unexpectedly while under anesthesia. The anesthesiologists administered halothane anesthesia, and, warned by the patient’s concern, stopped the anesthetic and the procedure when the patient developed hypertension, then hypotension, tachycardia, and sweating. Michael Denborough, a consultant internist with an interest in inherited diseases, was called to investigate. He then described many salient features of the syndrome.

After Denborough and Lovell [6] described the syndrome, many others described similar cases throughout the world. By the end of the 1960s, the syndrome was called *malignant hyperthermia* or *malignant hyperpyrexia*. The reason for the appellation was the mortality of greater than 80% and the strikingly elevated body temperature that accompanied the disorder. Other peculiar features that were described included muscle rigidity, rhabdomyolysis, and in some cases, rigidity limited to the jaw muscles after the muscle relaxant succinylcholine was administered.

At the first international workshop on MH, held in 1971 in Toronto, Canada, clinicians and basic researchers began to exchange information about MH. Veterinarians and pig breeders reported that certain breeds of pigs developed what seemed to be MH on a regular basis when stressed [7]. The breeds were known for their muscle mass and included Pietrain, Poland China, and others.

Although there was great concern initially that MH-susceptible humans would develop the syndrome with stress, that has not been shown to be the case [2, 3]. However, some MH susceptibles may develop the signs of MH with vigorous exercise and exposure to heat [9]. There are many other differences between human and swine MH. The inheritance of the syndrome is autosomal recessive in pigs but autosomal dominant in humans. Nevertheless, the pig develops typical signs of MH on exposure to anesthetics that trigger MH. The pig has served as a useful model, however, for understanding the pathophysiology of MH, determining

Table 1 Landmarks in malignant hyperthermia

Demonstration that biopsied muscle responds with abnormal contractures to halothane and to caffeine [8, 10]
Recognition that all potent volatile anesthetic gases are triggers for MH, as is the depolarizing relaxant succinylcholine [2, 3]
Demonstration that local anesthetics and intravenous anesthetics are not triggers of MH [2, 3]
The finding, in 1975, that dantrolene sodium is a specific treatment for MH and the introduction in clinical use in 1979 in the USA [4, 11]
The routine use of capnography in anesthesia and the recognition that elevated end-tidal carbon dioxide is an early sensitive and specific sign of MH [2, 3]
The creation of patient advocacy groups, registries, and hotlines throughout the world to assist anesthesia providers and others to recognize MH and guide treatment
Demonstration that mutations in a specific gene that elaborates a calcium channel in muscle, the ryanodine receptor, are responsible for almost all cases of pig MH and perhaps 50% of human MH [1]
Development of a “knock-in” mouse model of MH incorporating mutations that predispose to MH [13]
Introduction of molecular genetic testing for MH diagnosis in limited circumstances
Demonstration that time from diagnosis to treatment is crucial in enhancing survival [14]
Demonstration that early detection and mitigation of hyperthermia reduces mortality [67]
Cataloging of over 300 DNA variants associated with MH in the RYR 1 gene. Demonstration that the CACNA1S gene is associated with MH in some cases
Demonstration of prevalence of RYR 1 variants associated with MH in 1 in 2000 people
Association of MH susceptibility with several myopathies such as central core disease, multimincore disease, nemaline myopathy, and others

MH malignant hyperthermia

which drugs precipitate the syndrome, and determining the effective treatment of MH.

Since the early 1970s, there has been an enormous growth in knowledge and awareness of how to diagnose and treat MH syndrome. Landmark advances are outlined in Table 1. All of these findings and many others have led to the reduction of mortality from MH to less than 7% in developed countries [5, 12].

In a sense, the term *malignant hyperthermia* has become a misnomer. Hyperthermia often follows other metabolic signs of MH and is often not manifest when the diagnosis is made.

Furthermore, with prompt recognition and treatment, the fatality rate of MH is low. The syndrome includes *anesthesia-induced myodystrophy* and *rhabdomyolysis of anesthesia*.

Incidence

MH, being an inherited myopathy, should be amenable to epidemiologic investigation of incidence, prevalence, and perhaps penetrance. However, the data have been difficult to gather. The reason is that MH patients in general have no specific phenotype, other than when exposed to anesthetic drugs or in special environmental stressors; the signs of MH during anesthesia may be nonspecific and mimicked by other processes, such as rapid absorption of carbon dioxide during laparoscopic surgery, fever, iatrogenic overheating, and myotonia. In addition, until the late 1998, there was no specific ICD-9 (*International Classification of Diseases – ninth revision*) code for MH, and the syndrome did not appear in the diagnostic databases of diseases.

The prevalence of MH is approximately 1 in 100,000 instances of exposure to general anesthesia, and the incidence of clinical signs that resemble MH but for which the diagnosis is not certain is 1 in 5000 instances of exposure to anesthesia [15]. In one small study, 25% of MH diagnoses based on ICD 9 or ICD codes represented an incident case of MH [16]. Overall, approximately 1000 cases of MH are diagnosed each year in the USA. In addition, the incidence of MH in children is about three times higher than in adults [17]. The incidence of clinical MH depends primarily on the use of the trigger agents for MH and the gene prevalence in the population. In the USA and Canada, a higher incidence of MH is found in Ontario, Wisconsin, and various locales where there are families who harbor the genetic change causal for MH. MH has been identified in every country and ethnic group where it has been looked for [12].

One study has determined that the incidence of susceptibility to MH in one province of Quebec is about 1 in 200 individuals [18]. That study was

performed because many patients in the province had been tested for MH susceptibility with biopsy (see under Diagnostic Testing). The province was settled by a small number of families in the nineteenth century, and there had not been a large admixture of other families in the province. A few families with MH accounted for most of the cases.

A study examining surgical discharge diagnoses in NY state found that MH was recorded in one in 100,000 discharges [19].

Recent studies have examined the prevalence of DNA variants of the principle gene that is causal for MH, the ryanodine receptor gene (RYR1). Studies in France and Japan and one in Germany described a prevalence of MH-causative mutations of one in about 2000 people [20], while a study of patients in the Baltimore/Washington area directly measured a prevalence of pathologic DNA changes in one in 400 people [21].

The understanding of the very low penetrance of the syndrome is a crucial question in managing patients and their families. A great deal of further investigation is needed to determine the epidemiologic characteristics of the disorder with accuracy. To the best of our knowledge, there are fewer than five deaths from MH among the approximately thousand MH episodes each year in the USA.

Pathophysiology

Malignant hyperthermia is a disorder of skeletal muscle biochemistry and physiology, yet in the absence of triggering agents, there are no identifiable signs or symptoms. No muscle abnormalities are consistently observed in MH-susceptible people. Only small subsets of subjects with MH, identified either by clinical presentation or diagnostic testing, show evidence of muscle disorders. These include patients with central core disease, multiminicore disease, King-Denborough syndrome, Native American myopathy, and late-onset myopathies [23–26]. It is doubtful that other tissues are primarily responsible for the clinical manifestations of MH. Based on the

recognition that muscle rigidity was a dramatic manifestation of most cases of MH, Kalow and colleagues tested muscle biopsy specimens from susceptible pigs and humans for their response to caffeine, the agent known to produce muscle contracture secondary to calcium release from the sarcoplasmic reticulum [8]. They found that the response to biopsied skeletal muscle to caffeine, *in vitro*, was clearly abnormal. Contractures developed in muscle tissue of MH-susceptible subjects with concentrations as low as 0.5 mM, not observed in normal muscle. MH muscle also showed significant (>0.5 g) contractures on exposure to clinical concentrations of halothane [27–29]. The same findings were not found in the examination of smooth or cardiac muscle (Figures 3 and 4).

Further refinement of understanding of the pathophysiology of MH has focused on the mechanisms responsible for calcium control in muscle. Several proteins mediate calcium release and control intracellular calcium levels. Most attention has been focused on the ryanodine receptor, a calcium channel which mediates excitation-contraction coupling in skeletal muscle (Fig. 2) [1, 22, 23]. Excitation-contraction coupling occurs when an action potential along the muscle cell's T-tubule membrane is converted into an intracellular chemical signal, via Ca^{2+} ion flow, which drives muscle contraction. Specifically, a conformational change occurs in the voltage-dependent L-type calcium channel, which in turn triggers activation of the ryanodine 1 (RYR1) Ca^{2+} release channel in the terminal cisternae of the sarcoplasmic reticulum. Most attention has been focused on the ryanodine receptor; however, alterations in several other calcium signaling mechanisms and at least six other genes have been implicated in MH [30–33]. Specific MH-associated mutations have been identified in only three genes to date: RYR1, CACNA1S, which encodes the α -1S subunit of the voltage gated L-type calcium channel of the T-tubule, and the STAC3 gene associated with Native American myopathy [85].

Further investigations using calcium-sensitive dyes and calcium ion electrodes showed markedly increased levels of intracellular calcium in whole

muscle or cultured muscle from MH-affected animals and humans on exposure to potent inhalational anesthetics [34–36]. The purported primary defect in MH is related to enhanced release and/or leak of calcium from the terminal cisternae of the sarcoplasmic reticulum (Fig. 1) [22]. Increased resting myoplasmic Ca^{2+} has been measured in several MH-causative RYR1 mutations; exposure of MH myotubes to ryanodine, which blocks *open* RYR1 channels, is without effect. In this model increased resting myoplasmic calcium is therefore not due to increased RYR1 calcium release but most likely to a mechanism called store-operated extracellular calcium entry (SOCE) [37]. Reuptake does not seem to be at fault in these tissues [38]. The consequence of enhanced release/leak of calcium is prolonged muscle contraction resulting from release of inhibition of actin-myosin interaction. Adenosine triphosphate (ATP) levels decline as a result of activation of processes to sequester calcium, leading to anaerobic metabolism and acidosis. Declining levels of ATP lead to breakdown of membrane integrity and release of intracellular enzymes, such as creatine kinase (CK), along with myoglobin, potassium, and hydrogen ions.

Recent research focus has been placed on a mechanism termed store-overload-induced calcium release (SOICR) as a possible etiology for MH. In this condition RYR1 spontaneously releases Ca^{2+} from the sarcoplasmic reticulum once luminal Ca^{2+} concentrations reach a critical concentration. New evidence suggests that mutations in RYR1 may lower the threshold for SOICR, thus causing spontaneous release or leak of Ca^{2+} [39]. A similar mechanism could be demonstrated in the RYR2-mediated, stress-triggered condition of catecholaminergic polymorphic ventricular tachycardia (CPVT). CPVT leads to bidirectional ventricular tachycardia and sudden cardiac death. Parallels can be drawn between the RYR1-mediated mechanism in MH and the RYR2-associated mechanisms in CPVT, in that they both reduce the threshold for store-overload-induced calcium release [40].

Another mechanism of RYR1 regulation via $\text{Ca}_v1.1$, a pore forming subunit of the L-type Ca^{2+} channel encoded by CACNA1S, has recently

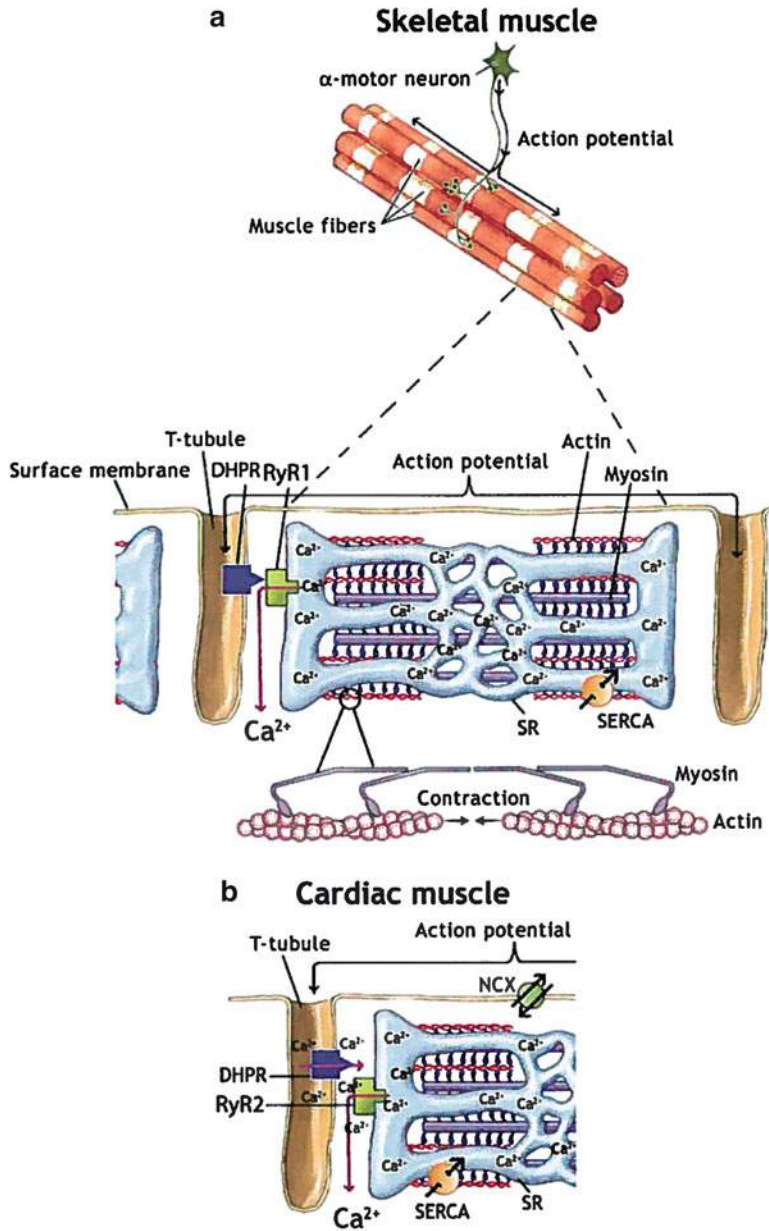


Fig. 1 Activation of the contractile machinery in skeletal and cardiac muscles. **(a)** An action potential travels along an α -motor neuron to a group of skeletal muscle fibers and triggers an action potential in each of the muscle fibers. The action potential in turn activated voltage-sensitive dihydropyridine receptors (DHPR). The DHPR opens ryanodine receptors (RyR) by mechanical interaction, resulting in release of Ca^{2+} from SR and a transient increase in myoplasmic Ca^{2+} , which enables actin and myosin interaction and force development. SR (sarcoplasmic reticulum) Ca^{2+} -ATPase (SERCA) pumps Ca^{2+} back into SR and myoplasmic Ca^{2+} returns to resting levels and

the contraction ceases. **(b)** The activation of the Ca^{2+} -dependent contractile machinery is almost identical in cardiac muscle, with the exception of the Ca^{2+} release process. The cardiac action potentials last longer compared to skeletal muscle, which results in Ca^{2+} influx through DHPRs, and these Ca^{2+} ions induce opening the RyR and Ca^{2+} release from SR. The increase in myoplasmic Ca^{2+} enables actin and myosin interaction. Myoplasmic Ca^{2+} return to resting levels by SERCA-mediated pumping of Ca^{2+} into SR and extrusion of Ca^{2+} via the Na^{+} - Ca^{2+} exchanger (NCX) (From *Calcium Signaling*, Islam MS ed, Springer 2012)

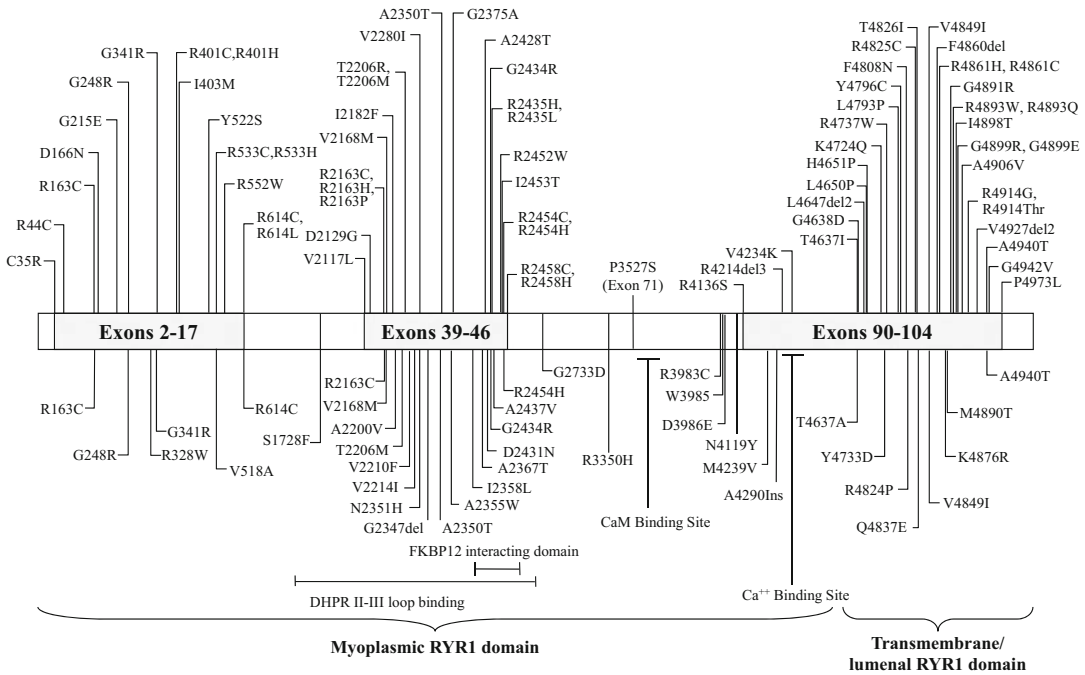


Fig. 2 Location of ryanodine receptor type 1 (*RYR1*) mutations associated with malignant hyperthermia susceptibility and central core disease. Mutations found in European and Australian malignant hyperthermia-susceptible/central core disease families are shown at the top; mutations in North American malignant hyperthermia-susceptible/central core disease families are shown at the bottom of the diagram. The mutations reported only in North

American MHS families and *RYR1* variants identified in North American MHS subjects are shown in bold. The three mutational hot spot areas are shadowed. CaM, calmodulin; DHPR, dihydropyridine receptor; FKBP 12, FK 506 binding protein 12. Diagram courtesy of Dr. N. Sambuughin. (Reprinted, with permission, from Anesthesiology, second edition. Longnecker DE et al., eds. McGraw-Hill, New York, 2012)

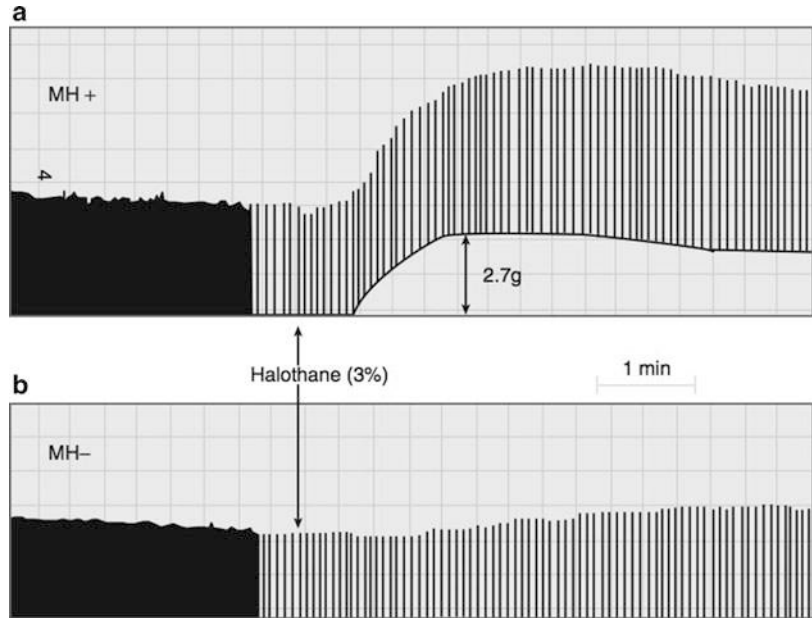
been elucidated. $\text{Ca}_v1.1$ activates RYR1 during excitation-contraction coupling, but it also suppresses the leak of Ca^{2+} ions from the sarcoplasmic reticulum when RYR1 channels are at rest. Disruption of this inhibitory regulation may explain increased sensitization of muscle cells to MH triggers [41].

Recent work by Eltit et al. [42] demonstrated that nonspecific sarcolemmal cation channels can cause Ca^{2+} and Na^+ overload both at rest and during an MH crisis [42]. Utilizing a knock-in mouse model, the study showed an overexpression of nonspecific sarcolemmal cation channels associated with influx of extracellular calcium and elevated resting intracellular calcium and sodium in the MH group. Halothane resulted in further increases in myoplasmic sodium and calcium in the MH animals.

Evidence of abnormal calcium control in MH-susceptible patients, even without exposure to anesthetic agents, is suggested by nuclear magnetic resonance studies in exercising human muscle in vivo [43–47]. These studies show greater inorganic phosphate levels at rest and with exercise, exercise-induced acidosis, and slower recovery of ATP levels in MH-susceptible patients. These changes do not lead to clinical signs of MH.

Although mutations in the ryanodine receptor appear to be an important factor in the pathophysiology of MH, only about 50–70% of MH-susceptible families have been linked to ryanodine mutations [1, 48]. The presence of a mutation also does not explain the interindividual and intraindividual variability in the clinical expression of MH syndrome. In several families, there has been discordance between the MH

Fig. 3 In vitro contracture response. Cut muscle bundles from the vastus muscle weighing approximately 150 mg are mounted in a temperature-controlled bath. The muscle is stimulated at 0.1 Hz with a supramaximal stimulus. Halothane 3% in 95% oxygen and 5% carbon dioxide are introduced into the bath. (a) 3 g contracture typical of malignant hyperthermia susceptibility. (b) Normal response to halothane



ryanodine genotype and phenotype as determined by the in vitro caffeine halothane contracture test (IVCT) [49–53].

Central core disease, a dominantly inherited neuromuscular weakness, is one of the myopathies strongly associated with MH, and mutations in the ryanodine receptor have been shown to be the most common cause for central core disease [54, 55]. Hypokalemic periodic paralysis is another myopathy that has been associated with mutations in the dihydropyridine receptor in the same region as mutations related to MH [56]. Some patients with these disorders have displayed clinical MH reactions, whereas others have not.

The fine details of calcium control and its alteration in MH patients require further study and examination to better characterize the clinical presentations of MH. As the field of molecular genetics is rapidly advancing, we can anticipate identification of new MH-causative genes and greater sensitivity and efficiency of genetic testing. Continued growth of genetic databases will be of great use for better understanding of the genotype/phenotype relationships in MH. There is a lot more to be learned about the exact mechanisms of MH. Nevertheless, the basic finding that MH

results from a hypermetabolic response to increased levels of intracellular calcium in skeletal muscle in genetically predisposed patients exposed to potent inhalational agents and/or succinylcholine remains an essential tenet of the pathophysiology of the disorder.

Diagnostic Testing

After the demonstration that biopsied skeletal muscle behaved abnormally on exposure to caffeine and to halothane [27, 28] in vitro, a standardized testing protocol to diagnose MH was developed. There are three major testing protocols in common use throughout the world [12]. The protocols in Europe [27] and North America [28] are similar [29]. The one in Japan is different [60].

In protocols using muscle bundles (Europe and North America) weighing about 100 mg, the tissue is tested on the same day as harvest. The muscle tested is either the vastus lateralis or the vastus medialis. Tests are conducted in duplicate or triplicate. The muscle is electrically stimulated to produce contractions of at least 0.5 g. Exposure to caffeine and to halothane results in contracture development (Figs. 3 and 4) in MH-susceptible individuals.

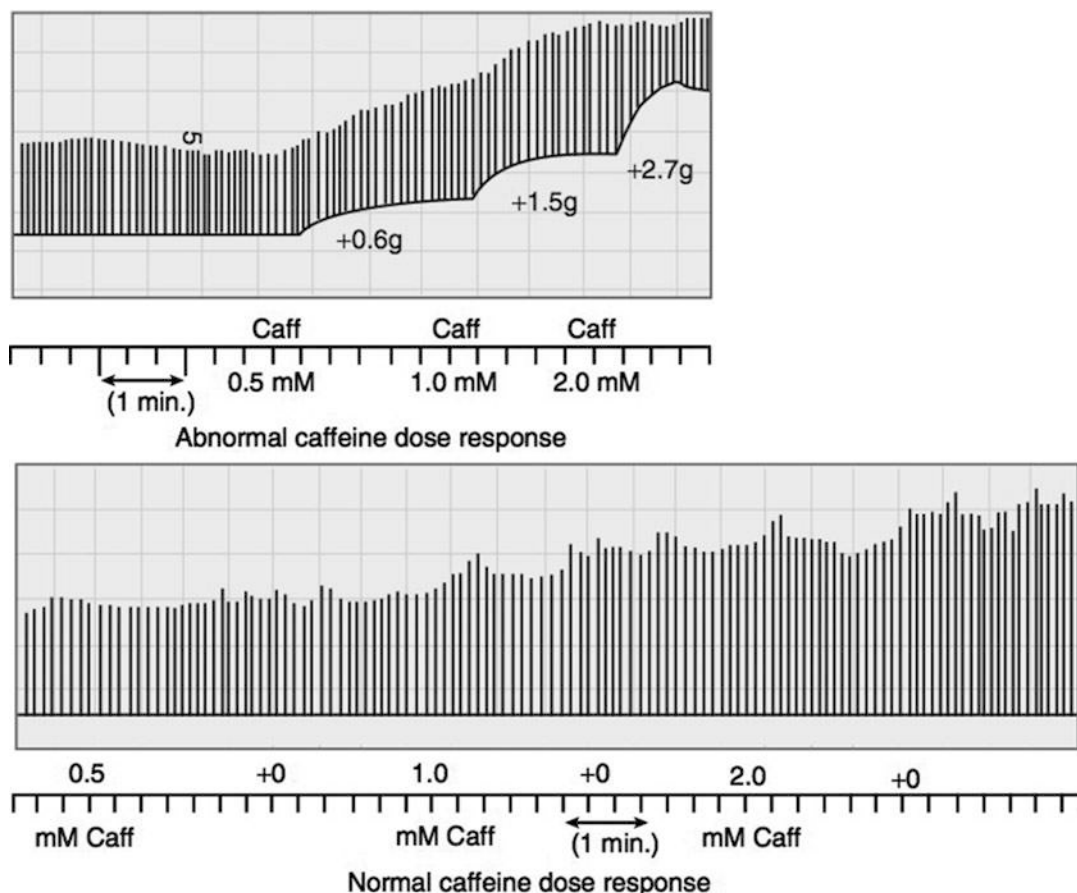


Fig. 4 Responses to caffeine in vitro. Same preparation with different muscle bundles as in Fig. 3 except the muscle bundle is exposed to incremental concentrations

of caffeine for 4 min each. A positive response indicating malignant hyperthermia susceptibility is a contracture of 0.3 g or more to 2 mM of caffeine

In the European protocol [58], exposure to halothane is done in increments of 0.5%, 1%, and 2%. A positive response is a contracture of at least 0.2 g on exposure to 2% or less of halothane (see Fig. 3). Other strips are exposed to incremental doses of caffeine (0.25, 0.5, 1, 1.5, 2, 3, and 4 mM), and a positive response is 0.2-g contracture to 2 mM of caffeine or less (see Fig. 2). If the response to both agents is positive, the patient is considered *MH susceptible*. If the test is positive to only one agent, the patient is designated as *MH equivocal* but for clinical purposes is considered as *MH susceptible*.

In the North American protocol [59], the exposure is to 3% halothane, and a contracture

of 0.5 g or greater is considered positive. Exposure to caffeine is essentially similar to that in Europe except that the concentrations are 0.5, 1, 2, 4, 8, and 32 mM. A contracture of greater than or equal to 0.3 g at 2 mM of caffeine is considered positive. Patients are considered *MH susceptible* if the response to one of the agents is abnormal.

Multicenter studies have shown a sensitivity of close to 100% [27, 28] but a specificity of about 82–93% in Europe [16, 28] and 78% in North America. In both tests, considerable interlaboratory variability is noted – not surprising, given that these are biologic tests. Because 5–15% of responses are considered equivocal by the European test, alternative agents have been

Table 2 Biopsy centers in the USA and Canada^a

The USA	
Bethesda, MD	Uniformed Services University of the Health Sciences (military only)
Winston-Salem, NC	Bowman Gray School of Medicine
Minneapolis, MN	University of Minnesota
Sacramento, CA	University of California, Davis
Canada	
Toronto, Ontario	Toronto General Hospital

^aFurther information may be obtained from the Malignant Hyperthermia Association of the United States (MHAUS) at 1-607-674-7901 or www.mhaus.org

used. Responses to ryanodine [29, 57] and to chlorocresol [61] have been shown to be abnormal in MH muscle.

There are five biopsy centers for MH in North America (Table 2) and more than 20 in Europe. Other biopsy centers exist in other countries, including Australia, New Zealand, Brazil, and Israel. The test is time-consuming and expensive to perform. Despite the promise of other testing procedures, such as determination of high-energy phosphate depletion with exercise in vivo as measured by nuclear magnetic resonance spectroscopy [43–47], the biopsy response to caffeine and halothane remains the gold standard diagnostic test.

In Japan, the diagnostic test also uses skeletal muscle, but muscle in which the sarcolemma has been chemically removed [60]. Such skinned muscle showed accentuated responses to calcium and to caffeine. However, comparison between the skinned muscle test and IVCT test using whole muscle bundles showed a discordance between the two tests. As a result, biopsy centers in Europe and North America have decided not to employ this test [62].

Histologic examination of the biopsied muscle usually reveals nonspecific findings, such as type 1 atrophy, internal nuclei, and variation of fiber size. A few patients show changes consistent with central core or minicore disease, however [63]. Aside from this occasional finding, there is no distinctive pathologic change in MH muscle

[64]. For diagnostic purposes, the patient must be sent to a biopsy center for testing.

With the demonstration of the association between *RYR1* mutations and MH susceptibility in certain families [1, 29], many believe that routine testing for ryanodine mutations has become essential [65]. Some investigators believe that if a known mutation in *RYR1* is found in a family member, other family members showing that mutation may be confirmed as MH susceptible. Further investigation is needed to rule out susceptibility if the mutation is not found in a family member. This is a promising and exciting prospect for simplified diagnosis of MH [27]. In Germany and in Australia, where several families have been identified and screened for *RYR1* mutations, 25% of families can be characterized by a *RYR1* mutation [66]. Family members may be evaluated by DNA testing for susceptibility to MH.

The virtue of molecular genetic testing is the high specificity and the fact that DNA may be harvested from white blood cells or buccal cells. Many other less invasive tests are in development. These include measurement of carbon dioxide production after microinjection of caffeine into muscle [67] and calcium release measurement on exposure of cultured muscle cells to halothane. B lymphocytes also manifest activity of the ryanodine receptor, and the calcium flux changes that are found in muscle may be shown in isolated B lymphocytes. Another study has demonstrated enhanced release of adenosine in B lymphocytes from MH susceptibles [68].

Consultation with an MH biopsy center director, a member of the professional advisory council of MHAUS and/or genetic counselor is advisable prior to referral for diagnostic testing.

Clinical Presentation

The clinical diagnosis of MH may be easy and straightforward or challenging. MH may be precipitated during surgery on exposure to the potent inhalational anesthetic agents and/or succinylcholine only. Other drugs used in anesthesia to produce insensibility or muscle paralysis are not triggers for MH (Table 3).

Table 3 Safe and unsafe pharmacologic agents in malignant hyperthermia

Malignant Hyperthermia Triggers
Succinylcholine
All potent inhalational anesthetics
Halothane
Desflurane
Sevoflurane
Isoflurane
Enflurane
Methoxyflurane
Ethers
Agents that do not trigger malignant hyperthermia
Nitrous oxide
All local anesthetics
Intravenous anesthetics (e.g., thiopental, etomidate, propofol, ketamine, dexmedetomidine)
Nondepolarizing muscle relaxants (e.g., curare, rocuronium, vecuronium, atracurium, cisatracurium, mivacurium, pancuronium)
Opioids (e.g., morphine, fentanyl, sufentanil)
Anxiolytics and benzodiazepines
Reversal agents (e.g., naloxone, flumazenil, anticholinesterases, anticholinergics)
Mixed opioid agonists/antagonists (e.g., nalbuphine, buprenorphine)
Droperidol/haloperidol

In the past, MH most often occurred shortly after induction of anesthesia and was marked by a paradoxical rigid response to succinylcholine, with tachycardia, hypertension, increase in end-tidal carbon dioxide, and fever [1–3]. Although this scenario still occurs, as anesthetic practice has evolved and succinylcholine use has declined, the manifestations of MH have also changed. MH now occurs later in the course of anesthesia and even in the recovery room [69].

The earliest, most sensitive, and specific sign of MH is an increase in end-tidal carbon dioxide that requires large minute ventilation to control. Patients who require two or more times predicted minute ventilation to maintain normocarbica are hypermetabolic. End-tidal carbon dioxide may increase to 50 or 100 mmHg during MH episodes. Besides MH, other causes of hypermetabolism

include sepsis, iatrogenic overheating, faulty monitor function, and rarely thyrotoxicosis or pheochromocytoma (see later discussion of differential diagnosis of MH). Tachycardia is also an early sign of MH, but the differential diagnosis of tachycardia is extensive.

Hyperthermia is often considered a late sign of MH, but recent studies demonstrate that this is not the case. It is one of the three most common early signs of MH [70]. If the patient's body temperature has increased to 40 °C (104 °F), early signs of MH have been missed. If core temperature exceeds 42 °C, disseminated intravascular coagulation almost always supervenes, leading to a high fatality rate. It is vital to monitor a patient's core temperature during all general anesthesia exposures lasting longer than about 20 min. Hyperthermia is sometimes an important tip-off to the diagnosis of MH. A recent study demonstrated that the mortality from MH is increased 13-fold when core temperature is not monitored [70]. All patients undergoing general anesthesia lasting for 30 min or more should have core temperature monitored (esophageal, tympanic, bladder, pulmonary arterial or nasopharyngeal). Other sites of temperature monitoring are not as indicative of core temperature.

Muscle rigidity during anesthesia exposure is another important, specific sign for MH [71]. One of the common forms of muscle rigidity that has been noted in MH is masseter muscle rigidity after the use of succinylcholine. Of children anesthetized with an inhalational agent followed by administered succinylcholine, 1% develop masseter muscle rigidity [72–74]. Clinical MH follows in about 20% of cases, but the onset may be delayed. It is not clear why some patients who are not MH susceptible also develop succinylcholine-induced muscle rigidity. When there is generalized muscle rigidity, MH is almost certain. Masseter rigidity along with generalized rigidity is virtually pathognomonic for MH [75].

Rhabdomyolysis is another characteristic feature of MH [76]. CK elevation may be dramatic and extreme, whereas myoglobinuria may occur soon after the onset of the MH episode.

Myoglobinuria and CK elevation peak at about 14 h after the episode, however, and repeated determinations of CK are needed to diagnose MH or confirm the suspicion of MH. An easy screening test for myoglobin is urine dipstick for blood in the absence of red blood cells. In some cases where MH is detected early and treatment begun promptly, elevation of CK may be minimal.

Hyperkalemia and hypocalcemia are the typical electrolyte changes during an MH episode. Hyperkalemia may lead to arrhythmias. Hyperkalemia sufficient to cause ventricular fibrillation or asystole has been reported after the use of trigger agents in patients with a wide variety of myopathies, especially central core disease, muscular dystrophy, and various forms of myotonia.

Nonspecific signs of MH include tachycardia, tachyarrhythmias, tachypnea, sweating, hypertension, and hypotension. Coagulation abnormalities are more common in patients experiencing marked hyperthermia. Arterial blood gas analysis is essential in confirming the diagnosis of MH in many cases. Typically, respiratory and metabolic acidosis are found. Hypoxemia is not common during MH. Venous blood gas is a good substitute for arterial sampling. Elevation of venous carbon dioxide tension and marked acidosis are seen during MH crisis.

The presentation of MH may consist of a mixture of all of the abovementioned signs or may be limited to only a few, making the diagnosis challenging. When MH is suspected but not easily confirmed, it is advisable to treat with dantrolene, control the metabolic signs, and investigate the patient later. Table 4 lists common signs of MH and their incidence.

Table 4 Signs of malignant hyperthermia

Signs	Incidence (first 30 min) (%)
Tachycardia	90
Hypercarbia	80
Rigidity	80
Hypertension	75
Hyperthermia	70

Time of Onset

Most episodes of MH occur in the early part of the anesthesia exposure, certainly within the first few hours. Late-onset postoperative rhabdomyolysis is unlikely to be MH, but frequently there are not enough data to allow a true differential diagnosis. Perioperative rhabdomyolysis or myoglobinuria may occur in patients who are not susceptible to MH [77].

Normal patients who are not susceptible to MH may experience tenfold to 100-fold increases in serum myoglobin [78] after succinylcholine; repeated administration (i.e., intermittent intravenous bolus) is associated with more prominent increases in myoglobin level. Other causes of perioperative rhabdomyolysis include (1) pressure-induced muscle ischemia from prolonged surgical positioning [79], (2) muscle ischemia from prolonged tourniquet inflation [80], (3) extensive soft tissue trauma, (4) electrical injury, and (5) underlying myopathy/enzymopathy (such as CPT2 deficiency) [81] or metabolic disorder, rendering muscle more susceptible to injury from ischemia, fever, or fasting. It is difficult to exclude MH from consideration with confidence unless the medical record clearly shows absence of hypermetabolism during anesthesia and in the early postoperative period. If the patient later undergoes a biopsy and is found to be MH susceptible by the caffeine halothane contracture test, there is a tendency to assume the episode was MH related. For example, if a patient develops flank pain and rhabdomyolysis starting more than 24 h after an uneventful 8-h anesthetic, and the subsequent caffeine halothane contracture test is positive for MH, it is possible that the patient is not truly MH susceptible [82]. It may be more likely that rhabdomyolysis was caused by skeletal muscle ischemia associated with intraoperative positioning, a previously subclinical metabolic myopathy, or morbid obesity. Whether this was an MH event is highly debatable, although based on contracture test results, the patient should be considered as MH susceptible. In the absence of other specific causes of rhabdomyolysis, such as

sepsis, the patient should be referred for neurologic evaluation for the presence of an occult myopathy or enzymopathy.

Malignant Hyperthermia-Like Conditions

Sudden Cardiac Arrest and Myopathies

In the early 1990s, a series of young, mostly male patients developed unexpected cardiac arrest soon after the induction of anesthesia or in the recovery room, and their cases were reported to the MH hotline [83]. Further investigations of these cases revealed that the patients were harboring myopathies that had not produced clinical signs and symptoms prior to the administration of anesthetic agents. The cardiac arrest in these cases was related to hyperkalemia, whereas hyperthermia, tachycardia, and muscle rigidity were not constant features in all of them. Rhabdomyolysis was, however, common.

After analysis of those events, the younger patients were identified as having classic Duchenne muscular dystrophy, whereas the older patients were found to have Becker's muscular dystrophy [83].

Since then RYR1 mutations have been implicated in a variety of inherited myopathies, and it has been increasingly important as well as difficult to delineate whether and to what extent these myopathies can predispose patients to an MH episode.

Increasing numbers of RYR1-related myopathies are being defined and added to the expanding spectrum of congenital myopathies. Along with the dominantly inherited core myopathies (e.g., central core disease and multiminicore disease), a growing collection of recessive noncore myopathies, with varying mutations along the RYR1 gene, are being investigated [84]. Mutations in RYR1 are considered the most common cause for inherited neuromuscular disease and are associated with a wide range of clinical symptoms from MH susceptibility to clinically recognized congenital myopathies.

Other, non-RYR1 related core myopathies are under investigation. Among them is a rare

myopathy associated with dysmorphic features and MH susceptibility found among patients of Native American heritage. A recessive mutation on the STAC3 gene, which is a component of the excitation-contraction coupling machinery, was isolated in these patients [85]. This myopathy has also been found in individuals who are not Native Americans (Jerome Parness, M.D., Ph.D., Dept. of Anesthesiology, University of Pittsburgh School of Medicine, "personal communication").

Most pediatric anesthesiologists have phased out the routine use of succinylcholine after a black box warning issued by the US Food and Drug Administration ordered a change in the package insert stating that it should be administered in children and young adults only in situations where the patient has a full stomach or a difficult airway. Rapid-onset nondepolarizing agents have largely replaced succinylcholine in the operating room and should be considered for routine use for intubation in the emergency department as well as intensive care units.

Awake Malignant Hyperthermia

MH in the awake state is much harder to diagnose than MH in the operating room. A large increase in the production of carbon dioxide in an immobile and anesthetized patient is unusual. The cold operating room, depression of thermoregulation, and frequent use of neuromuscular blockade make the classic signs and symptoms unusual except in an MH episode. Even patients who are febrile from bacteremia usually lose heat and reduce metabolic rate under anesthesia. Therefore clinical signs frequently suggest the diagnosis of MH early in the disease process in the operating room. The diagnosis can then be confirmed with laboratory tests and subsequent muscle biopsy for IVCT.

Increasing numbers of non-anesthetic-related or awake MH cases have been reported in the last decade. Some of these are related to extreme exertion during sport or exercise [86–88], heat stress [89–91], and sudden death [92]. As we gain more insight into RYR1-mutation-related conditions, it is becoming apparent that sequelae seen with MH can often be seen without the traditional triggering agents. For example,

a recent case report of recurrent fever-induced rhabdomyolysis in a patient who had never been exposed to anesthesia, but was subsequently found to have a novel mutation in the RYR1 gene, highlights this overlap [93]. A study of 39 families with cases of rhabdomyolysis and/or exertional myalgia found nine heterozygous RYR1 mutations in 14 families, further strengthening our understanding of the link between inherited neuromuscular disease and the possibility for malignant hyperthermia susceptibility [94].

Conditions that overlap in their presentation and/or genetic mutations will be discussed in greater detail in the following paragraphs. Suffice it to say here that they may not represent MH in many instances, and they are harder to recognize, diagnose, classify, and sometimes treat than a true “classic” MH case. Even the postoperative patient, who awakens from anesthesia shivering, who may or may not have been febrile preoperatively, is much more difficult to evaluate for MH susceptibility. Although most patients awaken with little to suggest hypermetabolism, many who are hypothermic in the operating room shiver on awakening. This shivering may be confused with evidence of MH [95], even though shivering or rigors are not signs of MH; shivering is frequently treated with low-dose meperidine or acetaminophen. MH is ruled out if this treatment results in lysis of fever. Some patients emerge from anesthesia with excitement and agitation and may need physical restraint. As a result there may be abnormal laboratory results such as lactic acidosis or elevated CK levels. This response, although uncommon, is still more frequent than the incidence of MH in the population (1 in 10,000). Most such patients are not MH susceptible [96, 97] based on IVCTs.

Non-anesthetic Drugs and Circumstances

While MH is often not recognized right away in the operating room, it is even harder to diagnose in the patient who has not had an anesthetic at all or who is more than 24 h postanesthetic; confirmed postanesthetic MH episodes present within 1 h

after discontinuation of anesthesia. In many instances MH is not immediately considered, especially if there is no personal or family history of MH. Aside from cases related to exertion and heat stress, non-anesthetic drugs and consumption of illicit substances have been implicated in triggering MH-like episodes.

Not everyone agrees that these cases are truly MH. Even with a positive IVCT, given its 10–20% false positive rate, a definitive MH diagnosis is uncertain. The more we understand the molecular genetic components and the biochemical mechanisms behind MH, as well as the mechanisms behind uncontrolled temperature elevation and rhabdomyolysis, the more we begin to see a multiplicity of subtypes and possible cumulative stressors and situations capable of triggering an MH-like episode.

Cocaine, for example, does not cause *in vitro* contracture of MH-susceptible muscle, and it does not change the response to low concentrations of halothane [98]. Intrinsic myotoxicity or direct stimulation of muscle metabolism also does not seem to be a factor. But *in vivo*, cocaine may potentiate triggering agents via its many effects on catecholamines, central excitation, and temperature regulation.

Because MH-susceptible muscle is known to be more sensitive to caffeine *in vitro*, one concern often raised is whether patients who are MH susceptible should avoid caffeine or the other methylxanthines such as theophylline. Sufficient evidence seems to have accumulated to indicate that both are safe at doses that are not toxic in normal individuals. Based on *in vitro* studies, it is possible that triggering agents will be more likely to cause an MH episode in patients who exhibit high levels of these agents [99].

Amide local anesthetics were previously thought to be harmful, because lidocaine may enhance *in vitro* contracture by inhibition of calcium sequestration into the sarcoplasmic reticulum. Reexamination has shown that lidocaine does not trigger MH in susceptible swine, even when given in doses above the convulsive threshold [100]. All local anesthetics, including the amides, are currently considered acceptable for anesthetic purposes [101, 102].

Other drugs and compounds have been suggested as triggers of MH or MH-like effects. A link between statin myopathies and MH is currently under investigation, since mutations in muscle disease genes, including RYR1, have been shown to exist in patients with statin induced myopathy [103]. It is still unclear whether statins pose a risk for MH during anesthesia in MH-susceptible patients. It appears reasonable to either avoid statins altogether in patients with MH susceptibility or, at the very least, be watchful for symptoms of rhabdomyolysis when statins are initiated in such patients.

Chlorocresol, a preservative in many drugs, is a potent, specific trigger in the IVCT [104] and is a trigger in vivo in susceptible pigs. However, large doses need to be given over a short period of time to see in vivo triggering. Since such high blood levels are close to the toxic dose in all animals, it is not likely that enough preservative to trigger an MH episode will ever be present in the blood stream [105]. For example, greater than 100 units *per kilogram* of insulin would contain the threshold dose of preservative to trigger MH.

Centrally acting agents, such as serotonin agonists and neuroleptic drugs, may produce a syndrome comprised of fever, acidosis, and rhabdomyolysis that resembles MH. Caroff and associates reported a high incidence of positive response to the IVCT in seven patients with previous NMS [106]. In contrast, Bello and coworkers reported normal IVCTs in 29 of 32 patients with previous NMS [107]. One should therefore not automatically assume that patients with NMS are MH susceptible, and to do so could put them at risk. Patients with severe NMS may benefit from electroconvulsive therapy, and the optimal anesthetic technique for this procedure includes the triggering agent succinylcholine. The rare possibility of an MH episode does not warrant prohibition of the use of succinylcholine in patients with acute NMS unless they are already exhibiting signs of rhabdomyolysis. Even though the pathophysiology of NMS is distinct from MH, dantrolene may benefit patients via reduction or abolition of muscle rigidity, temperature reduction, and attenuation of rhabdomyolysis [108].

A mention of methylene blue and its ability to act as an MAOI inhibitor is warranted in this section. The use of methylene blue in conjunction with a selective serotonin reuptake inhibitor has led to fatal toxicity in the postoperative setting, in part because the general anesthesia may have delayed or attenuated the typical presentation of serotonin syndrome and led to a protracted course [109]. This drug's association with serotonin syndrome and its relative frequent intraoperative use should put anesthesiologists on high alert for MH-like signs. Methylene blue should be avoided in patients currently taking an SSRI.

Infection

Infection as a trigger for MH has been studied in susceptible pigs. Endotoxin injection, and the febrile state that follows, does not lead to MH. The outcome of septic, MH-susceptible pigs was worse, however, when they were also given a triggering agent. This finding is not surprising, because both stressors are potentially lethal [110]. In humans, a study of patients and their families after a suspected MH episode associated with appendicitis showed that only one of 13 were MH susceptible, but three other patients died and were assumed to be MH susceptible [111]. Death occurred in two patients despite the administration of dantrolene. No criteria could distinguish the septic patients from the patients who were MH susceptible. One study did not find any MH susceptibility by IVCT in a group of patients who developed postoperative fever [96].

Exercise and Heat Stress

Rhabdomyolysis has a multitude of etiologies and is characterized by muscle breakdown and elevation of creatine kinase. Commonly seen in cases of MH, it can also be triggered by intense exercise or heat in certain patients. Exertional heat stroke may be associated with MH, but it is not identical [90, 112]. Whether MH-susceptible patients are at increased risk of exertional heat stroke remains a

topic of controversy. Exercise-related problems are infrequently reported in MH-susceptible patients; however, a 2001 case report of exercise-related death raised cause for concern [113]. In this case a patient with a history of anesthetic-induced MH developed muscle rigidity after football practice and subsequently developed elevation in CK and lethal ventricular fibrillation. The patient, his father, and other family members were identified as harboring a typical MH-causative mutation. Although frequently associated with heat stress, several deaths have been attributed to MH after or during exercise. Underlying cardiac arrhythmias were frequently found, and these deaths could therefore be easily dismissed as related to cardiac arrhythmias. Furthermore, many patients who have a diagnosis of MH susceptibility have undergone strenuous exercise with little evidence for an unusual response. While some patients have been exposed to exercise in a controlled environment and shown no adverse effects [114], many suspicious cases have been reported [87, 88, 115]. In a study of 12 young men who developed rhabdomyolysis after exertion, nine were positive on the halothane-caffeine contracture test, and three of those displayed one of the typical MH-causative mutations [116].

In a knock-in mouse model with human RYR1 malignant hyperthermia mutations, exercise alone did not show increased rhabdomyolysis, but with an increase in ambient temperature, animals died of malignant hyperthermia [117, 118]. In a model in which homozygotes were viable, it could be shown that gene dose (homozygous vs. heterozygous), male gender, and elevated environmental temperatures increased the risk of death in MH-susceptible animals [118]. These studies further support the apparent multifactorial etiology for triggering an MH-like episode. While exercise alone could bring on rhabdomyolysis in a recent family cohort study, it was most often only triggered by a combination of stimuli, such as heat, exercise, and alcohol [94].

Since rhabdomyolysis, acidosis, and hyperthermia may be attributed to exercise or resuscitation alone, muscle rigidity and postmortem fever seem to be the major diagnostic criteria for

malignant hyperthermia-related rhabdomyolysis [119]. Muscle biopsy for caffeine halothane contracture testing should not be ordered until the patients have recovered from rhabdomyolysis (≥ 6 months), because damaged muscle may give rise to abnormal IVCTs. One may, however, send muscle tissue for molecular genetic testing.

Differential Diagnosis

Given that the signs of MH consist of tachycardia, acidosis, hypercarbia, fever, and muscle destruction, either together or in various combinations, it is not surprising that other syndromes may resemble MH (Table 5). Sepsis probably is confused most often with MH. Patients undergoing urinary tract surgery; ear, nose, and throat surgery; or appendectomy for appendicitis develop fever and sometimes acidosis. Elevated CK also may occur during episodes of sepsis. In contrast to MH, muscle rigidity is uncommon, although rigors may be mistaken for rigidity. In addition, signs of sepsis are treated effectively with nonsteroidal anti-inflammatory drugs and antibiotics. MH does not respond to such nonspecific therapy. Dantrolene often may be associated with acute reduction of fever. This finding is also nonspecific, however. Differentiating sepsis from MH is often not possible clinically.

Brain injury from a variety of causes has also been mistaken for MH [120, 121]. Patients may

Table 5 Differential diagnosis of malignant hyperthermia

Amphetamine toxicity	Intracranial bleed
Anticholinergic syndrome	Lethal catatonia
Brain injury	Meningitis
Cocaine toxicity	Neuroleptic malignant syndrome
Contrast-induced neurotoxicity	Pheochromocytoma
Drug/alcohol withdrawal	Salicylate toxicity
Extrapyramidal syndrome	Sepsis
Heatstroke	Serotonin syndrome
Hypoxic encephalopathy	Sympathomimetic toxicity
Iatrogenic overheating	Thyrototoxicosis

become febrile from hypothalamic damage or hemorrhage into the cerebral ventricles and may appear rigid due to posturing. If adequate ventilation is not provided, they may become hypercapnic. Ongoing muscle destruction is often associated with high temperatures ($\geq 42^\circ\text{C}$ [107.6°F]). Seizures can also produce an image of muscle rigidity. In contrast to MH, treatment with neuromuscular blocking agents will relax muscles and prevent acidosis, though true seizure activity requires treatment with anticonvulsants to prevent brain injury.

Endocrine disorders, such as pheochromocytoma and thyrotoxicosis, may produce increased oxygen consumption, tachycardia, hypertension, fever, and cardiovascular collapse. They have occasionally been misdiagnosed as MH. Pheochromocytoma is particularly difficult to diagnose, since patients often do not report a history suggestive of episodes of hypertension [122].

Iatrogenic overheating has been misdiagnosed as MH. In these situations, the patient is usually completely draped, the patient is externally warmed, and the procedure is lengthy. The patient develops fever, hypercarbia, tachycardia, and tachypnea if unparalyzed. Simple undraping leads to lysis of the fever, especially in an unanesthetized patient.

NMS is an idiosyncratic adverse drug reaction to neuroleptic drugs as well as to the newer atypical neuroleptics such as olanzapine and clozapine. There is no pathognomonic feature, nor are there diagnostic tests available for this syndrome. In contrast to the typically rapid onset of MH, NMS usually develops over days to weeks after initiation of the neuroleptic drug. NMS patients typically present with fever, extrapyramidal symptoms (e.g., rigidity, shuffling gait, resting tremors, dyskinesia, elevated CK), altered consciousness, and autonomic instability. In NMS, temperature is infrequently greater than 39°C . MH-susceptible individuals tolerate neuroleptics, and individuals with NMS have tolerated general anesthetics and succinylcholine. Nondepolarizing paralytics (e.g., vecuronium or cisatracurium) cause muscle flaccidity in patients with NMS but do *not* resolve the rigidity of MH. Although NMS is rare in the perioperative

setting, a thorough medication history is essential in making a diagnosis. Dantrolene has been shown to be beneficial in treating NMS [108] (see ► Chap. 31, “Neuroleptic Malignant Syndrome”).

Many other drugs have been implicated in creating an MH-like presentation. Exposure to any drugs that greatly increase dopaminergic, serotonergic, or catecholaminergic function, or produce central anticholinergic syndrome, can produce signs similar to those of malignant hyperthermia. In contrast to the hypercarbia of an MH episode, respiratory alkalosis, complicated by metabolic acidosis in severe cases, would be the norm with poisoning from sympathomimetics or amphetamines.

A well-studied example is serotonin toxicity, leading to serotonin syndrome. This is yet another drug-induced hyperthermia syndrome, in this case due to greatly increased central nervous system serotonin. Serotonin syndrome is classically produced by the combination of an SSRI with a monoamine oxidase type A inhibitor. For example, antidepressants with or without opioid analgesics, such as meperidine, dextromethorphan, or fentanyl, lithium, or drugs of abuse such as lysergic acid diethylamide or methylenedioxymethamphetamine (MDMA) have been implicated. Methylene blue has also recently been shown to induce serotonin toxicity in combination with drugs having SSRI activity due to its potent monoamine oxidase inhibitor activity [123]. Serotonin syndrome is characterized by a constellation of neuromuscular, autonomic, and central nervous system manifestations and can superficially resemble both MH and NMS. The onset is typically fast (≤ 24 h) after introduction of the offending drug dose or combination, and it typically resolves within 24–36 h. The severity of muscle rigidity, rhabdomyolysis, and hyperthermia is typically less than that seen in MH or NMS but can be life threatening nonetheless. A comprehensive medical history helps establish the diagnosis. Most cases of serotonin syndrome are self limited with discontinuation of the offending drug or drug combination and administration of sedation and cooling measures, but central serotonin antagonism with cyproheptadine or olanzapine has been successfully used in

severe cases The role of dantrolene in life-threatening serotonin toxicity is unclear, with no reduction of mortality in an animal model [124]. Dantrolene, as an adjunct to supportive therapy including cooling measures, has been associated with good outcomes in cases of MDMA intoxication complicated by hyperthermia and rhabdomyolysis (see ► Chap. 24, “Serotonin Syndrome”).

Other causes of misdiagnosis of MH include faulty temperature monitoring devices, faulty calibration of capnograph, absorption of carbon dioxide during laparoscopic procedures, underventilation of a septic patient, and a variety of causes of fever.

Although the only way to diagnose MH definitively is by means of the CHCT (caffeine halothane contracture testing) or the IVCT, the constellation of clinical signs may be helpful in determining the likelihood that a clinical event was related to MH. The clinical grading scale employs a point system based on the presence of signs of MH to score an episode. The details of the scoring system may be found elsewhere [125]. The utility of the scoring system depends on the completeness of data that are collected in a given patient. At present, the scoring system is used as a research tool only.

Management of Patients with Known Malignant Hyperthermia Susceptibility

Patients with MH susceptibility should have a preanesthetic evaluation. Safe anesthesia consists of either regional anesthesia with local anesthesia (all local anesthetics are safe) or general anesthesia using nitrous oxide and/or intravenous agents such as propofol, barbiturates, benzodiazepines, opioids, or ketamine. Intravenous sedation may be appropriate depending on the procedure and other patient comorbidities. All nondepolarizing neuromuscular blocking agents are safe. All potent inhalational agents and succinylcholine are MH triggers and must be avoided. Currently used potent inhalational anesthetics include desflurane, sevoflurane, and isoflurane. Halothane, enflurane, methoxyflurane, cyclopropane, and ether are no

longer available for clinical use in humans in the USA. Dantrolene pretreatment is *not* necessary.

Preparation of older-generation anesthesia machines (“workstations”) consisted of removing, closing, or disabling gas vaporizers, flowing 10 L/min of oxygen or air through the machine for at least 20 min, and changing the carbon dioxide absorbent. If a ventilator is to be used, the rebreathing bag should be affixed to the Y-piece and the ventilator cycled at 5–8/min during the 20 min flushing. The goal of these measures is to reduce the residual level of volatile anesthetic to <5 ppm, which is very unlikely to trigger an acute MH episode in a susceptible individual [127] and far below the concentration that can be detected by conventional anesthetic gas analyzers.

Current generation anesthetic workstations, using the method described above, require far longer times (e.g., >1 h) to achieve <5 ppm residual anesthetic [127]. The insertion of an activated charcoal filter (e.g., Vapor-Clean®) into the inspiratory limb of the breathing circuit results in prompt (e.g., <2 min) reduction of residual volatile anesthetic levels to <5 ppm; the filter is inserted following a brief (<2 min) flush of the breathing circuit with at least 10 L/min fresh oxygen flow. Because of the potential of users to unintentionally insert the filter in the expiratory limb, the manufactured product includes two filters for placement on both limbs of the breathing circuit. The manufacturer also recommends that high fresh gas flow be maintained during delivery of trigger-free general anesthesia [128–130] (link: <http://www.dynasthetics.com/Vapor-Clean/Vapor-Clean-IFU.pdf>).

Treatment

The success in controlling deaths from MH is due to early recognition of the acute syndrome and prompt treatment with dantrolene sodium intravenously (level of evidence [LoE] II-3). Dantrolene is a hydantoin derivative that inhibits calcium leak or release from the sarcoplasmic reticulum. Additional studies suggest significant inhibition of RyR1-dependent calcium influx via store-operated calcium entry, though this

inhibition does not involve a direct inhibition of store-operated calcium entry channels. It has no effect on excitation-contraction coupling in cardiac or smooth muscle. In an animal model of ventricular fibrillation, dantrolene was shown to facilitate successful defibrillation and return of spontaneous circulation; this was associated with a significant reduction of fibrillation-induced diastolic calcium leak/elevation [131]. Toxicity is limited when given over only a few days. Long-term administration may be associated with hepatotoxicity. The elimination half-life is 7–12 h.

Traditional preparations of dantrolene are poorly soluble in water – an initial treatment dose of 200 mg (=10 bottles) in a 80 kg patient requires 600 mL sterile water for injection to dissolve. Dantrolene is supplied as a lyophilized powder with 3 g of mannitol and sodium hydroxide to maintain pH of 9–10. Dantrium[®] or Revonto[®] must be mixed with 60 mL of *sterile water* and shaken vigorously. Each vial contains 20 mg of dantrolene.

In 2014, the FDA approved Ryanodex[®] (Eagle Pharmaceuticals), a nanocrystalline formulation of dantrolene sodium, for clinical use. Ryanodex[®] is

Table 6 Malignant hyperthermia treatment protocol

When MH is identified, notify surgeon/proceduralist and call for help; if in a freestanding surgery center or office, call 911. Immediately discontinue volatile anesthetic. If surgery must proceed, maintain anesthesia with intravenous agents and nondepolarizing muscle relaxants as needed. High oxygen flow should be employed to hasten reduction of inhalational agent level in the breathing circuit. If available, insert Vapor-Clean [®] filters into the breathing circuit to more rapidly reduce inhalational anesthetic levels
Hyperventilation: increase minute ventilation to ≥ 200 mL/kg/min, e.g., 20–25 breaths/min \times 8–10 mL/kg tidal volume). Mechanical ventilation is recommended because simulation has shown that switching to manual ventilation usually results in significantly decreased minute ventilation [138] (LoE III)
Dantrolene should be mixed and a dose of 2.5 mg/kg injected rapidly
Repeat as frequently as needed until the patient responds with a decrease in ET CO_2 , decreased muscle rigidity, and/or lowered heart rate. While the crisis is usually controlled with doses <10 mg/kg, large doses (>10 mg/kg) may be required for patients with persistent contractures or rigidity. If giving large doses (>10 mg/kg) without symptom resolution, consider alternative diagnoses. During this time, if the patient is decompensating or if blood gas shows base excess ≥ -8 , bicarbonate should be given, 1–2 mEq/kg
If temperature ≥ 39 °C or rapidly rising, cooling should begin using cold intravenous isotonic crystalloid, surface cooling, or intraperitoneal lavage with cool isotonic solution as appropriate [139] (LoE II-3). Stop cooling when temperature is ≤ 38 °C
In the case of cardiac arrest, potassium levels should be obtained immediately. If elevated or if hyperkalemia is suspected but quick lab results are unavailable, treatment should begin with calcium chloride, glucose, and insulin along with hyperventilation and sodium bicarbonate. Epinephrine and other β_2 -agonists may be lifesaving
Treatment of metabolic acidosis includes dantrolene and sodium bicarbonate as needed. Minute ventilation may need to be further increased to compensate for additional CO_2 released by any administered sodium bicarbonate (500 mL CO_2 gas is produced with administration of 25 mL intravenous sodium bicarbonate)
Arrhythmias should be treated with antiarrhythmics, with the exception of verapamil or diltiazem, because they may produce hyperkalemia or myocardial depression in the presence of dantrolene [140]. If a patient already taking oral verapamil or diltiazem is suspected of having an acute MH crisis, one should not hesitate to give dantrolene and should not reduce the initial treatment dose or avoid giving additional dantrolene if there are persistent signs of hypermetabolism or rigidity. One should exercise caution in the treatment of wide QRS complex rhythms with lidocaine or procainamide, as this may be a sign of hyperkalemia, and treatment with class 1 antiarrhythmics may result in asystole [141]
Arterial blood gases, electrolytes, creatine kinase, and coagulation studies should be obtained
When the initial crisis is under control, the patient should receive 1 mg/kg of dantrolene every 4–6 h or an infusion of 0.25 mg/kg/h for at least 24 h. Signs of recrudescence such as recurrent hypercarbia (not due to fighting the ventilator), rigidity not resolving with sedation, or recurrent myoglobinuria mandate re-bolusing with dantrolene in order to rapidly control hypermetabolism and prevent deterioration. Creatine kinase should be assessed every 12–24 h until stable
If myoglobinuria occurs, vigorous diuresis should be instituted with fluid administration and alkalinization. Each vial of Dantrium [®] or Revonto [®] contains 3 g of mannitol; 2.5 mg/kg of these dantrolene preparations gives the patient 0.4 g/kg of mannitol. One should carefully and frequently assess volume status in order to avoid either hypovolemia with impaired organ perfusion or fluid overload

vastly more water soluble – 250 mg of Ryanodex powder (1 bottle) is dissolved in 5 mL sterile water. Preclinical study in MH-susceptible swine demonstrated efficacy in treating acute MH triggered by halothane [126]. Ryanodex® contains very little mannitol. It is recommended that at least 10 mg/kg of dantrolene for treatment of an MH crisis in a 70 kg patient be immediately available wherever general anesthesia with potent agents or succinylcholine is used. While the great majority of anesthesia-induced MH episodes are associated with potent inhalational anesthetics, there are a small number of documented cases where succinylcholine alone was administered [133, 134]. Short-term side effects of dantrolene include muscle weakness, phlebitis, nausea, and vomiting [135]. The drug does not impair respiration except in patients with underlying muscle disease.

Any facility where general anesthesia is administered should be prepared to treat MH. Ambulatory surgery centers or offices that use MH-triggering agents must have a plan in place for transfer of care to an emergency room that focuses on clear communication and ongoing urgent treatment of the MH crisis [137]; interruption or delay of treatment with dantrolene may result in death or severe complications from fulminant MH. A treatment protocol should be readily available, such as the one available from the MHAUS (Table 6). It is beneficial to refer to a cognitive aid, be it the MHAUS treatment protocol, an available iPhone app (link: <http://www.mhaus.org/healthcare-professionals/managing-a-crisis/iphone-app>), or the Stanford Emergency Manual (link: <http://emergencymanual.stanford.edu>) [137]. Table 7 lists suggested items to be kept in a treatment cart.

Help in diagnosing and managing clinical cases of MH is available through a hotline service offered by the Malignant Hyperthermia Association of the United States (MHAUS) at no cost. Experts in MH share responsibility in answering questions regarding MH and its treatment 7 days a week, 24 h per day. The hotline number is 1-800-MH-HYPER (1-800-644-9737). Outside the USA the number is 0011-315-464-7079. Further details about MHAUS are given subsequently. More than 1500 calls are handled by the hotline each year; only about 300 are related to actual MH cases.

Table 7 Treatment cart for care of malignant hyperthermia: suggested supplies and equipment (link: <http://www.mhaus.org/faqs/stocking-an-mh-cart>)

Dantrolene, 20 mg/vial, 36 vials or Ryanodex®, 250 mg/vial, 3 vials
Sterile water for injection USP in 50 or 100 mL vials for mixing Dantrium® or Revonto®
Refrigerated 0.9% Sodium Chloride or Plasma-Lyte-A, 2–3 l
Sodium bicarbonate, 8.4%, 50 mL ampules x 5
Glucose 50%, 50 mL ampules × 2
Furosemide, 10 mg/mL, 2 vials
Calcium chloride 10%, 10 mL vials × 2
Lidocaine 1%, 10 mL, 2 vials
Amiodarone HCl intravenous, 450 mg
Regular insulin, 100 U/mL × 1
Syringes (3 mL) for blood gas and electrolyte analysis or ABG kits × 6 for point-of-care monitors. Blood collection tubes for CK, PT, PTT, fibrin-split products, electrolytes, platelets
Arterial and central venous pressure kits
Plastic bags for ice
Mini-Spike or similar transfer pin to mix water with dantrolene
Urinary dipstick for hemoglobin (for detection of myoglobin)
Esophageal or nasopharyngeal temperature probes
Rectal or bladder temperature probes
CK creatine kinase, PT prothrombin time, PTT partial thromboplastin time

Sources of Information Concerning Malignant Hyperthermia

Updated information may be obtained from the MHAUS (www.mhaus.org; PO Box 1069, Sherburne, NY 13460, USA), a not-for-profit patient advocacy organization. Formed in 1981 to provide information to practitioners and patients regarding MH, MHAUS sponsors a hotline and the North American MH Registry and produces pamphlets, a newsletter, a fax-on-demand service, and a website (www.mhaus.org), among other services. The phone number is 1-607-674-7901. The board of directors of MHAUS consists of laypersons and professionals. Support for MHAUS is from a variety of sources, but mostly from voluntary contributions. In addition, MHAUS sponsors and supports the

Neuroleptic Malignant Syndrome Information Service (www.nmsis.org) with goals similar to the goals described previously. Another useful resource is GeneTests (www.genetests.org).

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Key Points in Hematologic Syndromes

1. Oxidant hemolysis, methemoglobinemia, and sulfhemoglobinemia share common etiologies and frequently coexist in the same patient.
2. Methemoglobinemia or sulfhemoglobinemia should be suspected when a cyanotic patient does not have a significantly depressed arterial P_aO_2 or when the history suggests toxic exposure to a known etiologic agent.
3. Methemoglobin impairs oxygen delivery by producing a functional anemia and by shifting the oxygen-hemoglobin dissociation curve to the left.
4. Oxygen carrying capacity can worsen, while methemoglobin fractions decrease or cyanosis improves if accompanying hemolysis produces significant decreases in hemoglobin concentrations.
5. Methylene blue enhances enzymatic reduction of methemoglobin but is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency.
6. Dual-wavelength pulse oximetry is unreliable in the presence of methemoglobinemia or sulfhemoglobinemia.
7. Co-oximeters vary widely in their ability to detect, measure, and report sulfhemoglobinemia; some report sulfhemoglobin as methemoglobin.

(continued)

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8. Sulfhemoglobin cannot transport oxygen but shifts the oxygen-hemoglobin dissociation curve to the right; impaired oxygen delivery usually is not a problem unless accompanying hemolysis or methemoglobinemia is significant.
9. Methylene blue does not lower sulfhemoglobin fractions. Sulfhemoglobin persists for the life of the erythrocyte.

Common Errors in Management of Hematologic Syndromes

Failure to realize that arterial P_aO_2 is usually normal or at baseline values in patients with methemoglobinemia

Not recognizing that percent saturations reported by many blood gas machines are calculated, rather than measured, and can be reported as normal despite hemoglobinopathies such as methemoglobinemia

Forgetting to consider the total hemoglobin concentration when assessing impairment of oxygen carrying capacity from methemoglobinemia

Failure to seek evidence of hemolysis in patients with methemoglobinemia and vice versa

Failure to understand whether a specific co-oximeter being used in patient management detects or reports sulfhemoglobinemia

Not realizing that dual-wavelength pulse oximetry does not provide reliable

measurements of saturation in the presence of methemoglobinemia or sulfhemoglobinemia

Forgetting that known glucose-6-phosphate dehydrogenase deficiency is a contraindication to therapy with methylene blue

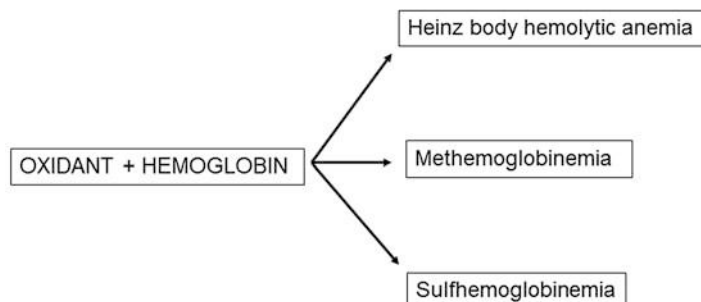
Failure to recognize that Heinz bodies cannot be seen on routine Wright's stain of blood

Three main syndromes result from erythrocytic oxidant stress. Removal of electrons from the protein portion of hemoglobin and other erythrocytic macromolecules leads to *oxidant hemolytic anemia*, characterized by Heinz bodies and bite cells. Removal of electrons from the ferrous iron in hemoglobin produces *methemoglobinemia*. Lastly, oxidation of hemoglobin's porphyrin ring by sulfur results in *sulfhemoglobinemia*. The etiology, pathophysiology, occurrence, diagnosis, and treatment of oxidant-induced hemolytic anemia, methemoglobinemia, and sulfhemoglobinemia are entangled (Fig. 1) [1–3].

Some chemical agents responsible for oxidant hemolysis, methemoglobinemia, or sulfhemoglobinemia frequently lack oxidizing potential in vitro. Their ability to produce oxidant stress is explained most commonly, however, by electrophiles produced from metabolism by cytochrome P-450 enzymes. For example, dapsone, benzocaine, and some sulfonamides are metabolized to hydroxylamines that are responsible for producing oxidant stress.

The circulating red blood cell lacks mitochondria and depends on glycolysis and the hexose monophosphate shunt for energy production (Fig. 2). Adenosine triphosphate produced in

Fig. 1 Consequences of erythrocytic oxidant stress



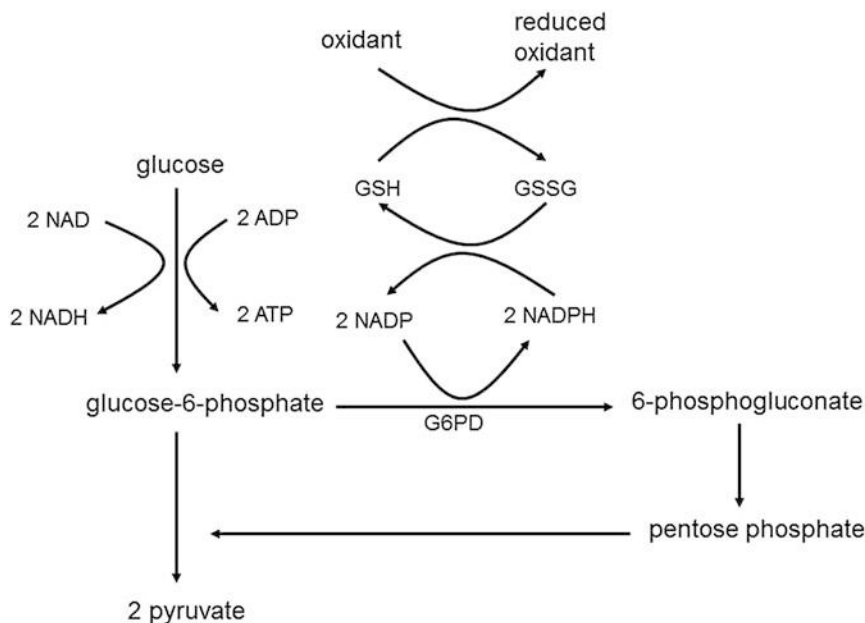


Fig. 2 Erythrocytic energy production. *ADP* adenosine diphosphate, *ATP* adenosine triphosphate, *G6PD* glucose-6-phosphate dehydrogenase, *GSH* reduced glutathione, *GSSG* oxidized glutathione, *NAD* nicotinamide

adenine dinucleotide, *NADH* reduced nicotinamide adenine dinucleotide, *NADP* nicotinamide adenine dinucleotide phosphate, *NADPH* reduced nicotinamide adenine dinucleotide phosphate

glycolysis meets energy requirements, whereas glycolytic production of reduced nicotinamide adenine dinucleotide (NADH) is essential in maintaining methemoglobin fractions within the normal range. The hexose monophosphate shunt produces reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is used to protect against oxidant-induced hemolysis [4].

Hemolysis

Pathophysiology and Etiology

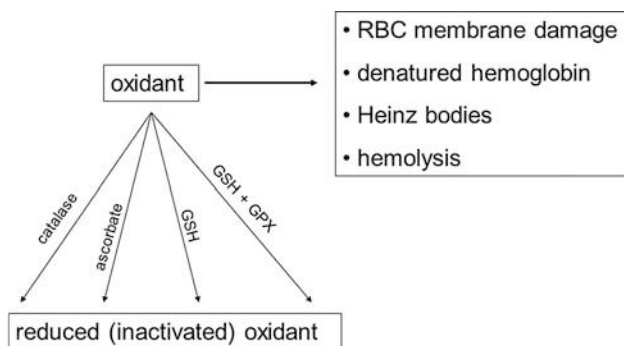
Erythrocytes constantly encounter oxidant stress from multiple sources, including food, infection, oxygen, drugs, and chemicals. Oxidation of the protein portion of hemoglobin results in denaturation and attachment of damaged protein to the internal cell membrane, which is visible as Heinz bodies with special staining of blood smears. Erythrocytes filled with denatured hemoglobin are trapped in the microcirculation of the spleen,

where pieces of plasma membrane are removed (resulting in bite cells) or where entire red blood cells undergo destruction, producing extravascular hemolysis (nonspherocytic) [3, 5]. Oxidant stress may produce hemolysis by several additional mechanisms, including depletion of intracellular glutathione stores with direct damage to the erythrocytic membrane and oxidation of other proteins, such as enzymes needed for erythrocyte integrity. Tremendous oxidant stress (e.g., chlorates) can produce intravascular hemolysis as well.

The erythrocyte protects itself from oxidant-induced hemolysis by reducing oxidants before protein denaturation occurs [4]. Reduced glutathione, nonenzymatically and enzymatically with glutathione peroxidase, is responsible for most reducing capacity in this regard. Catalase also reduces hydrogen peroxide; ascorbate is a mild reducing agent (Fig. 3).

Adequate stores of reduced glutathione are maintained within the erythrocyte through the conversion of NADPH to NADP (see Fig. 2). NADPH formation requires a properly

Fig. 3 Protection against hemolysis by reduction of oxidants. *GPX* glutathione peroxidase, *GSH* reduced glutathione, *RBC* red blood cell



functioning hexose monophosphate shunt. Patients who display congenital deficiency of glucose-6-phosphate dehydrogenase (G6PD), the first enzyme in the hexose monophosphate shunt, can be predisposed to hemolysis from sources of oxidant stress that would not affect normal phenotypes. The most common sources of oxidant stress producing hemolysis in these patients are infection, drugs, and food. Oxidant-induced hemolysis can be produced in anyone, however, if oxidant stress is severe enough, such as after overdose with numerous drugs (e.g., phenazopyridine, dapsone) (Table 1).

Logically, substances producing oxidant hemolysis share the ability to produce methemoglobinemia and sulfhemoglobinemia. Some agents are known better for producing hemolysis than accompanying dyshemoglobinemias, however. Naphthalene, an aromatic hydrocarbon, produces hemolysis [6] and less commonly is associated with severe methemoglobinemia. On the other hand, chlorates [7] produce hemolysis but also can cause marked methemoglobinemia.

Clinical Presentation and Diagnosis

Other than the expected effects of acute anemia, complications of hemolysis include hyperkalemia and pigment nephropathy. Jaundice may appear after a few days. Methemoglobinemia and occasionally sulfhemoglobinemia commonly accompany Heinz body hemolytic anemia, and evidence for this should be sought.

Hemolysis is diagnosed by showing decreases in blood hemoglobin and serum haptoglobin concentrations and a rise in plasma-free hemoglobin concentration. Hemoglobinuria results when plasma concentrations of hemoglobin increase sufficiently to saturate haptoglobin and turn plasma pink or red. In oxidant-induced disease, bite cells may be noted on routine Wright's stain of blood [3]. Heinz bodies can be detected with special staining, but they are not detectable with Wright's stain of blood. Spherocytes are typically absent or only mildly increased in number. Reticulocytosis is delayed for several days after onset of hemolysis.

Treatment

In general, treatment is supportive with blood transfusion, ensuring appropriate hydration, and monitoring for hyperkalemia. Specific therapies may be indicated with specific toxins (e.g., exchange transfusions for arsine, D-penicillamine for copper). Intravenous *N*-acetylcysteine prevented severe decreases in whole-blood glutathione concentration in cats with acetaminophen-induced methemoglobinemia [8], and in vitro studies in human erythrocytes revealed that incubation in solutions containing *N*-acetylcysteine can prevent oxidant hemolysis produced by various agents [9, 10]. No reports have shown *N*-acetylcysteine's effectiveness, however, at preventing or lessening oxidant hemolysis in humans with acute poisoning.

Table 1 Examples of agents producing oxidant stress^a

Acetanilid
Aminophenols
p-Aminosalicylic acid
Amyl nitrite
Aniline
Anilinoethanol
Arsine ^b
Benzocaine ^c
Benzoylphenylurea
Bismuth subnitrate
Bromoaniline
Bupivacaine ^c
Chloramine
Chlorates ^b
Chlorites
Chloroanilines
Chloroquine
Chromates ^b
Clofazimine
Dichromates
Cobalt preparations
Commercial inks
Copper sulfate ^b
Dapsone
Diaminodiphenylsulfone
Dimethylamine
Dimethylaminophenol
Dimethylaniline
Dimethyl sulfoxide
Dimethyltoluidine
Dinitrobenzene
Dinitrophenols
Dinitrotoluene
Flutamide
Hydrazines
Hydroquinone
4'-Hydroxyacetanilid
Hydroxylamine
Ifosfamide
Indoxacarb
Isobutyl nitrite
Lidocaine ^c
Local anesthetics ^c
Metaflumizone
Methylene blue
Metobromuron

(continued)

Table 1 (continued)

Metoclopramide
Monolinuron
Mushrooms
Naphthalene
Naphthylamine
Nitrates ^c
Nitric oxide
Nitrites
Nitroalkanes
Nitroaniline
Nitrobenzene
Nitroethane
Nitrofurans
Nitroglycerin
Nitrophenol
Pamaquine
Pendimethalin
Phenacetin
Phenazopyridine
Phenetidine
Phenols
p-Phenylenediamine
Phenylhydrazine
Phenylhydroxylamine
Piperazine
Plasmoquine
Prilocaine ^c
Primaquine
Propanil
Pyridine
Pyrogallol
Quinones
Rasburicase/pegloticase
Resorcinol
Riluzole
Sodium nitrite ^c
Stibine ^b
Sulfonamides
Sulfones
Sulofenur
Tetralin
Tetranitromethane tetronal
Thiocolchicoside
Toluenediamine
Toluidine
Trichlorocarbanilide

(continued)

Table 1 (continued)

Trinitrotoluene
Trional
Zopiclone

^aPoisoning (and sometimes therapeutic doses) by these agents variously produces combinations of Heinz body hemolytic anemia, methemoglobinemia, or sulfhemoglobinemia in individual patients. Why some patients develop methemoglobinemia, whereas others mainly develop sulfhemoglobinemia or hemolysis, is not well understood

^bKnown for producing extraordinarily severe hemolysis

^cHemolysis usually not significant after a single therapeutic dose, even when methemoglobinemia is present

Methemoglobinemia

Pathophysiology

Reduced hemoglobin (deoxyhemoglobin) contains four ferrous (Fe^{2+}) heme groups capable of binding and transporting oxygen. Oxidation to the ferric (Fe^{3+}) state produces methemoglobin. Oxidant stress produces denaturation of hemoglobin with hemolysis and methemoglobin, explaining the coexistence of both disorders in the same patient (see Fig. 1).

Reduced (ferrous) hemoglobin continuously undergoes conversion to methemoglobin within erythrocytes, to a large extent from the oxidizing power of oxygen. Values for methemoglobin are reported most commonly in percentages (fractions). These fractions represent the percentage of all hemoglobin pigments present as methemoglobin. Methemoglobin fractions in whole blood are normally less than 1–2%. When fractions exceed this value, methemoglobinemia is said to be present. Hemoglobinemia refers to the presence of excess hemoglobin in plasma, whereas methemoglobinemia refers to elevated circulating fractions of methemoglobin within erythrocytes.

Methemoglobin does not transport oxygen. Ferri heme groups impair unloading of oxygen by ferrous heme on the same hemoglobin tetramer, shifting the oxygen-hemoglobin dissociation curve to the left [4]. Serious signs and symptoms from methemoglobinemia result from impaired oxygen delivery to tissues and from cyanosis, which can be seen before significant impairment of oxygenation.

Visible cyanosis is produced by 5 g of normal deoxyhemoglobin per 1 dL of capillary blood [11]. Because methemoglobin is dark brown, however, only 1.5 g of methemoglobin per dL of blood is required to produce noticeable discoloration [12]. In nonanemic patients, about 10–15% methemoglobinemia produces cyanosis without significant impairment of oxygen delivery. Progressive increases in methemoglobin fractions to 20–40% in nonanemic patients are accompanied by headache, dyspnea, tachypnea, tachycardia, and mild hypertension. Further increases in methemoglobin fractions into the 40–55% range (without anemia) may begin to produce confusion, lethargy, and metabolic acidosis. Additional increases result in coma, seizures, bradycardia, ventricular dysrhythmias, and hypotension; near 70% methemoglobinemia results in death. We have seen one nonanemic patient who was awake with 73% methemoglobinemia after benzocaine exposure during a transesophageal echocardiogram who complained only of weakness and voices and noises sounding distant.

Anemic patients experience more severe impairment of oxygen delivery and more severe signs and symptoms at given methemoglobin fractions than nonanemic patients. Anemic patients also exhibit less profound cyanosis at given methemoglobin fractions.

Although inactivation of oxidants is the main mechanism by which oxidant hemolysis is prevented, oxidant inactivation remains relatively unimportant in maintaining methemoglobin fractions within the normal range. Patients with congenital glutathione deficiency, G6PD deficiency, catalase deficiency, and scurvy do not have elevated methemoglobin fractions. Rather, methemoglobin fractions are maintained at low levels by allowing methemoglobin to form and then immediately enzymatically reducing it back to ferrous hemoglobin.

Erythrocytic cytochrome- b_5 reductase accounts for virtually all normal methemoglobin reduction (Fig. 4) [13]. In this process, electrons from NADH (produced in glycolysis) are used to reduce cytochrome b_5 , which reduces methemoglobin to form ferrous hemoglobin. Normal enzymatic methemoglobin reduction requires an intact

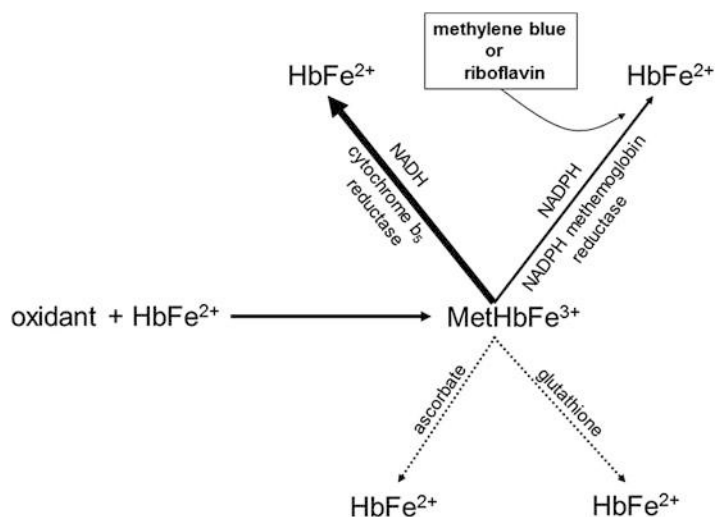


Fig. 4 Mechanisms of maintaining low methemoglobin (MetHbFe³⁺) fractions through MetHbFe³⁺ reduction. Significant MetHbFe³⁺ reduction in vivo occurs only through cytochrome-*b*₅ reductase, which uses reduced nicotine adenine dinucleotide (NADH) as a reducing agent. Methylene blue markedly enhances MetHbFe³⁺ reduction by acting as a cofactor for reduced nicotine adenine dinucleotide phosphate (NADPH) MetHbFe³⁺ reductase, an

enzyme that normally plays no role in MetHbFe³⁺ reduction. Riboflavin can act like methylene blue and has been used in cases of congenital methemoglobinemia. Ascorbate and glutathione are responsible for a minority of MetHbFe³⁺ reduction in vitro but play an insignificant role in normal MetHbFe³⁺ reduction and there is limited evidence for their effectiveness in treating methemoglobinemia. HbFe²⁺, normal ferrous hemoglobin

glycolytic pathway for NADH production, the presence of cytochrome *b*₅, and adequate activity of cytochrome-*b*₅ reductase. The normal rate of enzymatic methemoglobin reduction exceeds spontaneous background methemoglobin formation rate by several 100-fold. Heterozygous erythrocytic cytochrome-*b*₅ reductase-deficient patients ordinarily exhibit normal methemoglobin fractions but are predisposed to developing methemoglobinemia in response to oxidant stress. Compound heterozygous and homozygous patients display congenital methemoglobinemia [13, 14].

A second erythrocytic reducing enzyme, NADPH methemoglobin reductase, normally remains minimally active or completely inactive because of the absence of an electron transfer intermediate (e.g., cytochrome *b*₅) to serve as a cofactor for enzymatic methemoglobin reduction. Methylene blue (methylthioninium chloride) is an acceptable electron acceptor/donor intermediate, however, and markedly accelerates NADPH methemoglobin reductase activity [4]. In this pathway (see Fig. 4), electrons are transferred from NADPH (produced in the hexose monophosphate shunt) to

methylene blue to form leukomethylene blue. Leukomethylene blue donates an electron to methemoglobin to produce ferrous hemoglobin. Reduction of methemoglobin by this pathway requires an intact hexose monophosphate shunt, a cofactor such as methylene blue, and normal activity of erythrocytic NADPH methemoglobin reductase. In vitro, some methemoglobin reduction can be shown by glutathione and ascorbate, but these are thought to be relatively minor in vivo.

The predisposition of infants to methemoglobinemia is explained by normally low erythrocytic cytochrome-*b*₅ reductase activity and cytochrome *b*₅ concentrations. Oxidant stress resulting from gastroenteritis and other infections is the most common cause of acquired methemoglobinemia in this age group [15, 16].

Etiology

Congenital Causes

Patients with compound heterozygous or homozygous deficiency for erythrocytic cytochrome-*b*₅

reductase have congenital methemoglobinemia and can be treated with oral methylene blue to lower methemoglobin fractions. In addition, several mutant hemoglobin species (hemoglobin M) in which the iron remains in the ferric form have been described. Most of these patients have congenital methemoglobinemia unresponsive to methylene blue. Rare mutant unstable hemoglobins undergo denaturation to produce congenital Heinz body hemolytic anemias; some of these also oxidize to form methemoglobin. These hemoglobins would be expected to produce disease before adulthood [5, 13].

Acquired Causes

Most cases of methemoglobinemia in adults and non-neonates are acquired, resulting from exposure to chemical agents (see Table 1). One of the most common causes is benzocaine, which is metabolized to a methemoglobin-producing agent. Methemoglobinemia resulting from topical benzocaine spray used to perform transesophageal echocardiograms, endotracheal intubations, bronchoscopies, or other endoscopic procedures has been described repeatedly in the literature [17, 18]. The use of benzocaine-containing teething ointments and hemorrhoidal creams also has produced methemoglobinemia in some patients, even after therapeutic doses. Prilocaine is the second local anesthetic most closely associated with methemoglobinemia, but methemoglobinemia has resulted from many anesthetics, including lidocaine and bupivacaine [19, 20]. Methemoglobinemia usually follows overdose of phenazopyridine (Pyridium) or dapsone and occasionally results from therapeutic use. A plethora of additional prescription drugs have been associated with methemoglobinemia; examples are valproate [21], clofazimine [22], flutamide [23], and ifosfamide [24]. Oral overdoses with nitroglycerin and organic nitrates (which are esters of nitrite) and therapeutic doses of intravenous nitroglycerin are well known to produce methemoglobinemia [25].

The conversion of nitrates to nitrites by bacteria in the upper gastrointestinal tract has produced fatal methemoglobinemia in infants who ingest well water high in nitrate concentrations –

so-called well-water methemoglobinemia [26]. Nitrite contamination of public drinking water also explained a large outbreak of methemoglobinemia [27]. Methemoglobinemia results from ingestion of meat containing excessive amounts of sodium nitrite as a preservative [28] and from the recreational use of inhalational nitrites (e.g., isobutyl nitrite). Illicit drugs can be adulterated with local anesthetics as in the case of cocaine [29]. Aniline has been sold as the hallucinogen 2C-E, with resultant methemoglobinemia [30]. Topical contact with aniline dyes found in printing ink on diapers, leather dyes in new shoes, and commercial marking crayons has produced methemoglobinemia and death [4]. The ingestion of nitroethane, found in some over-the-counter fingernail products, produces methemoglobinemia [31]. In Asia, ingestions of the herbicide propanil is a cause of methemoglobinemia [32].

As expected, most agents producing methemoglobinemia also produce oxidant-induced hemolysis, and both disorders commonly coexist in the same patient. Hemolysis can be extraordinarily severe after poisonings by chlorates, arsine, stibine, and chromates. Methemoglobinemia resulting from local anesthetics usually is not accompanied by serious hemolysis. G6PD deficiency has not been reported to predispose to methemoglobinemia except for the suggestion that hemolysis in these patients masks methemoglobinemia because older erythrocytes predisposed to increased methemoglobin formation are the very same ones more susceptible to hemolysis [33].

Diagnosis

The use of multiwavelength co-oximetry allows for the diagnosis of methemoglobinemia. It is important that the sample is analyzed soon after collection as methemoglobin concentrations can increase *ex vivo*. Modern co-oximeters measure the absorption of multiple wavelengths of ultraviolet light by blood and calculate concentrations of oxyhemoglobin, reduced hemoglobin, methemoglobin, and carboxyhemoglobin. Because co-oximetry determines methemoglobin concentrations by

measuring absorption of light, substances that interfere with light absorption can produce false results on some co-oximeters, depending on the model. Hyperlipemia, such as that seen after the infusion of lipid emulsions or in patients with diabetes mellitus, has resulted in reporting of falsely elevated methemoglobin fractions [34]. Co-oximetry may be unreliable for several minutes immediately after a dose of methylene blue [35]. As discussed later, sulfhemoglobin is handled in various ways, depending on the specific instrument, but some co-oximeters cannot differentiate between sulfhemoglobin and methemoglobin, reporting elevated methemoglobin fractions in both instances.

Other diagnostic clues commonly lead to the presumed diagnosis of methemoglobinemia before co-oximetry is considered. Generalized cyanosis in the presence of a normal arterial PO_2 usually represents methemoglobinemia. As expected, cyanosis from methemoglobinemia persists despite oxygen therapy. Patients with significant methemoglobinemia may exhibit chocolate-colored or abnormally dark blood. When methemoglobin fractions exceed 10–15% in a nonanemic patient, a drop of blood allowed to dry on filter paper appears noticeably brown compared with venous blood from a normal person [36]. In fact, the degree of color change can be used to estimate methemoglobin fraction [37]. Many blood gas instruments do not measure percent hemoglobin saturation but report a calculated value derived from the P_aO_2 and pH. This calculated saturation represents what the saturation should be in the absence of abnormal hemoglobin pigments. In methemoglobinemia, the true percent saturation as determined by co-oximetry is lower than the calculated percent saturation as reported by many blood gas instruments. The difference between the calculated and measured saturation is termed the *saturation gap* and normally is less than 3–5% in arterial blood. Large saturation gaps in arterial blood almost always result from methemoglobin or carboxyhemoglobin and less commonly result from sulfhemoglobin.

Dual-wavelength pulse oximeters, the most commonly used devices, neither accurately nor reliably measure percent saturation in the presence

of methemoglobinemia [38]. Depending on the true oxygen saturation, dual-wavelength pulse oximetry may read falsely low or falsely high. The most common response to methemoglobinemia is that pulse oximeters read falsely high saturations, although reported saturations may decrease below the normal range. When the diagnosis of methemoglobinemia has been made, the pulse oximeter should be removed from the patient so that medical personnel are not misled by unreliable readings. Over the last several years, pulse co-oximeters have become available that measure methemoglobin fractions (Masimo Corporation, Irvine, CA) and appear to provide consistent results across a wide range of hypoxia states [39]. As these devices are incorporated into regular use, methemoglobinemia may become more commonly recognized.

Blood should be drawn to screen for hemolysis (hemoglobin, blood smear, Heinz body stain, plasma-free hemoglobin, serum haptoglobin), for arterial blood gases and co-oximetry, and for routine laboratory studies. Methemoglobinemia does not change measurement of total blood hemoglobin concentration by the clinical laboratory. However, as noted earlier, it is important that a full blood count is obtained as methemoglobin concentration should be interpreted in the context of total hemoglobin. An electrocardiogram may help exclude myocardial ischemia.

Methemoglobin fractions commonly increase after death. Postmortem methemoglobin concentrations do not reliably reflect antemortem methemoglobinemia [40].

Differential Diagnosis

Arterial P_aO_2 , in the absence of other causes of hypoxemia, is normal in methemoglobinemia, distinguishing abnormal coloration from hypoxia. The cyanosis from methemoglobinemia does not respond to oxygen therapy.

Patients with sulfide poisoning have been reported to exhibit an unusual, poorly characterized discoloration of the skin and other organs, mainly as a postmortem finding. Rare cases of tellurium exposures have produced blue discoloration. Some patients with severe cyanide toxicity

exhibit cyanosis, and many other signs and symptoms of cyanide poisoning would be similar to signs and symptoms of methemoglobinemia. Normal arterial P_aO_2 and increased saturation gaps also characterize carbon monoxide poisoning and sulfhemoglobinemia, and some co-oximeters measure and report sulfhemoglobin as methemoglobin. Skin discoloration from dermal contact with new blue clothing or blue towels has been confused with methemoglobinemia, but this discoloration is removed with washing the skin. Excessive administration of methylene blue can produce skin discoloration that may be confused with continuing methemoglobinemia or cyanosis from other causes.

Treatment

Patients should receive oxygen to maximize oxygen carrying capacity of remaining normal hemoglobin.

Asymptomatic Patients

Some patients with methemoglobinemia exhibit cyanosis but lack other signs and symptoms and do not require specific treatment. After exposure to the offending agent ends, methemoglobin levels usually return to normal within 36 h with some exceptions (e.g., dapsone, nitroethane). Most of these patients require admission to the hospital, however, to follow them clinically for worsening signs and symptoms, to monitor for onset of hemolysis, and to follow serial methemoglobin fractions. Assuming normal hemoglobin concentrations, asymptomatic patients usually exhibit methemoglobin fractions between 10% and 15%.

Symptomatic Patients

Patients who are symptomatic from methemoglobinemia (e.g., tachycardia, dyspnea, confusion, and headache) should be considered for specific antidotal therapy with methylene blue [41–43] (level of evidence II-2), in the absence of a history of G6PD deficiency (see later). Parenteral methylene blue should be given intravenously over 3–5 min at an initial dose of 1–2 mg/kg

(0.1–0.2 mL/kg of a 1% solution). Resolution of cyanosis usually occurs within 5–25 min. If the patient is seriously symptomatic and no response occurs within 15 min or if the patient remains moderately symptomatic without any improvement for 30–60 min, repeat doses of 1 mg/kg (0.1 mL/kg of a 1% solution) should be given. If methemoglobin levels are readily available, repeat determinations of methemoglobin fractions should be performed before repeat dosing of methylene blue because large doses of methylene blue produce discoloration of the skin. The total amount of methylene blue given during the first few hours generally should not exceed 5–7 mg/kg. Intraosseous infusion of methylene blue has been described when intravenous access cannot be obtained [44].

Patients with methemoglobinemia always should be closely followed for evidence of hemolysis because the latter is common whether or not patients receive methylene blue. Hemolysis may be clinically apparent on presentation or, most commonly, appears 2–3 days after admission and after methemoglobin fractions have decreased.

Some toxins are known for producing methemoglobinemia that is refractory or only partially responsive to methylene blue therapy. In most instances, this situation results from the inability of methemoglobin reduction, even in the presence of methylene blue, to keep up with profound oxidant stress. Examples of these toxins include aniline, nitrobenzene, and chlorates [7, 45, 46].

Some methemoglobin-producing toxins possess long half-lives and produce prolonged methemoglobinemia. Dapsone produces methemoglobinemia and hemolysis lasting for days [47, 48]. In these cases, it may be necessary to administer methylene blue as a continuous infusion. Methylene blue is dissolved in the crystalloid of choice and, based only on case reports, started at 0.1 mg/kg/h (0.01 mL/kg/h of a 1% methylene blue solution) [47], although personal experience indicates that higher rates may be required at times. It is important to follow serial methemoglobin fractions and total hemoglobin concentrations.

Most methylene blue is excreted unchanged by the kidneys. Although patients with renal

insufficiency do not require changes in initial methylene blue doses, they should receive lower continuous infusion doses of the drug based on creatinine clearance. No specific guidelines for dosing in renal failure patients have been developed.

Methylene blue should not be given to patients with *known* G6PD deficiency. These patients have low red blood cell NADPH concentrations, impairing augmentation of NADPH methemoglobin reductase by methylene blue [49]. Methylene blue triggers hemolysis in patients with G6PD deficiency, which would impair oxygen delivery further [2, 50]. Methylene blue should never be withheld from symptomatic patients, however, simply because a history of G6PD deficiency cannot be excluded.

Large doses of methylene blue in normal volunteers have been associated with dysuria, substernal chest pain, nausea, tachycardia, hypertension, and anxiety [51]. In our experience, however, patients with methemoglobinemia do not voice or experience these effects from methylene blue. Urine initially turns blue and then green. Although authors have cautioned that methylene blue paradoxically may increase methemoglobin fractions when given in large doses (e.g., 5 mg/kg over 35–70 min) [52], this has not been thought to be a significant problem in humans receiving recommended doses. This phenomenon has been attributed largely to results of *in vitro* studies during hypoxic conditions [53, 54]. Worsening hemolysis also has been alleged after methylene blue therapy, even in patients with normal G6PD activity, but these allegations mainly arise from case reports in which hemolysis was expected from the agent producing methemoglobinemia [55], making causal relationships unclear.

Fetuses and newborns seem to be sensitive to hemolytic actions of methylene blue. Intra-amniotic injections of methylene blue, sometimes using large doses, have been associated with delivery of newborns with Heinz body hemolytic anemia. Hemolysis also has been reported in newborns receiving methylene blue through feeding tubes [56, 57]. Reports of newborns with methemoglobinemia after intra-amniotic injection of methylene blue [58] could reflect a peculiar

susceptibility of neonates, the effects of a large relative dose of methylene blue, or *in utero* hypoxic conditions favoring methylene blue-induced oxidant stress in the fetus. Regardless of these concerns, the administration of methylene blue to a symptomatic patient with methemoglobinemia has never been proved to worsen methemoglobinemia.

Cimetidine has been used to help control methemoglobinemia from dapsone. Cimetidine inhibits cytochrome P-450 conversion of dapsone to the oxidizing metabolite responsible for methemoglobinemia, dapsone hydroxylamine. In patients receiving 1,200 mg/day of cimetidine orally while taking therapeutic doses of dapsone, circulating methemoglobin fractions decreased by an average of 25% [59] (level I). However, evidence for cimetidine's effectiveness in treatment for dapsone *overdose* should be considered level III as there are no studies describing its effectiveness in this setting. Ascorbic acid works slowly and generally is considered ineffective for treatment of acute acquired methemoglobinemia [4].

Riboflavin also can accept electrons from NADPH methemoglobin reductase and enhance methemoglobin reduction in a manner similar to that of methylene blue. Although endogenous riboflavin concentrations are not high enough to account for significant methemoglobin reduction, large oral doses (e.g., 60–100 mg/day) have been used successfully in patients with congenital methemoglobinemia [60, 61]. The safety and efficacy of intravenous or oral riboflavin for the treatment of acquired acute methemoglobinemia have not been described.

Incubation of erythrocytes in high concentrations of *N*-acetylcysteine seems to enhance methemoglobin reduction [62]. These concentrations of *N*-acetylcysteine cannot be achieved safely in humans, however, and a randomized controlled trial found that conventional doses of intravenous *N*-acetylcysteine were ineffective in reducing nitrite-induced methemoglobin fractions in human volunteers [63].

It is important always to monitor total oxygen carrying capacity by following total hemoglobin concentrations, methemoglobin fractions, and true percent saturation of oxyhemoglobin. A

decrease in methemoglobin fraction from 25% to 15% would result in worsened oxygen delivery if accompanying hemolysis has resulted in a decrease of the hemoglobin concentration from 15 g/dL to 5 g/dL. In addition, the development of anemia alone may result in resolution of cyanosis despite worsening of oxygen delivery, without a decrease in methemoglobin fractions. In most persons, 15% methemoglobinemia with a hemoglobin concentration of 15 g/dL would produce visible cyanosis, whereas 20% methemoglobinemia in patients with a hemoglobin concentration of 5 g/dL produces no visible discoloration and yet may be lethal. Interpreting disappearance of cyanosis to mean that the patient has improved must be done with caution.

After initial signs and symptoms of methemoglobinemia have been addressed, routine gastrointestinal and skin decontamination should be performed as indicated. If the clinician chooses to use ascorbic acid in treating acquired methemoglobinemia, recommended doses historically have been 0.5–1 g of ascorbic acid given every 6 h intravenously or orally [4], though a recent anecdotal report describes using higher doses (described below) [64]. Evidence supporting ascorbic acid’s effectiveness in treating acquired methemoglobinemia is level III.

Failure to Respond to Methylene Blue

When patients with methemoglobinemia do not improve with methylene blue therapy, several possibilities should be considered (Table 2). First, exposure to large amounts of drugs or chemicals can produce methemoglobin at rates greater than reducing capacity, even with methylene blue therapy. When methemoglobin fractions do not return to normal because of continued methemoglobin formation, methylene blue therapy almost always results in at least a transient decrease in methemoglobin fractions. As noted earlier, recurrent methemoglobinemia is common after exposure to etiologic agents with prolonged absorption or long half-lives. Second, patients who do not respond to methylene blue also may be suffering from unrecognized G6PD deficiency. Third, patients with congenital NADPH methemoglobin

Table 2 Possible explanations when methemoglobinemia fails to respond to methylene blue

Overwhelming oxidant stress from ingestant or toxin
G6PD deficiency
NADPH methemoglobin reductase deficiency
Sulfhemoglobinemia
Blue skin discoloration from other sources
Hypoxemia (recheck arterial PO ₂)
<i>G6PD</i> glucose-6-phosphate dehydrogenase, <i>NADPH</i> reduced nicotinamide adenine dinucleotide phosphate

reductase deficiency also fail to respond to methylene blue [4]. Fourth, sulfhemoglobinemia can be mistaken for methemoglobinemia (see later). Fifth, repeated doses or large doses of methylene blue produce blue skin coloration that may be mistaken for methemoglobinemia [65].

For patients who cannot receive or fail to respond to methylene blue, treatment options are limited. Blood transfusions and exchange transfusions [46] have been used and suggested whenever refractory methemoglobin fractions approach 70% in nonanemic patients. Hyperbaric oxygen can be a temporizing measure that provides adequate oxygen delivery during preparation of blood transfusions. Oxygen toxicity limits the amount of time a patient can stay in a hyperbaric chamber, however. Oral riboflavin could be given (60–100 mg/day divided into three doses), but its efficacy is unknown in this setting, and it would not be expected to be effective in patients with G6PD deficiency. Intravenous ascorbic acid (500 mg) also can be given [4], although it is stated that it works too slowly to be helpful for acquired methemoglobinemia. High-dose ascorbic acid (10 g IV q 6 h) has been described in dapsone poisoning [64].

Sulfhemoglobin

Background and Characteristics

Sulfhemoglobin is a green molecule in which a sulfur atom has been incorporated into the porphyrin ring of hemoglobin [66]. Sulfhemoglobin cannot transport oxygen. No significant circulating sulfhemoglobin normally exists, but

sulfhemoglobin fractions increase in some persons in response to oxidant stress. In contrast to methemoglobin, sulfhemoglobin persists for the life of the erythrocyte and does not undergo conversion back to hemoglobin. Only 0.5 g/dL of sulfhemoglobin produces slate-gray cyanosis (e.g., approximately 3% sulfhemoglobin in a patient with a total hemoglobin concentration of 16 g/L).

Although sulfhemoglobin cannot transport oxygen, additional factors usually prevent serious impairment of oxygen delivery in nonanemic patients. During sulfhemoglobinemia, hemoglobin tetramers usually contain only one or two sulfurated heme isomers, preventing extremely elevated sulfhemoglobin fractions. Sulfurated heme moieties in hemoglobin shift unaffected heme moieties toward the unliganded confirmation, reducing oxygen affinity of normal heme subunits and shifting the oxygen-hemoglobin dissociation curve to the right, which enhances oxygen delivery to tissues and partially ameliorates the effects of reduced oxygen binding capacity [67]. In contrast, methemoglobin and carboxyhemoglobin shift the dissociation curve to the left, compounding impaired oxygen delivery to tissues.

Sulfhemoglobin, methemoglobin, and hemoglobin M possess similar light absorption spectra. This fact prevented many early authors from distinguishing among these three pigments. Some multiwavelength co-oximeters today report sulfhemoglobin as methemoglobin. In addition, early studies of “sulfhemoglobinemia” from hydrogen sulfide mixed with blood in vitro may have represented nothing more than a mixture of oxidized, denatured hemoglobin pigments that were unrelated to what is termed sulfhemoglobin today [68]. Readers must interpret cautiously confusing older medical literature on reports of sulfhemoglobinemia, which has been suggested to be better termed *pseudosulfhemoglobin* [69]. These articles might represent true reports of sulfhemoglobinemia, methemoglobinemia, hemoglobin M disease, various species of denatured hemoglobin from hydrogen sulfide mixed with blood in vitro, combinations of the aforementioned, or perhaps other chemical compounds.

Formation and Etiology

Agents that produce sulfhemoglobinemia (see Table 1) usually are known better for their ability to produce methemoglobinemia and hemolysis. Methemoglobinemia and sulfhemoglobinemia have followed exposures to metoclopramide [70, 71], flutamide [23, 72], dapsone [73], and phenazopyridine [74]. Methemoglobinemia, sulfhemoglobinemia, and especially hemolysis may coexist in the same patient [73]. Why exposure to the same substance produces sulfhemoglobinemia in one person, methemoglobinemia in another, and both in another person remains unknown.

Sulfhemoglobin forms when elemental sulfur binds to the β -pyrrole ring of the heme moiety, where it persists for the life of the erythrocyte [66]. Although early authors suggested that the sulfur responsible for oxidizing hemoglobin was found in the etiologic chemical, many drugs that produce sulfhemoglobinemia do not contain sulfur. It also was an older belief that vague gastrointestinal dysfunction alone produced hemolytic anemia, sulfhemoglobinemia, and methemoglobinemia from the presumed absorption of endogenously produced nitrites and sulfides – so-called enterogenous cyanosis. Evidence indicates, however, that patients with enterogenous cyanosis were ingesting surreptitiously analgesics known to cause such disorders [75].

Animal studies suggest that sulfur from intestinal bacterial metabolism in combination with oxidant stress from various agents might be responsible for sulfhemoglobin formation. Rats with jejunal pouches that received phenacetin were more likely to develop sulfhemoglobinemia than controls; neomycin prevented phenacetin-induced sulfhemoglobin formation [76]. Neomycin use for treatment of sulfhemoglobinemia in humans has been described in case reports [77].

Diagnosis

In early attempts to clarify what was being measured when “sulfhemoglobin” was reported to be present, Michel and Harris [78] reported that the

addition of cyanide or dithionite (hydrosulfite) to blood eliminated the spectral absorption of methemoglobin immediately, whereas the spectral absorption of sulfhemoglobin remained. This simple test did not exclude hemoglobin M (or perhaps other oxidation products of hemoglobin), however, which also remains after addition of these compounds. Carrico and colleagues [79] reported that carbon monoxide would bind to sulfhemoglobin to produce carbonmonoxysulfhemoglobin, a compound with a downfield shift, whereas neither methemoglobin nor hemoglobin M bound carbon monoxide. Light absorption in the presence of cyanide (or dithionite) and carbon monoxide, then, served for several years as laboratory tools to measure “sulfhemoglobin” fractions and concentrations, although it is not known confidently exactly what species always was being measured. Park and Nagel [67] reported that electrophoresis with isoelectric focusing reliably delineates the three pigments, and isoelectric focusing generally serves as the gold standard today, although various methods of analysis (e.g., gas chromatography, manual spectrophotometry) are used at reference laboratories.

Results from isoelectric focusing, manual spectrophotometric analysis, or other reference methods do not return for hours to days, whereas multiwavelength co-oximetry results are available within minutes in most intensive care units. Different brands of co-oximeters and various models from the same manufacturer vary in how they handle sulfhemoglobin [80]. The older IL 282 and IL 482 (Instrumentation Laboratory, Inc., Lexington, MA) do not distinguish between methemoglobin and sulfhemoglobin and report sulfhemoglobin as methemoglobin [71, 72, 81]. Zwart and colleagues [82] showed that a reported methemoglobin fraction greater than 10% in combination with a negative carboxyhemoglobin fraction on these instruments suggests that at least some sulfhemoglobin is present. Conversely the IL 682 is said to indicate sulfhemoglobin fractions greater than 1.5% [81]. Some multiwavelength co-oximeters will alert that sulfhemoglobin is present, but not provide quantification [83]. Wu and Kenny [84] noted that Radiometer OSM3 co-oximeter reported falsely elevated oxygen

saturations in the presence of sulfhemoglobinemia, unless the blood specimen was analyzed with a service program configuration that could be activated only by a company representative. The intensivist must be familiar with how his or her particular co-oximeter handles and reports sulfhemoglobin (if at all) and sometimes must remain skeptical of claims made by a manufacturer regarding the ability to detect and quantify sulfhemoglobin accurately.

Few data exist on accuracy of dual-wavelength pulse oximetry in the presence of sulfhemoglobinemia. We have seen one woman with slate-gray cyanosis and 18.6% sulfhemoglobin (total hemoglobin 9 g/dL) whose pulse oximeter read in the 60% range despite an elevated arterial P_{aO_2} and absent methemoglobin (true saturation about 81%). Aravindhan and Chisholm [67] described a 48-year-old woman with an arterial P_{aO_2} of 99 mmHg, 28% sulfhemoglobinemia, and a pulse oximeter reading of 85% (true saturation about 72%). Langford and Sheikh [85] noted a pulse oximeter reading of 92–94% saturation with a sulfhemoglobin fraction of 16% (true saturation about 84%).

Clinical Presentation

The diagnosis of sulfhemoglobinemia usually is considered when confronted with a cyanotic or slate-gray patient who has a normal P_{aO_2} . Depending on the co-oximeter being used, methemoglobin fractions may be reported as normal, or methemoglobin fractions may be reported as elevated and remain so after methylene blue therapy (other causes of this scenario were described previously). Except for discoloration, most patients with sulfhemoglobinemia remain asymptomatic, unless other abnormal hemoglobins are present (e.g., methemoglobin), or the typical accompanying oxidant hemolytic anemia is severe. Discoloration most often appears slate gray and lasts for weeks or months due to the irreversible nature of sulfhemoglobin [12]. The coexistence of methemoglobinemia and anemia may alter the color of cyanosis and clinical symptoms.

Historically the most common drugs causing sulfhemoglobinemia were acetanilid, phenacetin, and sulfonamides. Bromo-Seltzer was the most common cause, but acetanilid, the offending ingredient, since has been removed as an ingredient. More recent reports describe sulfhemoglobinemia resulting from dapsone [73], dimethyl sulfoxide [86], flutamide [72], metoclopramide [71], and phenazopyridine [74].

Treatment

There is no specific antidote for sulfhemoglobinemia. No beneficial effect results from therapy with methylene blue. Treatment centers on ensuring adequate oxygen delivery to tissues by correcting coexistent methemoglobinemia and anemia (from hemolysis) and ensuring maximal oxygen carrying capacity with administration of oxygen when the patient is symptomatic. Transfusions usually are required only in patients whose coexisting hemolytic anemia is severe, which increases the total hemoglobin concentration and decreases the sulfhemoglobin fraction. Patients need follow-up on an outpatient basis for several weeks because sulfhemoglobin concentrations decrease only as the red blood cell population is replaced in the absence of the offending agent.

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Neuroleptic malignant syndrome (NMS) is an uncommon but potentially fatal idiosyncratic complication of antipsychotic drug therapy. It was first described in 1960 when Delay and colleagues [1] reported rigidity and fever associated with haloperidol therapy. The syndrome subsequently was named and classified as a drug-induced extrapyramidal syndrome (EPS) by Delay and Deniker in 1968 [2]. The term *neuroleptic malignant syndrome* is derived from the French *syndrome malin des neuroleptiques* [3]. Although now infrequently fatal and not always associated with antipsychotic therapy, NMS remains the preferred term to describe this illness.

NMS is a heterogeneous disorder with a wide spectrum of clinical severity [4, 5]. It is commonly characterized by the tetrad of altered consciousness, fever, muscular rigidity, and autonomic dysfunction [6]. NMS has been reported with nearly all antipsychotic drugs [7]. It also has been reported with other drugs that antagonize dopaminergic neurotransmission in the central nervous system (CNS) (e.g., amoxapine, metoclopramide, lithium) and in patients with Parkinson's disease who abruptly discontinue dopamine agonist therapy [5, 8–20]. Many drugs that are not known to antagonize dopamine neurotransmission rarely have been implicated as etiologic agents for NMS (Table 1) [21–42]. These drugs produce movement disorders, muscular rigidity, and fever by a mechanism different from that of NMS and are better characterized as producing NMS-like syndromes rather than true NMS.

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Table 1 Agents reported to cause neuroleptic malignant syndrome

Antipsychotic agents	Non-antipsychotic agents
Typical agents	Agents that deplete dopamine
Butyrophenone	α -Methylparatyrosine [10]
Droperidol	Reserpine
Haloperidol	Tetrabenazine [10, 21]
Dihydroindolone	
Molindone	Antiepileptics
Diphenylbutylpiperidine	Carbamazepine [22, 23] ^a
Pimozide	Phenytoin [24] ^a
Phenothiazine	Valproic acid [38] ^a
Aliphatic	Lamotrigine [39]
Chlorpromazine	
Promethazine	Cyclic antidepressants
Piperazine	Amitriptyline [21, 25] ^a
Fluphenazine	Desipramine [26] ^a
Perphenazine	Dothiepin [27, 28] ^a
Prochlorperazine	Imipramine [30] ^a
Trifluoperazine	Maprotiline [31] ^a
Piperidine	Trimipramine [32] ^a
Mesoridazine	
Thioridazine	Selective serotonin reuptake inhibitors:
Thioxanthene	Fluoxetine [29, 40] ^a
Chlorprothixene	Paroxetine [40] ^a
Clopenithiol	
Flupenthixol	Dopamine receptor antagonists
Thiothixene	Amoxapine [17, 18]
Zuclopenthixol	Metoclopramide [14–16]
Atypical agents	Miscellaneous agents
7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl	Cocaine [33] ^a
	Estrogen [42] ^a
Aripiprazole	Monoamine oxidase inhibitors
Benzamides	Phenelzine [25, 35] ^a
Raclopride	
Remoxipride	Psychotropic agents
Sulpiride	Lithium [17, 20]
Sultopride	
Benzisothiazol piperazine	Skeletal muscle relaxants
Ziprasidone	Cyclobenzaprine [36] ^a
Benzisoxazole	Diazepam [37] ^a
Risperidone	Lorazepam [21] ^a
Paliperidone	

(continued)

Table 1 (continued)

Antipsychotic agents	Non-antipsychotic agents
Dibenzodiazepine	Withdrawal of dopamine agonists
Clozapine	Amantadine [9, 10, 12]
Dibenzo-oxepino pyrrole	Bromocriptine [9–11]
Asenapine	Levodopa/carbidopa [11, 13]
Dibenzothiazepine	
Quetiapine	
Dibenzoxazepine	
Loxapine	
Thienobenzodiazepine	
Olanzapine ^a	

^aAlthough these agents have been reported to cause neuroleptic malignant syndrome (NMS), evidence consists of one or two case reports for each agent, and the reported cases often have coingestants that may produce muscular rigidity and fever. For each case, the syndrome reported should be characterized as an NMS-like syndrome rather than true NMS

To date, more than 1,000 cases of NMS have been reported in the literature, largely as individual case reports, case series, and reviews [4, 5, 21, 41–44]. Collectively, these cases have heightened awareness of NMS, facilitated its early recognition, promoted a reduction of suspected risk factors, and allowed more timely treatment. As a result, the incidence and mortality from NMS have decreased since the 1980s [5, 7, 44–47]. However, the lack of animal models and controlled, prospective treatment studies for NMS has hampered a full understanding of its pathophysiology and optimal treatment. Further study is necessary to reduce the incidence, morbidity, and mortality from NMS.

Epidemiology

Incidence

NMS is uncommon. From retrospective studies, reported incidences have ranged from 0.02% to 3.2% of individuals exposed to neuroleptic drugs [6, 43, 50]. In four prospective studies, incidences ranged from 0.02% to 2.2% [47–49, 50a]. In one

prospective study, Keck documented four cases in 2,695 patients treated with antipsychotics from 1986 until 1990 [47]. The agents implicated for each patient were fluphenazine (patient 1); fluphenazine, chlorpromazine, amantadine, and lithium (patient 2); perphenazine (patient 3); and chlorpromazine, perphenazine, and fluoxetine (patient 4). Gelenberg et al. note a single case in 1,470 treated patients in 1 year, from 1986 to 1987 [49]. The patient developed NMS during treatment with haloperidol and amitriptyline. In a study by Spivak et al., there described 19 cases among 78,708 treated patients over a 10-year period from 1986 to 1995; 84.2% of patients that developed NMS were treated with haloperidol [48]. Estimates of frequency are influenced by diagnostic criteria, patient populations studied, prevalence of risk factors, setting, and methods of data collection [6]. If NMS were recognized across a spectrum of severity and widened diagnostic criteria were employed to diagnose it, the prevalence of this disorder would be higher. When data are pooled from many studies, NMS is estimated to occur in 2 of every 1,000 patients treated with antipsychotics [6].

Demographics

NMS occurs in all age groups. Most cases occur in patients between 20 and 50 years old with a mean age of 40 [5–7, 43]. This age distribution likely reflects the pattern of antipsychotic drug use in society rather than a true age predilection for the disease [5, 6]. NMS occurs approximately twice as often in men compared with women [5–7]. This occurrence also likely reflects the pattern of neuroleptic use, with a higher frequency of use in men.

Risk Factors

Several potential risk factors for the development of NMS have been identified from case series and reviews. These include rapid initiation of antipsychotic therapy; use of high-potency agents and/or depot preparations; dehydration; severe agitation or catatonia; requirement of restraints or

seclusion; preexisting organic brain disease, mental retardation, or affective disorder; previous treatment with electroconvulsive therapy (ECT); previous history of NMS; poorly controlled EPS; and concomitant use of predisposing drugs, such as lithium, anticholinergic agents, and anti-Parkinson agents [5–7, 43, 45]. In two similarly designed case-control studies in which 43 patients with NMS were compared with 75 matched neuroleptic-treated controls, risk factors were better delineated [51, 52]. NMS was more likely to occur in patients who had been agitated, been dehydrated, required restraint or seclusion, received a larger number of intramuscular injections, and received larger doses of neuroleptic agents soon after hospital admission (rapid dose titration).

NMS has been associated with all antipsychotic agents. Most cases have been reported, however, with high-potency agents and depot preparations. NMS also has been reported with atypical antipsychotics, but it is not yet known whether its incidence is lower with use of these newer agents. In one review of 115 cases of NMS, 57% were attributed to haloperidol, 16% to fluphenazine, and 17% to a depot preparation [5]. The higher frequency of NMS associated with higher-potency antipsychotic agents may reflect their more frequent prescribing pattern or rates of administration, however, and not a true increased risk. In this same review, the low-potency agent chlorpromazine was implicated in 24% of cases of NMS; its overrepresentation in NMS cases probably reflects its frequent use at the time of the study [5]. Whether the incidence of NMS is truly higher with depot preparations is not clear either. In this same NMS case review, the depot preparation fluphenazine decanoate was implicated in 16% of cases compared with 5% for patients treated with oral fluphenazine. In contrast, oral haloperidol was implicated in 57% of NMS cases compared with 1% for its depot preparation [5].

NMS is idiosyncratic. Its occurrence is not correlated with dose, and it usually occurs with antipsychotic serum concentrations in the therapeutic range [5–7, 43, 45]. Although NMS may occur at any time during therapy, it usually

appears in the first 1–2 weeks of treatment or soon after a change in dosage [5–7, 43]. The rate of increase of neuroleptic dose correlates with the likelihood of developing NMS [43, 51]. The decline in the incidence of NMS may reflect an appreciation of this risk factor and a significant decline in “rapid tranquilization” of agitated psychiatric patients [47, 49, 50].

NMS occurs independent of race, geographic location, environmental temperature, and humidity [5–7]. There is no seasonal variation in incidence [6]. Although there have been rare reports of NMS occurring within the same family, there does not seem to be any significant genetic predisposition to its occurrence [5–7, 53]. Although individuals with preexisting affective and organic brain disorders are at greater risk for developing NMS, the illness occurs across the neuropsychiatric disease spectrum and occurs in patients without organic and functional brain disorders as well [5–7, 51, 54].

Pathophysiology

Although the pathophysiology of NMS is not fully understood, it primarily involves dopaminergic hypoactivity in the CNS [6–8, 55, 56]. Several lines of clinical evidence support this theory. First, all antipsychotic agents have been associated with NMS, and all share the ability to bind and antagonize D₂-dopamine receptors [55, 57, 58]. Second, other agents that block D₂-receptors (e.g., amoxapine, metoclopramide) or result in depletion of dopamine (e.g., reserpine, α -methylparatyrosine, tetrabenazine) have been reported to produce NMS [5, 8, 10, 14–18, 59]. Third, the abrupt discontinuation of dopamine agonists (e.g., amantadine, levodopa/carbidopa) in patients with Parkinson's disease has been reported to produce a syndrome identical to NMS [8–13]. Fourth, treatment with dopamine agonists (e.g., bromocriptine, amantadine) improves the signs and symptoms of NMS [5, 6, 43, 44, 60–65]. Fifth, if dopamine agonist therapy is withdrawn prematurely from patients with NMS who have been treated, signs and symptoms may return [65]. Sixth, a significant reduction of the dopamine metabolite homovanillic acid has

been observed in the cerebrospinal fluid of some patients with NMS compared with control subjects [66].

Functionally, the signs and symptoms of NMS largely can be explained by medication-induced blockade of D₂-dopamine receptors in the hypothalamus, striatum, mesocortical and mesolimbic areas, peripheral sympathetic nerve terminals, and vasculature [8, 55, 67]. Neuroleptic blockade of D₂ receptors in the nigrostriatum may produce muscle rigidity and parkinsonism [55, 67]. Neuroleptic blockade of D₂ receptors in the thermoregulatory center (preoptic area) of the anterior hypothalamus may produce hyperthermia [55, 67]. Injection of dopamine into the preoptic area of the hypothalamus of animals results in hypothermia, and this effect can be blocked by haloperidol [68]. Intraventricular injection of the dopamine receptor antagonist chlorpromazine causes a rise in core temperature [69]. The fever of NMS is the result of increased heat production from muscle rigidity, impaired heat dissipation, and possibly a higher set-point of core temperature in the hypothalamus. Drug-induced blockade of mesocortical and mesolimbic D₂ pathways partly mediates the altered mentation of NMS [55]. Neuroleptic antagonism of dopamine receptors present on peripheral sympathetic nerve terminals and vascular smooth muscle cells may mediate the autonomic dysfunction associated with NMS [70]. Antagonism of presynaptic D₂ autoreceptors increases the release of norepinephrine, whereas antagonism of postsynaptic D₂ receptors results in vascular relaxation in select areas [71]. Supersensitivity of these receptors that results from repeated dopamine antagonist administration contributes to autonomic irregularity. Clinically, tachycardia, hypertension, blood pressure lability, diaphoresis, pallor, tachypnea, and incontinence may result.

The time delay between the administration of antipsychotic drugs and the occurrence of NMS suggests that factors other than acute effects of drug itself are operative in the initiation of the syndrome. Centrally, nigrostriatal and mesolimbic regions have presynaptic D₂ autoreceptors, which diminish the release of dopamine when stimulated [71]. Peripherally, sympathetic ganglia and

postganglionic sympathetic nerve terminals have presynaptic D₂ autoreceptors, which diminish the release of norepinephrine when stimulated [72]. Exposure to antipsychotic agents may initiate the development of supersensitivity at the presynaptic and the postsynaptic dopamine receptors. Autoreceptors are more sensitive to dopamine, however, than are postsynaptic receptors and are affected to a greater degree [71]. Supersensitivity at the presynaptic area results in decreased dopamine output and contributes to dopaminergic hypoactivity. Although supersensitivity of postsynaptic receptors occurs with repeated neuroleptic administration, the acute administration of rapidly escalating doses predominantly results in postsynaptic depolarization blockade [71, 73]. When postsynaptic blockade is coupled with presynaptic downregulation (decreased dopamine production and release), marked dopaminergic hypoactivity results, and patients are at risk for NMS. Why NMS occurs in such a small minority of patients treated with neuroleptics is unknown.

NMS and EPS (e.g., acute dystonia, parkinsonism, akathisia) are closely related entities, both of which result from neuroleptic blockade of nigrostriatal D₂ receptors [55, 57, 67, 73]. NMS is often considered a severe form of EPS with fever that has progressed from unrecognized or inadequately treated milder forms of EPS [4, 5, 7, 54, 74, 75]. Despite its similarity to EPS, however, NMS has a unique pathophysiology that probably reflects complicated, time-dependent neuroreceptor effects yet to be elucidated. Anticholinergic agents are not efficacious for the treatment of NMS but are highly effective for acute dystonia and parkinsonism. Time-dependent changes in neuroreceptor function may be responsible for a lack of response to these agents in the setting of NMS.

The pathophysiology of NMS may involve iron. Iron is a positive modulator of dopamine receptor activity. Low serum iron levels often are found in patients with NMS and may lead to a decreased expression of dopamine receptors in the brain [76, 77]. It is not known whether low serum iron levels are a primary cause of NMS or occur as a result of the illness. Low serum iron may simply

reflect a nonspecific acute phase response in certain patients with NMS [78].

Although dopaminergic blockade is central to the pathobiology of NMS, the alterations of other neurotransmitter systems are likely important as well. Neuroleptics may modulate the activity of a variety of other neurochemicals (e.g., γ -aminobutyric acid [GABA], acetylcholine, norepinephrine, serotonin, glutamate, aspartate, enkephalin, dynorphin, substance P, somatostatin, cholecystokinin, neurotensin, vasoactive intestinal peptide, and various prostaglandins) through specific receptor binding or indirectly as a result of altered dopamine neurotransmission [8, 56]. Imbalance between dopaminergic activity and one or more of these neurochemicals may mediate the signs and symptoms of NMS. The interactions are complex, varied throughout the CNS, and not well understood. In addition to striatal D₂-receptor antagonism, the muscular rigidity and akinesia associated with NMS result from alterations in levels of substance P, dynorphin, enkephalin, glutamate, and GABA in various basal ganglial pathways [8, 56].

One provocative theory suggests that NMS results from disinhibition of glutamatergic and other excitatory amino acid pathways in the CNS [56, 79]. Normally, excitatory amino acid activity in corticostriatal and subthalamic pathways is antagonized by nigrostriatal dopaminergic neurons. Blockade of dopamine receptors by antipsychotic drugs disinhibits the *N*-methyl-D-aspartate (NMDA) glutamate receptor, resulting in an excess of glutamatergic neurotransmission and the rigidity of NMS [56, 79]. There is evidence to support this theory. Amantadine, an NMDA-receptor antagonist, ameliorates the rigidity of NMS and induces hypothermia in animals [56, 80]. GABA-receptor agonists (e.g., benzodiazepines) inhibit glutamate neurotransmission and are helpful in the treatment of NMS [5, 8, 56].

Direct skeletal muscle effects from neuroleptics may mediate partly the rigidity, fever, and serum elevations of creatine kinase associated with NMS. In vitro, neuroleptics have been shown to inhibit calmodulin, increase ionized calcium, and result in skeletal muscle fiber contraction; this action may be inhibited by dantrolene

[81–83]. A primary peripheral cause of NMS is unlikely, however, because dantrolene sometimes is ineffective for the treatment of this syndrome [5, 21, 44, 84].

Clinical Features

NMS is most commonly characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction [5, 6]. Fever and muscular rigidity usually are present but are not required for diagnosis. NMS is a heterogeneous syndrome that occurs across a spectrum of severity [4]. Signs and symptoms vary and are influenced by the timing of diagnosis and treatment. Fever (temperature $\geq 38^\circ\text{C}$ [100.4°F]) occurs in 79–100% of patients, and temperatures exceed 40°C in approximately 40% of patients [5, 6, 21, 42–44]. Muscular rigidity is present in 92–97% of patients and is usually parkinsonian or “lead pipe” in nature [5, 6, 8, 43, 44, 85]. The rigidity of NMS typically is unresponsive to anticholinergic treatment [5, 6]. Mental status alteration is reported in 97% of cases and may range from mild inattentiveness, lethargy, and confusion to severe unresponsive catatonia, stupor, and coma [5, 6, 8, 44, 85]. Agitation and delirium also have been described. Autonomic dysfunction has been reported in 100% of patients and includes fever, tachycardia, tachypnea, hypertension or hypotension, blood pressure lability, diaphoresis, sialorrhea, pallor, flushing, urinary incontinence, and cardiac dysrhythmias [5–7, 43, 44, 85].

Extrapyramidal movement disorders frequently are present in patients with NMS and include tremor, bradykinesia, akinesia, hypomimia, festinating gait, chorea, dystonias (e.g., opisthotonos, trismus, blepharospasm, buccofacial dyskinesia, and oculogyric crisis), nystagmus, opsoclonus, dysphagia, dysarthria, and aphonia [5–7, 44, 85]. These findings are expected if one accepts NMS as an extreme form of EPS. Other neurologic abnormalities include akinetic mutism, hyperreflexia, extensor plantar responses, ataxia, abnormal flexor or extensor posturing, ocular flutter, impaired upward gaze, and seizures [5–7, 43, 44, 85].

Clinical Course

Although NMS may occur at any time during neuroleptic therapy, most cases (66–89%) occur within 2 weeks of drug initiation, dose increase, or change to a different agent [5, 6, 43, 44]. NMS peaks within 72 hours of symptom onset in most patients (79–90%) [5, 6, 43, 44]. In one review of 115 cases of NMS, however, it took 4–30 days for 18 (21%) patients to evolve into the full syndrome [5]. When neuroleptics are stopped, signs and symptoms of NMS resolve within 1–61 days [5, 6, 43, 44]. In one study of 65 patients not treated with dantrolene or dopamine agonists, the mean duration of NMS was 9.6 ± 9.1 days [84]. The duration of illness is not different in pediatric patients [44]. The clinical course is nearly twice as long, however, for patients who have received intramuscular depot preparations [5, 6, 43]. In one study of 115 patients, the mean duration of NMS was 13 days for non-depot neuroleptics and 26 days for depot agents [5].

Most cases of NMS seem to follow a sequence of development. Mental status changes or muscular rigidity precedes autonomic dysfunction and hyperthermia in 82.3% of cases [74]. These findings support the theory that psychomotor agitation and muscular rigidity contribute to the development of fever. Early recognition of confusion, catatonia, or worsening EPS may facilitate prompt treatment and halt progression to a fulminant syndrome [54, 74].

Laboratory Findings

Although laboratory abnormalities frequently are present with NMS, none are specific to or pathognomonic for NMS. Elevation of serum creatine phosphokinase (CPK) (greater than three times normal) is the most frequent laboratory abnormality, present in 97% of patients [5, 6]. Current, consensus-based, expert opinion states that elevations of CPK of at least four times the upper limit of normal are commonly seen in patients with NMS and this degree of elevation is used to support diagnosis [86]. Elevation of CPK reflects myonecrosis and often is associated with

rhabdomyolysis, myoglobinuria, and acute renal failure from acute tubular necrosis. Myonecrosis results from muscular rigidity, fever, and psychomotor agitation. Leukocytosis (white blood cell count 10,000–40,000/mm³), with or without a left shift, is present in 70–98% of patients [5–7, 43, 44]. Other laboratory abnormalities that may occur include hypernatremia or hyponatremia, mild elevations of hepatic aminotransferases, and low serum iron [5–7]. Patients with NMS may develop anion gap metabolic acidosis (due to increased lactic acid), hypoxemia, and elevations of creatinine and coagulation parameters [5–7, 43].

For patients with NMS, results of lumbar puncture, radionuclide brain scans, and computed tomography and magnetic resonance imaging of the head are usually normal or show nonspecific abnormalities [5–7, 43]. Electroencephalograms are normal or suggest nonspecific encephalopathy [5]. In one review of 45 patients with NMS who had electroencephalograms, 21 (47%) had nonspecific slowing, and 20 (44%) had normal studies [5]. Electromyograms and muscle biopsy specimens are normal or show nonspecific changes [5–7, 43]. Postmortem histopathologic examinations of the brain do not reveal specific structural abnormalities associated with NMS [6, 7].

Complications and Mortality

Medical complications from NMS are more likely to occur in patients with a higher severity of illness (e.g., longer duration, higher fever) or preexisting comorbid conditions (e.g., organic brain syndrome, mental retardation) [5–7, 21, 42, 43]. Rhabdomyolysis is the most frequent complication [5, 6]. Other complications include renal failure, aspiration pneumonia, pulmonary edema, pulmonary embolism, respiratory failure, sepsis, coagulopathy, disseminated intravascular coagulation, sepsis, seizures, myocardial infarction, peripheral neuropathy, periarticular ossification, necrotizing enterocolitis, cardiac arrhythmias, and cardiorespiratory arrest [5–8].

NMS initially was characterized as “malignant” because of its fatal outcome in a significant

percentage of patients. Before 1986 the mortality rates ranged from 17% to 28%, whereas since 1986 they have ranged from 0% to 11.6% [5–8, 42–47, 87, 88]. In one review of 77 cases of NMS in adolescents and children from 1966 to 1998, mortality and serious sequelae rates were 9% and 20%, respectively [44]. As in adults, the mortality rate has declined since the mid-1980s; no fatalities in children have been reported in the over 20 cases published since 1986 [44]. Mortality is correlated closely with the severity of hyperthermia. In one review of 374 patients with NMS, survival was 100% for patients with peak temperature <38 °C, 88% for patients with peak temperature between 39.0 and 39.9 °C, but only 44% for patients with peak temperature >42 °C [42]. The duration of hyperthermia is also associated with the incidence of secondary complications and lethality. In one retrospective review from Australia, first generation antipsychotics were associated with a higher mortality as compared to second generation antipsychotics [89]. In all patients with NMS, death is usually secondary to respiratory failure (e.g., aspiration pneumonia, hypoventilation), cardiovascular collapse, myoglobinuric renal failure, arrhythmias, thromboembolism (e.g., pulmonary embolism), and disseminated intravascular coagulation [5–7, 43]. In one case series, renal failure was associated with a 56% mortality rate [46]. Most adult patients who recover from NMS recover fully and do not manifest persistent neurologic sequelae [5–7].

Diagnosis

Confirmatory laboratory tests do not exist for NMS, and diagnosis is based on history, suggestive physical findings, and a high level of suspicion in the appropriate clinical setting. It is unclear whether NMS is a qualitatively distinct entity with all-or-none clinical expression or an extrapyramidal complication that occurs at the end of a spectrum of neuroleptic-induced side effects. Some investigators believe that the diagnosis should not be made unless all four classic features (i.e., fever, muscular rigidity, altered mentation, and autonomic dysfunction) are present [6, 90, 91].

Other investigators believe that NMS is a heterogeneous disorder that may be diagnosed in its milder, atypical, and incipient forms [4, 5, 54, 74, 75]. To date, a lack of uniform diagnostic criteria in the literature has produced inconsistencies in diagnosis [92]. Adoption of a single set of standardized but flexible criteria to assist diagnosis is important to advance understanding of NMS and to differentiate it from other illnesses. The use of rigid diagnostic criteria may

unnecessarily delay diagnosis and treatment, whereas flexible criteria may reduce morbidity by ensuring earlier recognition and prompt intervention [4, 54, 74, 75, 92]. Sets of clinical criteria that seem to allow for some flexibility in diagnosis are presented in Table 2 [93, 94]. Recent exposure to a dopamine antagonist, or withdrawal of a dopamine agonist, and the presence of fever and muscle rigidity are typically required to make the diagnosis of NMS. Unlike DSM-IV that identifies

Table 2 Three sets of diagnostic criteria for neuroleptic malignant syndrome

Caroff et al. [93]	American Psychiatric Association DSM-IV criteria [94]	Gurrera et al. [95] consensus-based expert criteria
1. Treatment with neuroleptics within 7 days of illness onset (2–4 weeks for depot agents)	A. Development of muscle rigidity and fever associated with the use of neuroleptics	1. Exposure to dopamine antagonist, or dopamine agonist withdrawal, within the past 72 h
2. Hyperthermia (>38 °C)	B. ≥Two of the following:	2. Hyperthermia (>100.4 °F or >38.0 °C on at least 2 occasions, measured orally)
3. Muscle rigidity	Change in level of consciousness	3. Rigidity
4. Five of the following:	Mutism	4. Mental status alteration (reduced or fluctuating level of consciousness)
Change in mental status	Tachycardia	5. Creatine kinase elevation (at least four times the upper limit of normal)
Tachycardia	Hypertension or labile blood pressure	6. Sympathetic nervous system lability, defined as at least 2 of the following:
Hypertension or hypotension		Blood pressure elevation (systolic or diastolic ≥25% above baseline)
Tachypnea or hypoxia	Diaphoresis	Blood pressure fluctuation (≥20 mmHg diastolic change or ≥25 mmHg systolic change within 24 h)
Diaphoresis or sialorrhea	Dysphagia	Diaphoresis
Dysarthria or dysphagia	Tremor	Urinary incontinence
Tremor	Incontinence	7. Hypermetabolism, defined as heart-rate increase (≥25% above baseline) and respiratory-rate increase (≥50% above baseline)
Incontinence	Leukocytosis	8. Negative workup for infectious, toxic, metabolic, or neurologic causes
Increased CPK or myoglobinuria	Laboratory evidence of muscle injury (e.g., elevated CPK)	
Leukocytosis		
Metabolic acidosis	C. Symptoms in A and B are not due to another substance or to a neurologic or general medical condition	
	D. Symptoms in A and B are not better accounted for by a mental disorder	
5. Exclusion of other drug-induced, systemic, or neuropsychiatric illness		

criteria for diagnosis (see Table 2), DSM-V describes common NMS features [86]. In a review by Gurrera et al., criteria for diagnosis of NMS was adjudicated by consensus of an expert panel [95].

Differential Diagnosis

The diagnosis of NMS should be considered whenever a patient develops fever and muscular rigidity while taking neuroleptics. Early signs of NMS also may include an unexpected deterioration of mental status, new catatonia, and the development of EPS refractory to anticholinergic therapy [54, 74]. Because NMS is an uncommon syndrome, however, the diagnosis should not be made before other causes have been considered and ruled out. Patients initially suspected of having NMS often have other medical disorders that account for their signs and symptoms [4, 96]. Recently, an NMDA-receptor encephalitis associated with ovarian or testicular teratomas has been described that has features (i.e., delirium, hyperthermia, seizures, autonomic instability, and abnormal movements) similar to NMS. Therefore, consideration to serum and cerebrospinal fluid (more sensitive) testing for anti-NMDA-receptor antibodies should be considered [97, 98]. Alternative conditions that should be part of the differential diagnosis of NMS are listed in Table 3.

One disorder that is difficult to differentiate from NMS is lethal catatonia. Lethal catatonia is a rapidly progressive, idiopathic psychiatric syndrome that is characterized by catalepsy, rigidity, waxy flexibility, stupor, mutism, fever, autonomic instability, and death [6–8, 99]. In contrast to NMS, lethal catatonia begins with extreme agitation that, if unchecked, leads to exhaustion and mutism; rigidity is a late finding. Neuroleptics are ineffective in lethal catatonia [99]. Withdrawal of neuroleptics is recommended when either NMS or lethal catatonia is suspected [99].

With the widespread use of pro-serotonergic agents, serotonin syndrome [SS] (see ► Chap. 24, “Serotonin Syndrome”) is an important part of the differential diagnosis of any drug-induced hyperthermia. Similar to NMS, SS is a clinical

Table 3 Differential diagnosis of neuroleptic malignant syndrome

Toxin-mediated alternative diagnoses
Anticholinergic agents
Central hallucinogens (e.g., ketamine, LSD, MDMA, MDEA, PCP)
Cyclic antidepressants
Drug-induced parkinsonism (e.g., amoxapine, carbon monoxide, carbon disulfide, cyanide, disulfiram, ethylene glycol, methanol, metoclopramide, MPTP, neuroleptics)
Drug interactions (e.g., monoamine oxidase inhibitor tyramine reaction, serotonin syndrome)
Drug withdrawal states (e.g., sedative-hypnotics, barbiturates, benzodiazepines, ethanol; baclofen; dopamine agonists)
Heavy metals (e.g., manganese, mercury, lead)
Lithium
Monoamine oxidase inhibitors
Salicylates
Serotonin syndrome
Strychnine
Sympathomimetics (e.g., amphetamines, cocaine, designer drugs, methylxanthines)
Non-toxin-mediated alternative diagnoses
Cerebrovascular accident (e.g., hemorrhagic stroke)
CNS tumors
Endocrinopathies (e.g., pheochromocytoma, thyrotoxicosis)
Heatstroke
Infections (e.g., brain abscess, CNS HIV infection, meningoencephalitis, postinfectious encephalomyelitis, pneumonia, sepsis, rabies, tetanus)
Malignant hyperthermia
NMDA-receptor encephalitis
Seizures
Stiff-man syndrome
Systemic lupus erythematosus
Trauma

CNS central nervous system, *HIV* human immunodeficiency virus, *LSD* lysergic acid diethylamide, *MDEA* 3,4-methylenedioxyamphetamine, *MDMA* 3,4-methylenedioxymethamphetamine, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *PCP* phenylcyclohexyl piperidine (phencyclidine)

syndrome characterized by mental status alterations, muscular rigidity, autonomic instability, hyperthermia, and serum CPK elevations. Although agent exposure history is critical for syndrome differentiation, the rate of onset and time to peak illness severity and physical exam

findings can greatly assist diagnosis. SS is characterized by (1) signs and symptoms that develop and peak over hours [rather than days with NMS] and (2) muscular rigidity that is defined by hyperreflexia and clonus [unlike lead pipe rigidity with NMS] [100].

Although NMS and malignant hyperthermia (see ► Chap. 29, “Malignant Hyperthermia”) have similar clinical characteristics, they are differentiated easily on the basis of history, clinical setting, and rapidity of onset. The two illnesses are distinct clinical entities with different pathophysiology. Malignant hyperthermia is a rare genetically transmitted abnormality of skeletal muscle calcium metabolism. After exposure to certain anesthetic agents (e.g., succinylcholine, halothane) or stress, enhanced release and impaired reuptake of calcium occur from muscle cell sarcoplasmic reticulum. Excessive excitation-contraction coupling and a syndrome of muscle rigidity and fever that may appear clinically similar to NMS result. In contrast to NMS, however, malignant hyperthermia has a genetic predisposition, it is associated with general anesthesia and not neuroleptic therapy, it is characterized by rapid onset and high mortality, and its rigidity does not respond to nondepolarizing paralytic agents [5–8, 90]. In addition, muscle fibers from patients with malignant hyperthermia have positive in vitro contraction responses to caffeine and halothane, whereas muscle fibers from patients with NMS do not contract [101].

Evaluation

The history should include the duration of neuroleptic treatment; identity, dosing pattern, and route of administration of the neuroleptic; concurrent medications; identity of any preexisting illness and NMS risk factors; and time of onset, nature, sequence, and progression of signs and symptoms. The ingestion of other substances should be documented. The initial physical examination should include a detailed assessment of vital signs, cardiopulmonary status, and neurologic function. There are no bioassays that can confirm

the diagnosis of NMS. Laboratory and adjunctive diagnostic tests are used primarily to exclude alternative diagnoses and complications [6, 7]. Typical laboratory evaluation may include a complete blood count; blood cultures; measurement of serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, CPK, thyroid-stimulating hormone, and iron; a toxicologic screen of blood or urine or both; a urinalysis; and an electrocardiogram. Pregnancy testing is suggested for women of childbearing age. NMDA-receptor antibodies should be tested for if there is any clinical suspicion of NMDA-receptor encephalitis. There is no known direct effect of NMS on pregnancy or the fetus. Sicker patients also require measurements of coagulation parameters, liver function tests, arterial blood gas analysis, and a chest radiograph. Quantitative serum concentrations of concurrent medications (e.g., lithium) should be obtained. Other studies that may be necessary to exclude alternative diagnoses include a lumbar puncture, electroencephalogram, and computed tomography or magnetic resonance imaging of the head. Serial evaluations of vital signs, neurologic function, and serum CPK are important to determine the course of the illness and the need for further testing and intervention.

Treatment

Prevention is the most important aspect of treatment [54]. Risk factors (e.g., dehydration, agitation) should be identified and modified when possible, and neuroleptics should be discontinued in instances in which the incipient phase of NMS (e.g., severe EPS) is suspected. Management of suspected or established cases of NMS requires immediate withdrawal of neuroleptics and NMS-potentiating drugs (e.g., anticholinergics, lithium), exclusion of other medical conditions that may simulate NMS, and aggressive supportive care. The role of adjunctive pharmacotherapies is less well established. Supportive care includes provision of adequate ventilation and oxygenation; rehydration; temperature reduction; nutritional support; low-dose heparin to prevent

thromboembolic disease; and treatment of metabolic, renal, and cardiopulmonary complications [7]. Because NMS is an idiosyncratic complication that results from therapeutic dosing of neuroleptics, gastrointestinal decontamination is not indicated if the diagnosis of NMS is secure. Empirical antibiotic administration is recommended because of the initial difficulty in differentiating NMS from systemic infection. Prophylactic intubation should be considered for patients with excessive sialorrhea, swallowing dysfunction, coma, significant hypoxemia and acidosis, and rigidity with severe hyperthermia. Rehydration should be aggressive and rapid to achieve a minimum urine output of 50–100 mL/h (1 mL/kg/h) to avoid renal failure (level of evidence [LoE] III).

The effectiveness of specific treatments for NMS remains unclear; no individual therapy or combination of therapies has been shown to be universally effective or clearly superior to supportive care alone [5–7, 54, 58]. Evidence to support efficacy of individual agents is not based on controlled, prospective studies but largely on inferences from retrospective data and case reports. Selection bias, variation in the onset and severity of NMS, lack of standardized drug-dosing protocols, multiple simultaneous treatments, and the self-limited course of NMS make it difficult to establish the relative efficacy of any specific therapy compared with supportive care alone [5–7, 54, 58]. The possibility of a prospective, controlled study is unlikely because of the low incidence of NMS. Specific treatment measures that have been suggested include dantrolene, nondepolarizing neuromuscular paralysis, benzodiazepines, bromocriptine, amantadine, levodopa/carbidopa, nifedipine, nitroprusside, and ECT. All of these measures have been reported effective anecdotally in the management of NMS (LoE III).

Most evidence does not support the use of anticholinergic agents for the treatment of NMS. Anticholinergic agents do not decrease the incidence of NMS when coadministered with neuroleptics, and they are usually ineffective at reducing clinical effects or shortening the duration of illness for established cases of NMS [5, 6, 8,

43, 81]. Anticholinergics may worsen hyperthermia by impairing heat dissipation. In one retrospective review of NMS in children and adolescents, however, anticholinergic therapy was associated with a shorter duration of illness [44].

Dantrolene, a hydantoin derivative, inhibits ionized calcium release from the sarcoplasmic reticulum (see ► Chap. 142, “Dantrolene” for a discussion of its clinical pharmacology). It causes direct muscle relaxation by uncoupling excitation-contraction in skeletal muscle. It is used mainly to treat NMS-associated hyperthermia and rigidity. By reducing tonic contraction of skeletal muscles, dantrolene reduces thermogenesis and CPK release. It is given orally or by intravenous infusion. Initially, dantrolene should be administered at doses of 1–2.5 mg/kg every 6 h [5–8, 90]. Doses of up to 10 mg/kg/day are considered safe [5–8, 90]. Dantrolene should be continued until the signs and symptoms of NMS resolve, typically after 5–10 days of therapy [8, 28, 102] (LoE III). On resolution of clinical manifestations of NMS, some authorities recommend that dantrolene be tapered over 3–10 days to avoid syndrome recrudescence [50, 71, 102] (LoE III). Dantrolene may produce a variety of adverse effects, including muscle weakness, lethargy, nausea, vomiting, diarrhea, and urinary incontinence. Hepatotoxicity and seizures may occur with doses >10 mg/kg/day and when treatment extends beyond 60 days [6]. In one review of 534 cases of NMS, a positive response was noted in 84% of 44 patients treated with dantrolene alone [42].

Bromocriptine, amantadine, carbidopa-levodopa, and levodopa alone are dopamine agonists that are given to overcome neuroleptic-induced dopaminergic blockade. Dopamine agonists are given alone or in conjunction with dantrolene or other muscle relaxants. Bromocriptine, a dopamine receptor agonist, initially is administered in doses of 2.5–10 mg three to four times daily [5–7, 88]. Doses of 20 mg four times daily have been used [5–8, 44]. The appropriate dosing in children is not well established [44]. Bromocriptine is administered until the signs and symptoms of NMS resolve, typically after 5–10 days of therapy [8, 28, 102]. Duration

of treatment has ranged from 2 to 56 days [62, 64, 71] (LoE for bromocriptine use: III). Abrupt discontinuation of bromocriptine has resulted in recrudescence of the signs and symptoms of NMS [65, 71]. As with dantrolene, it is recommended that bromocriptine be tapered over 3–10 days on symptom resolution [54, 75, 102].

Amantadine, which enhances presynaptic dopamine release, is given orally two times daily (100–200 mg/dose) [6, 43, 90]. The therapeutic actions of amantadine also are mediated by its noncompetitive antagonism at the NMDA-glutamate receptor [56, 79, 80] (LoE for amantadine use: III). Sinemet, which increases presynaptic dopamine stores, is given orally three to four times daily (25/250–75/300 mg dose) [43, 85, 103]. In one review of 536 cases of NMS, bromocriptine was administered alone to 42 patients and was effective for 88% [42]. In this same review, amantadine and levodopa each were used in 16 cases; amantadine was effective in all, and levodopa was effective for 94% of patients [42]. These patients were treated concurrently with other pharmacotherapies, however, and the independent effects of amantadine and levodopa alone are unclear. In one study of adolescents and children with NMS, bromocriptine and levodopa were associated with a significantly shorter duration of illness [44]. In some cases of NMS, premature discontinuation of bromocriptine treatment has resulted in relapse of the syndrome; subsequent reinitiation of the drug has been effective [8, 65, 71].

Studies that have examined the efficacy of dantrolene and dopamine agonists have been largely retrospective. In one retrospective analysis of 67 cases of NMS, dantrolene or bromocriptine reduced the time to clinical improvement and resolution compared with supportive care alone [88]. Mean response time to clinical improvement was 1.0 day for bromocriptine, 1.7 days for dantrolene, and 6.8 days for supportive care alone. Mean time to complete resolution was 9.0 days for dantrolene, 9.8 days for bromocriptine, and 15.8 days for supportive care alone. A prospective, open, nonrandomized study of 20 patients with NMS showed a more prolonged illness and greater complication rates with

bromocriptine or dantrolene treatment, however, compared with supportive care alone [104]. The mean duration of illness was 9.9 days for patients treated with bromocriptine or dantrolene versus 6.8 days for patients treated supportively. The treatment groups in this study had a higher incidence of underlying medical illness, which may have biased results. In retrospective analyses, dopamine agonists have been reported to reduce NMS mortality rates significantly from 21% to 9.2% [105, 106]. When used alone, bromocriptine reduces mortality to 7.8% and amantadine reduces mortality to <6% [105, 106]. The combination of dantrolene with bromocriptine does not offer additional survival advantage over either drug alone [105].

Benzodiazepines have shown efficacy as adjunctive therapy for NMS [107–111]. Benzodiazepines not only decrease neuromuscular agitation in a nonspecific manner but also inhibit glutamatergic neurotransmission as GABA-receptor agonists [5, 8, 10, 43, 81, 107, 111]. Administration of benzodiazepines early in the course of illness may diminish psychomotor agitation and muscular rigidity and halt progression to the fulminant hyperthermic syndrome. Benzodiazepines also may hasten recovery from NMS [110, 111]. In one retrospective study of 16 patients with NMS, clinical improvement was noted within 24–72 hours of benzodiazepine treatment initiation (e.g., lorazepam) [111]; this compares favorably with the rates of recovery reported with other pharmacotherapies and with supportive care alone [5, 6, 111]. Initial intravenous doses of diazepam (0.1–0.2 mg/kg) or lorazepam (0.05–0.1 mg/kg) may be repeated at 10- to 30-min intervals until the desirable effect is achieved or CNS or respiratory depression occurs (LoE for benzodiazepine use: III). Although experience is limited, phenobarbital (5–10 mg/kg intravenously) may be used if psychomotor agitation is resistant to repeated benzodiazepine therapy (LoE for phenobarbital use: III).

ECT has been an effective treatment for NMS [5–8, 21, 42, 112, 113]. The beneficial effects are believed to result from an increased turnover of dopamine in the brain and increased receptor sensitivity to dopamine after ECT [114]. In one

review of 29 cases of NMS treated with ECT, a positive response was noted in 83% of patients [115]. Some investigators suggest that the incidence of mortality for NMS patients treated with ECT is lower than for patients treated supportively [115]. Cardiac arrhythmias, cerebral edema, and death have occurred after ECT in a few patients, however [6]. ECT may be reserved more appropriately for patients who fail to respond to standard pharmacotherapies or have refractory catatonia (LoE for ECT use: III).

Prompt reduction of NMS-associated muscle rigidity and hyperthermia can be expected to minimize the risk of rhabdomyolysis, renal failure, pneumonia, respiratory failure, disseminated intravascular coagulation, and cardiovascular collapse. These complications are responsible for most NMS-associated deaths, making their prevention paramount [5–7, 21, 42–44, 81, 90]. The severity of hyperthermia is correlated closely with the likelihood of death in patients with NMS [42, 44]. Although hypothalamic thermoregulatory dysfunction may have a causal role in NMS-associated fever, thermogenesis ultimately is due to tonic skeletal muscle contraction [5–8, 81, 84, 90]. Rapid muscle relaxation is the goal in patients who are severely ill (LoE III). Bromocriptine and dantrolene often take 1 or more days to reduce fever and rigidity in patients with NMS [88]. In select instances, when patients are extremely rigid and have temperatures that exceed 40 °C, it makes intuitive sense to use nondepolarizing neuromuscular paralysis (e.g., pancuronium) to achieve the most rapid, predictable, and effective reduction of rigidity and fever. Pancuronium has been used successfully to control rigidity and fever rapidly in two case reports; one of the patients had failed dantrolene therapy [84, 116]. A reasonable first approach to manage the rigidity and fever associated with NMS includes intravenous benzodiazepines (diazepam, 0.1–0.4 mg/kg, or lorazepam, 0.05–0.1 mg/kg), antipyretics, evaporative cooling, ice packs, cooled intravenous fluids, and dopamine agonist therapy (e.g., bromocriptine). Adjunctive dantrolene therapy may be beneficial as well. If rigidity persists and patient temperature exceeds 40 °C, timely neuromuscular paralysis is

recommended. Immediate paralysis also is recommended for patients who have severe hyperthermia and rigidity on initial presentation.

The sequence, type, and rapidity of intervention depend on the time course and severity of illness. In general, all patients suspected of having NMS should be admitted initially to an intensive care unit for aggressive supportive care. In 2007, Strawn et al. adapted a treatment algorithm from Woodbury and Woodbury to recommend treatments based on severity [112, 113]. For mild NMS, they recommend benzodiazepines. For moderate NMS, they recommend benzodiazepines along with either bromocriptine or amantadine. For severe NMS, they do not support the use of benzodiazepines but rather recommend dantrolene and dopamine agonist therapy (i.e., bromocriptine or amantadine). ECT may be considered as adjunctive therapy for those with moderate and severe forms of NMS [112, 113]. When the appropriate disposition or management of a patient is in question, consultation with a medical toxicologist is recommended.

To date, evidence suggests that patients with a history of NMS have a significantly greater risk for syndrome recurrence when an antipsychotic agent is reintroduced. In one review of 47 patients in whom antipsychotic drugs were reintroduced, 14 (30%) developed recurrent episodes of NMS [87]. The risk is greater when high-potency (greater D₂-receptor binding affinity) and long-acting (depot) agents are reintroduced. Of 21 patients, ten (48%) developed a recurrent episode when rechallenged with a high-potency agent compared with four (15%) of 26 patients rechallenged with a low-potency agent [87]. When reinitiation of neuroleptic therapy is necessary to treat severe psychotic illness in a patient with a history of NMS, steps should be taken to minimize the risk of syndrome recurrence. Potential risk factors, such as patient agitation and dehydration, should be minimized. The risk of recurrence is reduced significantly (8% versus 86% recurrence rate) if reintroduction of neuroleptic therapy is delayed by at least 2 weeks from an initial NMS episode [81, 117, 118]. When neuroleptics are reinitiated, low-potency or atypical agents (e.g., clozapine) should be used. In addition, low doses should be

used initially, dose titration should be gradual, and patients should be monitored closely for incipient signs of NMS [5, 6, 8, 43, 81].

Key Points in Neuroleptic Malignant Syndrome

1. When NMS is first suspected, neuroleptic agents should be discontinued immediately.
2. The diagnosis of NMS should be considered whenever a patient develops fever and muscular rigidity while taking neuroleptics.
3. The diagnosis of NMS should not be made before other medical conditions have been considered and ruled out.
4. Timely and aggressive supportive care is the most important aspect of treatment.
5. Prompt reduction of muscle rigidity and fever minimizes medical complications and optimizes survival.
6. Because NMS is a life-threatening medical emergency, all patients suspected of having the illness should be managed initially in an intensive care unit.

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The first known reference to rhabdomyolysis is said to be in the Bible in the Book of Numbers, [1] in which an illness is described that occurred in Israelites after eating hemlock-fed quail. Rhabdomyolysis is a potentially life-threatening syndrome that can develop from a variety of causes. The term “Rhabdomyolysis” literally translates to “dissolution of striped [skeletal] muscle.” It is the final common pathway of a number of different processes, all of which end in skeletal muscle injury. An elevated plasma creatinine kinase (CK) level is the most sensitive laboratory finding pertaining to muscle injury; whereas hyperkalemia, acute kidney injury, and compartment syndrome represent the major life-threatening complications [2]. The clinical and biochemical syndrome of rhabdomyolysis occurs when skeletal muscle cell disruption causes release of muscle cell contents (CK, lactate dehydrogenase, aldolase, myoglobin, purines, potassium, and phosphates) into the interstitial space and plasma. Although direct mechanical trauma, compression, excessive muscle activity, and ischemia are frequent causes, direct xenobiotic-induced rhabdomyolysis results from toxic insult to the cell membrane, affecting its ability to maintain ion gradients. Although rhabdomyolysis does not indicate irreversible necrosis of muscle, life-threatening illness and multi-organ insufficiency may result [3, 4].

Most cases of rhabdomyolysis in adults are multifactorial, but those related to poisoning are generally due to one of the three clinical scenarios.

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The first includes patients that develop a xenobiotic-induced sympathomimetic or hyperadrenergic state that may include seizures and/or psychomotor agitation. Second are patients with significant decreased levels of consciousness who develop muscle injury from unrelieved pressure on gravity-dependent body parts and prolonged immobilization. There are unique drugs or toxins that cause rhabdomyolysis due to direct toxicity. Examples of these unique causes include ethanol, doxylamine [5] intoxication, use of lipid-lowering agents, and ingestions of the mushroom *Tricholoma equestre* [6].

Pathophysiology

Although there are a large number of drugs or toxins that can cause rhabdomyolysis, the pathogenesis appears to follow a final common pathway, ultimately leading to myocyte destruction and release of muscle components into the circulation. In the normal myocyte, the sarcolemma has a thin membrane that encloses striated muscle fibers and contains numerous pumps that regulate cellular electrochemical gradients. The intercellular sodium concentration is normally maintained at 10 mEq/L by a sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump located in the sarcolemma [7]. The Na/K-ATPase pump actively promotes sodium efflux from the cell causing the interior of the cell to be electro-negative. This electrochemical gradient result causes calcium efflux via the sodium/calcium exchange. Moreover, low cytosolic calcium levels are also maintained by an active calcium exchanger (Ca²⁺ ATPase pump) that promotes calcium entry into the sarcoplasmic reticulum and mitochondria [8]. The above processes are energy dependent.

Adenosine triphosphate (ATP) depletion, which appears to be the end result of most causes of rhabdomyolysis, results in Na/K-ATPase and Ca²⁺ ATPase pump dysfunction resulting in an increase in cellular permeability. Sodium, chloride, and water movement into the cell then is due to either plasma membrane disruption or reduced ATP production [3, 4, 9–11].

Accumulation of sodium in the cytoplasm leads to an increase in intracellular calcium concentration (which is normally very low relative to the extracellular concentration). This excess calcium then increases the activity of intracellular proteolytic enzymes that degrade the muscle cell. As the myocyte degenerates, large quantities of potassium, aldolase, phosphate, urate, creatinine kinase, lactate dehydrogenase, aspartate transaminase, and myoglobin leak into the circulation [7, 9, 10].

When myoglobin is released from myocytes, it becomes protein bound (50% at serum concentrations < 23 mg/dL) and is rapidly metabolized to bilirubin [12]. Under physiological conditions, the plasma concentration of myoglobin is very low (0–0.003 mg/dL). Free myoglobin is rapidly filtered by renal glomeruli, with an elimination half-life of 1–3 h and disappearance from the circulation within 6 h of release [13, 14]. However, if more than 100 g of skeletal muscle is damaged, the circulating myoglobin levels exceed the protein-binding capacity of the plasma and can precipitate in the glomerular filtrate [2]. Myoglobin may be released in sudden, massive amounts making it detectable before creatinine kinase [15] (Fig. 1).

Drug-Induced Rhabdomyolysis

Examples of drugs, toxins, or other agents that are associated with rhabdomyolysis are listed in Table 1 [16]. Toxicant-induced agitation, seizures, withdrawal, and hyperthermia are typical underlying features leading to rhabdomyolysis. Even in the absence of coma or seizures, ethanol ingestion (especially binge drinking) can cause muscle damage and rhabdomyolysis by an unknown mechanism [17]. However, it has been theorized that altered muscle ion homeostasis occurs because of changes in sodium-potassium transport pump activity allowing increased sodium entry into the cell [18, 19]. Nutritional deficiencies, hypophosphatemia, and hypokalemia may be coexistent risk factors for the development of rhabdomyolysis [3, 20, 21]. Cholesterol-lowering drugs of the statin class are also associated with

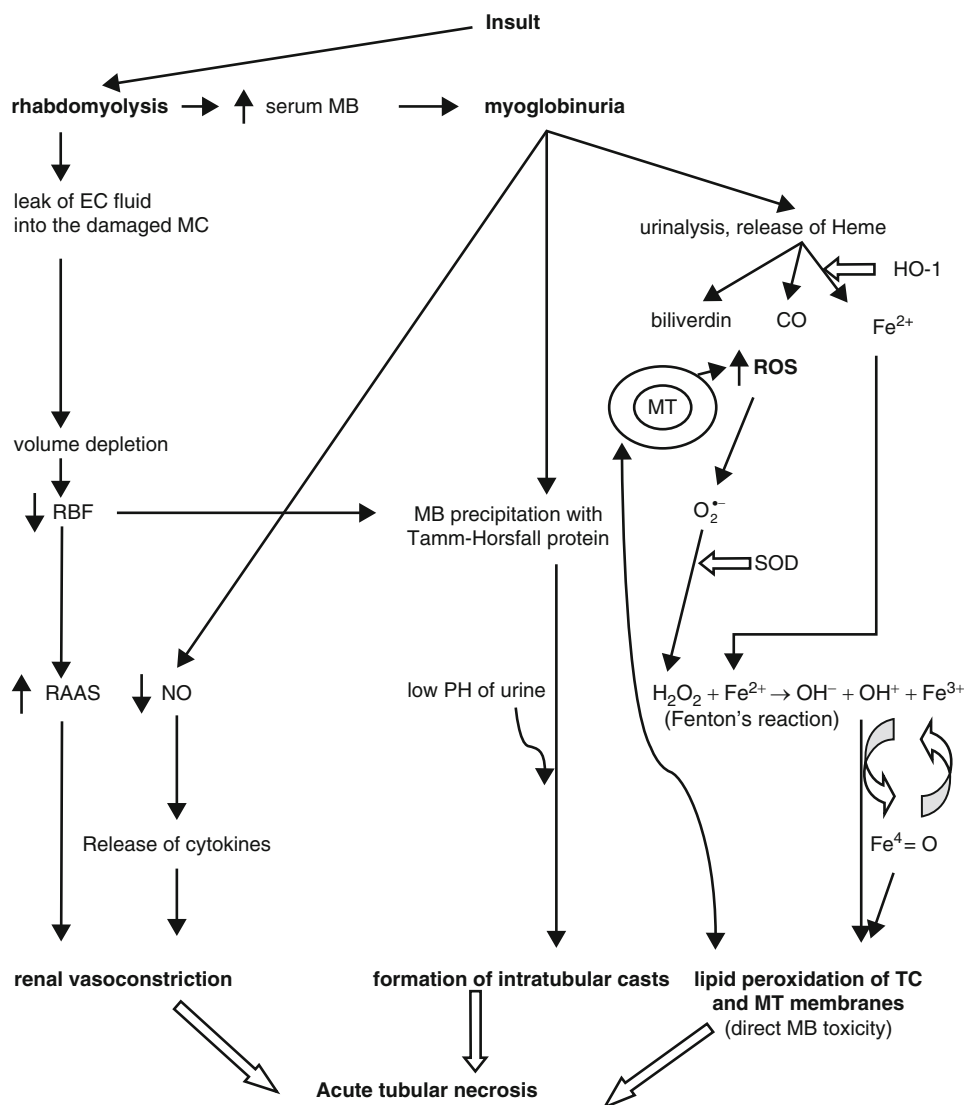


Fig. 1 Pathophysiology of rhabdomyolysis-induced acute kidney injury. *CO* carbon monoxide, *EC* extracellular, Fe^{2+} ferrous iron, Fe^{3+} ferric iron, Fe^4O , ferryl iron, *HO-1* heme oxygenase-1, H_2O_2 hydrogen peroxide, *MB* myoglobin, *MC* muscle cell, *MT* mitochondria, *NO* nitric oxide, OH^-

hydroxyl anion, $O_2^{\bullet-}$ superoxide radical, OH^\bullet hydroxyl radical, *RAAS* renin-angiotensin-aldosterone system, *RBF* renal blood flow, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *TC* tubular cell (Petejova and Martinek [56]. Used through a creative Commons license)

drug-induced rhabdomyolysis in the absence of other major clinical manifestations of toxicity [22]. Other unique and classic causes of rhabdomyolysis include doxylamine [5] intoxication and ingestion of the mushroom *Tricholoma equestre* [Saviuc].

Statins

Statin-associated rhabdomyolysis is rare but a well-known adverse effect of this class of drugs. Statin-induced myotoxicity is dose dependent. The concept of a dose-dependent increased risk

Table 1 Drugs and toxins associated with rhabdomyolysis[16]

Class	Examples
H2 antagonists	Famotidine, cimetidine
Analgesics and anti-inflammatory agents	Salicylates, acetaminophen, propoxyphene, opiates, buprenorphine, ibuprofen, diclofenac, phenylbutazone, sulfasalazine, glucocorticoids, pethidine, colchicine
Anesthetics	Inhalation anesthetics, propofol, ketamine, glutethimide
Antibiotics, antifungals, and antivirals	Chloroquine, hydroxychloroquine, daptomycin, fluoroquinolones, trimethoprim/sulfamethoxazole, amphotericin B, itraconazole, isoniazid, zidovudine, ritonavir, didanosine
Antidepressants, antipsychotics, and mood stabilizers	All classes antidepressants, haloperidol, risperidone, thioridazine, loxapine, amoxapine, lithium, chlorpromazine
Antihistamines and antimuscarinics	Doxylamine, diphenhydramine, all antimuscarinics
Beta-adrenergic antagonists	Oxprenolol, labetalol
Cholesterol lowering	Fibrates, HMG-CoAse reductase inhibitors (statins)
Chemotherapeutic and immunosuppressant medications	Vincristine, cytarabine, mitoxantrone, arsenic trioxide, cyclosporine A, alpha interferon, interleukin 2, azathioprine, tacrolimus, trabectedin, leflunomide
Alcohols and recreational drugs	Ethanol, ethylene glycol, methanol, heroin, methadone, cocaine, amphetamines, LSD, ecstasy, marijuana, PCP, synthetic cathinones
Sedatives/hypnotics	Diazepam, temazepam, lorazepam, chloral hydrate, barbiturates
Miscellaneous	Amiodarone, D-penicillamine, vitamin A, vitamin B6, insulin, nifedipine, phenytoin, valproate, tryptophan, laxatives, diuretics, streptokinase, aminocaproic acid, caffeine, theophylline, terbutaline, vasopressin
Toxins and environmental	Hemlock, hemlock herbs from quail, wild mushrooms (<i>Amanita phalloides</i> , <i>Tricholoma equestre</i>), snake venoms, Hymenoptera, giant desert centipede, black widow spider, toluene, carbon monoxide, hyperthermia, hypothermia, thujone containing plants (<i>Artemisia absinthium</i> [wormwood], <i>Salvia officinalis</i> [sage], <i>Tanacetum vulgare</i> [tansy], <i>Achillea millefolium</i> [yarrow], <i>Thuja plicata</i> [red cedar], and <i>Thuja occidentalis</i> [white cedar]), seafood poisoning (Haff disease due to freshwater fish, buffalo fish, crayfish, Atlantic salmon, pomfret; palytoxin due to marine reef fish, bottom feeding fish, crabs, anemones)
Tyrosine kinase inhibitors	Sunitinib, imatinib, erlotinib (when combined with simvastatin)

of statin-related muscular adverse effects is supported by the results of a meta-analysis. Overall, the observed excess of rhabdomyolysis was 4 per 10,000 patients with more intensive versus less intensive statin therapy compared with 1 per 10,000 patients on standard statin regimens versus control (at least 2 years follow-up) [23]. Although the exact mechanism of statin-associated myopathy is unclear, there appears to be vulnerability related to gene polymorphism in addition to several intracellular mechanisms. Functional variation of the hepatic uptake transporter SLCO1B1 has been implicated in statin-induced myopathy. An analysis by Carr et al. revealed the SLCO1B1 c.521 T > C single-nucleotide polymorphism to be a significant risk factor for severe myopathy

[24]. Meta-analysis showed an association between c.521C > T and simvastatin-induced myopathy, although power for other statins was limited in their study. Pathophysiologically, statins appear to deplete geranylgeranyl pyrophosphate, thereby reducing prenylated Rab. Intracellular vesicle traffic is consequently suppressed inviting mitochondrial dysfunction and ATP depletion [23, 25]. Studies have also suggested that variation in the coenzyme Q2 (COQ2) homologue gene may predispose individuals to statin-induced myopathy. In addition, abnormal mitochondrial respiratory function is caused by statin-induced coenzyme Q10 deficiency [43]. Puccetti et al. demonstrated an association between both rosuvastatin- and

atorvastatin-induced myopathy and the rs4693075 polymorphism in the COQ2 gene [26]. An association of another COQ2 variant (rs4693570) and statin-induced myalgia has also been described [27].

Some concomitant medications appear to increase the risk of statin-associated myopathy. Among the 601 cases of statin-associated rhabdomyolysis investigated by Omar et al. [28], the most common concomitant medications were mibefradil (99 patients) fibrates (80 patients), ciclosporin (51 patients), macrolide antibiotics (42 patients), warfarin (33 patients), digoxin (26 patients), and azole antifungals (12 patients).

Doxylamine

Rhabdomyolysis in uncomplicated antihistamine overdoses is uncommon. Severe cases of rhabdomyolysis following antihistamine exposures typically are associated with the development of seizures and hyperthermia [29–31]. Doxylamine, an over-the-counter drug used primarily as a sleep-inducing agent, however, is associated with rhabdomyolysis in the absence of prolonged sedation, agitation, or delirium or seizures [32]. Early studies reported that the incidence of rhabdomyolysis following doxylamine was relatively low [33]. In contrast, in urban emergency departments in Korea, doxylamine overdose accounts for 25% of visits due to drug overdose [34] and the incidence of rhabdomyolysis ranges from 32% to 77% [5, 35, 36]. In addition, rhabdomyolysis developed in 21.0% (35/169) of patients who had creatinine kinase levels within the reference range at presentation [32].

The mechanism for rhabdomyolysis in doxylamine overdose is uncertain. In the multivariate regression analysis, by Kim et al., the amount of doxylamine ingested and the initial heart rate were reliable associative factors for the development of rhabdomyolysis [Kim]. In a prospective study by Jo et al., looking at doxylamine overdose, their bivariate analysis in patients who developed rhabdomyolysis differed from those

who did not in the amount of doxylamine ingested (36.2 vs. 17.2 mg/kg, p 0.003). Initial value of serum Cr (1.3 vs. 0.8 mg/dL, p 0.022) was significantly higher and the arterial pH (7.36 vs. 7.43, p 0.032) was significantly lower in patients with rhabdomyolysis than those without [5]. In their study rhabdomyolysis was common, occurring in 87% of patients who ingested more than 20 mg/kg.

Tricholoma (equestre/flavovirens)

Several cases of massive rhabdomyolysis have been reported since 1993 in France and 2001 in Poland after ingestion of large amounts of an edible and, until then, valuable species of mushroom called *Tricholoma equestre* (common name “Man on Horseback”). Several of these cases of rhabdomyolysis were associated with respiratory complications and myocarditis leading to death [6]. The toxic dose or underlying predisposing factors for susceptibility in humans are unknown. *Tricholoma equestre* toxicity appears to require extremely large doses, in the order of 100–400 g at each meal over repeated meals [37]. The myotoxic component of *Tricholoma equestre* has not been identified. The mushroom contains triterpenoids, a high steroid and aldehyde content, indoles, and acetylenic compounds [38]. The onset is 24–72 h after the last meal, with presenting symptoms of muscle weakness, fatigue, anorexia, and muscle pain in lower extremities, progressing over several days, followed by dark urine.

Water Hemlock

Rhabdomyolysis is common in water hemlock poisoning. Patients often complain of muscle pain and tenderness at the time of presentation. It is likely to occur in patients with recurrent seizures but has also been seen in patients in the absence of seizures, although to a lesser degree. In the absence of seizures, the mechanism of myotoxicity is unknown [39–41].

Cocaine

Cocaine use leads to rhabdomyolysis through psychomotor agitation, seizures, and impaired behavioral responses [42, 43]. Serum CK values have been reported up to 100,000 U/L (1700 *ukat*/L). In large doses, cocaine has direct toxic effects on skeletal muscle causing myofibrillar degeneration. In addition, muscle ischemia from vasoconstriction may predispose to further muscle injury. Although crack cocaine is the most reported in the literature, all forms of cocaine use can cause rhabdomyolysis. A prospective case series of patients presenting to an emergency department with complaints related to cocaine use showed a high incidence of cocaine-associated rhabdomyolysis. Of all cocaine users, 24% had rhabdomyolysis, defined by an elevation of creatinine kinase of more than fivefold that of the mean level (>1000 U/L; 17 *ukat*/L). The same study found that only 13% of the patients presenting with rhabdomyolysis experienced any of the classic signs or symptoms (nausea, vomiting, myalgias, muscle swelling and tenderness, weakness) [44].

Patients at highest risk for complications from rhabdomyolysis are patients presenting with signs of sympathomimetic toxicity. A retrospective study showed that patients with acute cocaine intoxication who had admission serum creatinine kinase levels < 1000 U/L (<17 *ukat*/L), a normal serum creatinine concentration, a normal WBC, and no more than one additional risk factor for rhabdomyolysis (i.e., muscular activity, other mind-altering drugs, seizures) were unlikely to develop rhabdomyolysis [45].

Propofol

Propofol is widely used as a short-acting anesthetic and for sedation of critical ill patients. Current recommendations suggest a dosage less than 8 mg/kg/h and application not longer than 2 days in adults [46–48]. Rhabdomyolysis occurs most frequently with high doses of propofol after 96 h of administration [49]. On a molecular level, propofol is toxic for mitochondria and elevates

malonyl-carnitine concentrations [50]. It uncouples oxidative phosphorylation and inhibits the respiratory chain at complexes II and IV [51–53]. In particular, fatty acid transport is inhibited by elevated malonyl-carnitine levels that impair entry of long-chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain at complex II [53].

Rhabdomyolysis may accompany propofol infusion syndrome, a rare but extremely dangerous complication of propofol administration. Certain risk factors for the development of propofol infusion syndrome are described, most notably propofol doses and durations of administration. Based on the data from case reports and case series, it is not recommended to administer propofol for more than 48 h or infusions more than 4 mg/kg/h (67 mcg/kg/min). Other potential risk factors for the development are critical illness (sepsis, head trauma, status epilepticus, etc.), use of vasopressors and glucocorticosteroids, carbohydrate depletion (liver disease, starvation, or malnutrition), carnitine deficiency, and subclinical mitochondrial disease [54]. The syndrome commonly presents as an otherwise unexplained high anion gap metabolic acidosis (due to elevation in lactic acid), rhabdomyolysis, hyperkalemia, acute kidney injury, elevated liver enzymes, and cardiac dysfunction [54].

Clinical and Laboratory Manifestations

An elevated serum CK is the most sensitive and reliable indicator of muscle injury. Table 2 lists the common features of diagnosis of rhabdomyolysis and subsequent acute kidney injury. The definitive diagnosis of rhabdomyolysis requires an elevation of CK levels to more than five times normal. The isoenzyme CK-MM (found in skeletal and cardiac muscle) is responsible in large part for the elevation in serum CK; the CK-MB fraction (found primarily in cardiac but also in skeletal muscle) should not exceed 5% of the total CK level. Serum CK generally rises 2–12 h after the onset of muscle injury and peaks 24–72 h, after which it declines at the relatively constant rate of 39% of the previous day's value [55]. Creatinine kinase

Table 2 Diagnosis of rhabdomyolysis and subsequent acute kidney injury (Adapted from Petejova and Martinek [56])

Clinical presentation
Muscular weakness, myalgia, swelling, tenderness, stiffness
Fever, feelings of nausea, vomiting, tachycardia
Oligoanuria or anuria in connection with renal damage or in the presence of volume depletion
Signs/symptoms of associated drug/toxin toxicity
Laboratory findings
Serum: creatinine, urea nitrogen, creatinine phosphokinase, myoglobin, ions (potassium, phosphorus, calcium), lactate dehydrogenase, transaminases, acid–base balance
Urine: myoglobin or positive dipstick test without any erythrocytes

values that fail to decrease in this manner suggest ongoing muscle injury.

Serum myoglobin increases within a few hours of muscle injury, before the increase in serum creatinine kinase. Because the metabolism of protein-bound myoglobin to bilirubin and the renal excretion of free myoglobin occurs rapidly, serum myoglobin concentration are typically normal 1–6 h after cessation of muscle injury in the presence of normal renal function [20]. Consequently, absence of myoglobinuria does not preclude the diagnosis of rhabdomyolysis. Variables that determine the presence of myoglobin in the urine include the glomerular filtration rate, the concentration of plasma myoglobin, the degree of plasma protein binding, and the rate of urine production and flow [57–59].

Dark brown urine, positive for blood on a reagent strip but without red blood cells on microscopic examination, indicates the presence of myoglobin [11]. Although the renal myoglobin threshold is 1 mg/dL, the urine does not become discolored until its myoglobin concentration is great than 100 mg/dL. Urine dipsticks containing orthotoluidine react with the globin fraction of hemoglobin and myoglobin. If red blood cells are present, the orthotoluidine reaction does not differentiate hemoglobin from myoglobin. Radioimmunoassay, immunoelectrophoresis, and hemagglutination are more specific than urine dipstick methods but also significantly more expensive [11].

Muscle cell disruption results in the release of potassium, phosphate, and urate. Acidemia and renal insufficiency may increase serum potassium concentrations further. Hypocalcemia, the result of deposition of calcium in the damaged muscle, may be present with or without acute kidney injury. It is usually clinically insignificant, unless it occurs in the setting of severe hyperkalemia or ventricular dysfunction [45]. In approximately 30% of patients with acute kidney injury and rhabdomyolysis, hypercalcemia occurs in the subsequent diuresis phase of the renal impairment. Parathyroid hormone concentrations are typically normal or low, but 1,25-dihydroxycholecalciferol concentrations are much greater in the hypercalcemic patients than in patients who do not develop hypercalcemia [60].

Aldolase, lactate dehydrogenase, and aspartate transaminase activities are frequently elevated as well but only aldolase is specific for muscle injury. Creatinine may be elevated from both renal insufficiency and from the release of creatine from muscle and its spontaneous hydration to creatinine [11].

Complications

Acute Kidney Injury

The primary complication of rhabdomyolysis is acute kidney injury, which occurs in approximately 30% of patients [56, 61]. Risk factors for acute kidney injury in the setting of drug or toxin exposure are less studied than in traumatic or medical-associated rhabdomyolysis. In general, risk factors for acute kidney injury in the presence of rhabdomyolysis include hyperkalemia, hyperphosphatemia, dehydration, sepsis, intravascular volume depletion, high serum myoglobin concentrations, and low myoglobin clearance [18, 56].

The concentration of heme pigments resulting in acute kidney injury is not well understood. At urine pH less than 5.6, myoglobin dissociates into ferrihemate and globin. Ferrihemate depresses renal tubular transport mechanisms and causes a subsequent deterioration in renal function [14, 62]. Myoglobin (molecular weight 17,500 Da)

may interfere with the endogenous vasodilator nitric oxide, causing a decrease in GFR. Myoglobin and other muscle constituents, such as urate, which is metabolized to uric acid, may deposit in the tubules. Other theories include the presence of oxygen free radicals. Animal experiments show that myoglobin causes renal damage when dehydration is present. Contributing factors seem to be concentrated urine with low urine flow and urine pH less than 5.6. Published clinical reviews conclude that patients with hyperkalemia, hyperphosphatemia, high serum myoglobin concentrations, and low myoglobin clearance seem to be at risk for development of acute kidney injury [9, 18, 63–66].

Other severe systemic complications include disseminated intravascular coagulopathy and acute compartment syndrome from swelling muscle and reduced macrocirculation and microcirculation of injured limbs. Extracted fluid from the circulation into the swollen muscle groups may lead to hypotension and shock [67, 68].

Treatment

There are no randomized, controlled trials in the treatment of rhabdomyolysis that offer definitive guidance for treatment. Only a few interventional clinical trials in rhabdomyolysis have been reported in the past decade. There are even less data for treatment guidelines studying rhabdomyolysis management in the poisoned patient. Most recommendations are based on retrospective observational studies with small numbers of patients, animal models, case reports or series, and opinion. As with other disease states, management guidelines for the poisoned patient are often extrapolated from the care of nonpoisoned patients. The lack of high-quality evidence must be acknowledged and considered when reviewing recommendations for interventions [68].

The treatment of rhabdomyolysis involves several components in the poisoned patient (Table 3). The cornerstone of treatment centers on the prevention of acute kidney injury. No single marker or predictive model has been able to reliably

Table 3 Components in the treatment of rhabdomyolysis in the toxicology patient (Adapted from Zimmerman and Shen [68])

Discontinuation of offending agent causing skeletal muscle injury
Control of sympathomimetic features and/or seizures
Extracellular fluid expansion (Maintain good urine output, stable hemodynamics)
Rapid identification of potentially life-threatening complications
Avoid agents that impair renal blood flow autoregulation (NSAIDs, ACE inhibitors, ARBs)

assess the risk of acute kidney injury, especially in the poisoned patient.

There is complete agreement that early and aggressive volume resuscitation, sufficient to restore adequate renal perfusion and increase urine flow, is the standard of care in preventing acute kidney injury in patients with rhabdomyolysis (Level II-2 recommendation) [2, 68–73]. In animals with rhabdomyolysis that had a low urinary pH, dehydration predisposed to renal injury, which was prevented with urinary dilution [55, 66, 74]. In addition, hypovolemia may occur as a result of movement of fluid into the traumatized muscle and/or to hyperthermia.

The type of fluid and the total volume of fluid remain matters of opinion. A target of 6–12 L within 24 h is a reasonable goal, as long as complications from volume overload can be avoided [68]. Strict observance of adequate urine output should be instituted with a goal rate of 2 mL/kg body weight/h [72]. Although there are no standard protocols in the literature for the duration of fluid administration, intravenous fluids should be continued until the level of creatinine kinase in the plasma decreases to less than 1000 U/L (17 *ukat*/L) or until the development of oliguric acute kidney injury limits further fluid administration [68, 71].

Although research is limited, isotonic saline is preferred because it is readily available and does not contain potassium [68]. A prospective, randomized trial compared the effects of lactated Ringer's versus 0.9% saline administered at 400 mL/h in patients with mild rhabdomyolysis

secondary to doxylamine [75]. At the end of 12 h of infusion, the serum and urine pH were higher in the lactated Ringer's group; however, the clinical significance of this outcome is unclear.

Administering bicarbonate solution to prevent rhabdomyolysis-induced acute kidney injury is a consideration but evidence of a clinical benefit is lacking (Class II-2 recommendation). Clinical reports [76] suggest that alkaline diuresis may be effective in preventing acute renal insufficiency, but there are no prospective randomized studies to support this. The concept of urinary alkalization derives from the known precipitation of myoglobin in an acidic environment, and therefore urinary alkalization (pH <6.5) theoretically can decrease the deposition of myoglobin in renal tubules. Alkalization of the urine may be difficult to achieve without causing a systemic metabolic alkalosis. Conversely, some bicarbonate-containing fluids may be helpful if 0.9% saline administration results in a dilutional metabolic acidosis [68]. A current consensus statement suggests that sodium bicarbonate administration is not necessary and not superior to normal saline diuresis in increasing urine pH [77].

The use of mannitol to promote urine output and prevent acute kidney injury has also appeared in practice and the literature. However, there is even less convincing evidence for mannitol administration (Class III Recommendation). Mannitol has not been evaluated in the poisoned patient as a sole intervention in a controlled trial of rhabdomyolysis. The same small retrospective studies of bicarbonate administered with mannitol in rhabdomyolysis are cited to suggest treatment success with mannitol [78, 79]. Although many mechanisms have been postulated regarding the renoprotective effects of mannitol, prevention of heme protein trapping by diuretic action explains most of the data [63, 80]. A variety of dosing regimens using intermittent bolus and continuous infusion of mannitol are reported. Routine use of mannitol is not recommended for rhabdomyolysis, and it should not be administered to hypovolemic or anuric patients [68].

Similar to mannitol, the use of loop diuretics in the routine management of rhabdomyolysis is not

recommended (Class III recommendation). Diuretics have been advocated to "convert" oliguria or anuria to nonoliguria but with very limited published experience. Care must be taken not to exacerbate hypokalemia or hypocalcemia if loop diuretics are used; conversely, use may be beneficial to treat hyperkalemia before renal recovery or hemodialysis [68].

Renal replacement therapies remain a mainstay of treatment in patients that develop rhabdomyolysis-associated acute kidney injury (Class II-1). Hemodialysis and continuous kidney replacement methods have been investigated in several studies [81–83]. The initiation of renal replacement therapy in clinical practice should not be managed by the myoglobin or creatinine kinase serum concentration but by the status of renal impairment, with complications such as life-threatening hyperkalemia, hypercalcemia, hyperazotemia, anuria, or volume overload without response to diuretic therapy [56, 77, 80]. Myoglobin has a molecular mass of 17 kDa and is poorly removed from circulation using conventional extracorporeal techniques. Therefore, intermittent hemodialysis is mostly mandated by renal or metabolic indications or drug/toxin removal. Preventive extracorporeal elimination is not routinely indicated [56].

Electrolyte disturbances that occur in the setting of rhabdomyolysis should be treated in a standard fashion. Be aware that hyperkalemia may occur within a few hours of onset of rhabdomyolysis and may be severe enough to require intervention [72]. Hyperphosphatemia may require administration of phosphate binders and treatment is dictated by the degree of phosphate elevation. In addition, hypocalcemia may occur early in the clinical course of rhabdomyolysis [66]. However, calcium should not be administered unless hyperkalemia or ventricular dysfunction occurs since calcium infusion may increase deposition of calcium in injured muscle. Hypercalcemia seen during the diuretic phase of acute kidney injury is usually self-limited and requires only conservative treatment and fluid replacement [84].

Prognosis

Outcomes from rhabdomyolysis in the poisoned patient are not known. Considering all causes of rhabdomyolysis, most patients with acute renal failure from rhabdomyolysis recover function within a few months [68]. It is reasonable to extrapolate that mortality of patients with rhabdomyolysis and acute renal failure is likely higher than in patients with no renal failure [78].

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Part III

Medication Safety in the Intensive Care Unit

Philip Moore and Keith Burkhardt

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Adverse drug reactions (ADRs) are undesirable effects of medications used in normal doses [1]. ADRs can occur during treatment in an intensive care unit (ICU) or result in ICU admissions. A meta-analysis of 4139 studies suggests the incidence of ADRs among hospitalized patients is 17% [2]. Because of underreporting and misdiagnosis, the incidence of ADRs may be much higher and has been reported to be as high as 36% [3]. Critically ill patients are at especially high risk because of medical complexity, numerous high-alert medications, complex and often challenging drug dosing and medication regimens, and opportunity for error related to the distractions of the ICU environment [4]. Table 1 summarizes the ADRs included in this chapter.

ADRs are among the leading causes of death in hospitalized patients [1, 5]. Other serious effects include disability, prolonged hospitalization, and increased healthcare costs. These costs are variable depending on the severity, but each ADR could cost \$6000–9000 and increase the length of stay by a median of 8.8 days [4, 6]. One observational study of ICU patients found an incidence of 20.2%, or 80.5 events per 1000 patient days, of which 13% were life threatening and/or fatal [7].

Medical toxicologists can help to decrease healthcare costs and reduce length of stay by assisting with the rapid detection and treatment of ADRs. This benefits both the patient and healthcare system. This chapter will provide a background for identifying ADRs as well as

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Table 1 Adverse drug reactions (ADRs) in the ICU chapter overview. ADRs are categorized alphabetically by organ system

Allergic/hypersensitivity ADRs	Angioedema
	Bronchospasm
	Infusion reactions
	DRESS
Dermatologic ADRs	SJS and TEN
Cardiovascular ADRs	Arrhythmias and conduction disturbances
	QT prolongation
	Hypotension
	Cardiogenic shock
	Distributive shock
Hematologic ADRs	Thrombocytopenia
	Methemoglobinemia
Pulmonary ADRs	Drug-induced respiratory disease
	Airway dysfunction
	Parenchymal and interstitial lung disease
	Pulmonary edema and vasculopathy
	Pulmonary arterial hypertension
	Neuromuscular respiratory disease
Gastrointestinal ADRs	Constipation/ileus
	Delayed absorption
	Diarrhea
	Hepatotoxicity
	Pancreatitis
Renal ADRs	Acute renal failure: prerenal, intrarenal, and postrenal nephrotoxicity and nephrotic syndrome
Neurologic ADRs	Delirium
	Seizures

Abbreviations: drug reaction with eosinophilia and systemic symptoms (*DRESS*), Steven–Johnson syndrome, toxic epidermal necrolysis (*TEN*)

describing various types. ADRs will be summarized by organ system, incorporating post-marketing surveillance to identify higher-risk ICU drugs. Drugs commonly used in the ICU for the management of poisoned patients are the primary focus of this chapter.

Table 2 Naranjo Adverse Drug Reaction Probability Scale. A ten-question probability scale assigns points to each response. If the response is unknown, a score of 0 is assigned. From the total score, drug–ADR causality can be stratified as definite (≥ 9), probable (5–8), possible (1–4), and doubtful (≤ 0)

	Question	Yes	No
1	Previous reports on this reaction?	+1	0
2	Timing-ADR appear after drug administration?	+2	−1
3	Did the ADR improve after the drug was discontinued or after an antagonist was administered?	+1	0
4	Did the ADR reappear when the drug was readministered?	+2	−1
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2
6	Did the reaction reappear when a placebo was given?	−1	+1
7	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0
10	Was the ADR confirmed by any objective evidence?	+1	0
	Total:		

Modified from Naranjo et al. [8]

Background

When an ADR is suspected, a Naranjo probability score can be used to standardize the assessment, with presumed causality assigned based on total score (see Table 2) [8].

The higher the score, the more likely an ADR occurred. Mechanisms by which these medications cause ADRs include pharmacogenetic, pharmacokinetic, and metabolite accumulation and/or combinations and are described in Table 3. Table 4 summarizes one commonly used scoring system for grading adverse drug reactions.

The incidence of specific drug–ADR combinations is low, requiring large databases and statistical analysis to identify emerging trends. Advances in information technology have

allowed pharmacovigilance and post-marketing surveillance systems to calculate observed to the expected number of drug-event pairs (proportional reporting ratios (PRRs)) [9–13]. The Empirical Bayesian Geometric Mean (EBGM) is calculated from the PRR and accounts for differences in reporting rates and variables within the dataset [14]. False positives, which are inherent to data mining systems, are avoided by increasing the number of reports and increasing PRR or EBGM, thereby strengthening the signal [12, 14]. Both PRR and EBGM ratios shrink toward one, and values ≥ 2 are considered to be the safety signal thresholds that warrant further evaluation. Previous studies have suggested PRRs to be more sensitive and EBGM more specific [12, 15]. Some studies minimize false negatives by using more than one data mining system;

however, well-known drugs associated with ADRs continue to be missed, which is possibly secondary to underreporting. These are often older medications such as nitroglycerine infusions [16]. There are limited literature studies on ICU ADRs compared to medication error evaluation.

Organ System ADRs

Allergic/Hypersensitivity ADRs

Infusion Reactions

Infusion reactions (drug-mediated hypersensitivity, infusion-related toxicity, cytokine storm, cytokine-release syndrome, anaphylactoid reaction, and serum sickness-like illness) are associated with a spectrum of variability and heterogeneity for both individual and drug; symptoms may include anxiety, diaphoresis, rigors/chills, fever, pruritus, urticaria, angioedema, headache, nausea, emesis, diarrhea, chest pain, dyspnea, wheezing/bronchospasm, hypoxia, respiratory failure, hypotension, and death [17–21]. Symptoms can occur shortly after the infusion begins but can have delayed onset; symptoms may decrease when the infusion rate is discontinued or slowed but symptoms may persist.

Drug classes associated with infusion reactions include antimetabolites (drugs interfering with nucleic acid synthesis), antimicrobials, electrolytes and nutrients, enzymes, and immunomodulators [17]. The implicated final common pathway for each medication may include mast cell

Table 3 Types of ADRs

1	Exaggeration of drug's normal/desired pharmacological mode of action
2	Continuing action/reaction, persisting for longer than expected time period
3	Delayed onset of action
4	Withdrawal
5	Unexpected failure of therapy
6	Idiosyncratic response not expected from normal pharmacological mode of action
7	Drug–drug interaction
8	Other pharmacokinetic interaction
9	Other pharmacodynamic interaction

Modified from American College of Medical Toxicology ToxIC Database available at <http://www.acmt.net/cgi/page.cgi/Toxic1.html>

Table 4 CTCAE grading of adverse drug reactions. ADRs can be mild or moderate or result in death; signs/symptoms, interventions, and limitations to ADLs are used to grade the severity with a score of 1–5

Grade	Description	Signs/symptoms	Intervention	ADLs
1	Mild	Asymptomatic or mild	None	
2	Moderate	Minimal	Noninvasive intervention	Limited
3	Severe	Significant but not immediately life threatening	Hospitalization and/or prolongation	Disabling
4	Life threatening	Life-threatening consequences	Urgent intervention indicated	Disabling
5	Death			

Modified from the US Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 available at <http://evs.nci.nih.gov/ftp1/CTCAE/About.html> (Accessed Aug 18, 2015)

Abbreviations: ADL activities of daily living, CTCAE common terminology criteria for adverse events

activation and nitric oxide (NO) signaling via nitric oxide synthase (e.g., *N*-acetylcysteine [22, 23] and calcium [24]), NO donors and NO-like compounds (e.g., nitroprusside [25]), reactive oxygen and nitrogen species (e.g., amphotericin [26]), S-nitrosylation and transnitrosylation (e.g., adenosine [27–29], iron, *N*-acetylcysteine, and nitroprusside), histamine release (e.g., amphotericin [26], *N*-acetylcysteine [20], and vancomycin [30]), and cytokine release (e.g., amphotericin [26], *N*-acetylcysteine [20], and immunoglobulins) [31–34]. Sometimes, clinical effects are caused by an excipient such as polyethoxylated castor oil which has been used as the solubilizing vehicle for phytonadione [35]. Some drugs such as *N*-acetylcysteine have been prospectively studied. When administered rapidly, *N*-acetylcysteine has caused mild, moderate, and severe infusion reactions for up to 60%, 30%, and 10% of patients, respectively [20]. This association may be underreported, as this drug does not appear in the table of drugs associated with infusion reactions. The medical toxicologist may see infusion reactions related to IV *N*-acetylcysteine, although slower infusion rates have made this less common [20, 21, 23, 36, 37].

For ICU patients, electrolytes had the highest association with infusion reactions followed by immunomodulatory drugs, antiarrhythmics, antifungals, and antibiotics (Table 5). Treatment involves discontinuing or slowing the rate of infusion for the suspected drug or pretreating with antihistamine and prostaglandin inhibitors.

Drug-Induced Angioedema

Angioedema, or rapid localized edema of the deep dermis, subcutaneous, or submucosal tissues, can be idiopathic, or it can be mediated by bradykinin or mast cells [38]. Angioedema associated with the use of drugs can manifest after the first dose of a drug, but for some drugs, such as those targeting the renin–angiotensin–aldosterone system, it can occur at any time [39]. The presence of angioedema with wheals or urticaria suggests the etiology involves mast cells. Culprit medications include nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics, often acting through the inhibition of cyclooxygenase resulting in alteration in the metabolism of arachidonic acid with increased leukotrienes [40–42]. Angioedema without wheals or urticaria could be bradykinin mediated, which implicates angiotensin-converting enzyme inhibitors [38]. Bradykinin

Table 5 ICU drugs highly associated with infusion reactions from two post-marketing surveillance systems: Molecular Analysis of Side Effects (*MASE*) and the FDA’s Adverse Event Reporting System (*FAERS*). Statistical criteria for *MASE* was set as $PRR \geq 2.0$ and $N \geq 30$

reports and for *FAERS* as $EBGM \geq 2.0$ and $N \geq 30$ reports. Drugs are grouped by drug class and then displayed with comparison data. Using two systems improved the sensitivity of drug detection

Classification	Generic name	FAERS		MASE	
		<i>N</i>	EBGM	<i>N</i>	PRR
Analgesic	Meperidine	–	–	32	3.9
Antiarrhythmic	Adenosine	29	19.4	33	18
Antibiotic	Meropenem	–	–	34	3.1
	Ceftriaxone	20	1.3	33	3.1
	Vancomycin	109	6.8	162	4.7
Antifungal	Amphotericin B	58	7.0	66	4.9
Electrolytes	CaCl and KCl	34	26.6	8	1.7
	Ferric Na Gluc	55	37.6	–	–
	Iron dextran	68	48.1	66	48.9
	Iron sucrose	57	27.0	–	–
Immunomodulator	Ig	314	17.4	68	9
	Rho-Ig	32	13.3	–	–
Mucolytic	Acetylcysteine	16	5.0	25	2.8

Abbreviations: calcium (*Ca*), chloride (*Cl*), immunoglobulin (*Ig*), and potassium (*K*)

accumulation results in an increased vascular permeability resulting in angioedema [42].

Drugs acting on the renin–angiotensin–aldosterone system are commonly implicated, but several other classes have also been implicated including antibiotics, aspirin, NSAIDs, antifungals, calcium channel blockers, diuretics, and lidocaine [43–45]. ACE inhibitors [ACEI] have been associated with angioedema, and incidence rates for specific drugs have been reported for captopril (7.17 events per 1000 persons) [46], enalapril (6.85 events per 1000 persons) [45], lisinopril (4.09 events per 1000 persons) and ramipril (2.92 events per 1000 persons) [47]. Other studies have reported cumulative incidence of angioedema per 1000 persons for the class of ACEIs as 1.79, 1.80, and 2.95 [39, 48, 49]. Comparing drugs targeting the renin–angiotensin–aldosterone system, one cohort study found risk for angioedema three times

higher for ACEIs and renin inhibitors than for the control group (Table 6) [39].

Treatment involves stopping the implicated medication(s) and monitoring the patient for at least 6 h [42, 50]. If angioedema is secondary to mast cell activation, antihistamines, epinephrine, and corticosteroids may be effective. These will be less effective if bradykinin is implicated [50]. Cases of ACEI-induced angioedema can continue to occur for weeks despite discontinuing therapy [42]. If an ACEI is implicated, changing to angiotensin receptor blockers is associated with a 10% risk of angioedema recurrence [51]. When bradykinin-mediated angioedema is suspected and life threatening, bradykinin antagonists (e.g., icatibant) and C1 inhibitor concentrates (e.g., ecallantide, an inhibitor of kallikrein) may be effective, but their cost is prohibitive for routine use [42, 50,

Table 6 Comparative risk of angioedema (AE) associated with drugs that target the renin–angiotensin–aldosterone system (Modified from Toh et al. [39]). Incidence rates were calculated for angiotensin receptor blockers (ARBs) and compared to the entire class of angiotensin-converting enzyme inhibitors (ACEIs) using beta-blockers as a control

group as they are generally not thought to be associated with AE. Incidence reported per 1000 persons with 95% confidence interval. Hazard ratio reported with 95% confidence interval. Severe reactions were those that required ICU admission

Class/generic name	N	Incidence	HR	N (severe)	Incidence (severe)	HR (severe)
ACEIs	3301	1.79 (1.73–1.85)	3.04 (2.81–3.27)	326	0.18 (0.16–0.20)	4.91 (3.62–6.65)
ARBs	288	0.62 (0.55–0.69)	1.16 (1.00–1.34)	10	0.02 (0.01–0.04)	0.56 (0.28–1.14)
Candesartan	4	0.33 (0.09–0.83)	0.95 (0.35–2.55)			
Eprosartan	0					
Irbesartan	24	0.54 (0.35–0.81)	1.11 (0.73–1.67)			
Losartan	94	0.88 (0.71–1.08)	1.53 (1.23–1.90)	3	0.03 (0.01–0.08)	1.01 (0.31–3.34)
Olmesartan	39	0.42 (0.30–0.57)	0.88 (0.63–1.22)	1	0.01 (0.00–0.06)	0.83 (0.11–6.57)
Telmisartan	11	0.42 (0.21–0.74)	0.86 (0.47–1.56)			
Valsartan	110	0.6 (0.49–0.72)	1.08 (0.88–1.34)	6	0.03 (0.01–0.07)	1.14 (0.46–2.82)
Renin inhibitor						
Aliskiren	7	1.44 (0.58–2.96)	2.85 (1.34–6.04)	1	0.21 (0.01–1.14)	8.84 (1.13–69.41)
Beta-blockers	915	0.58 (0.54–0.61)	1	51	0.03 (0.02–0.04)	1

[52, 53]. Fresh frozen plasma contains angiotensin-converting enzyme and C1 esterase inhibitor and can reverse bradykinin-mediated angioedema [52, 53].

Drug-Induced Bronchospasm

A Swiss post-marketing surveillance system found that bronchospasm was present in 2% of reported ADRs; 55% of these cases are classified as serious [54]. Implicated drug classes include analgesics and NSAIDs in 24% (64.5% serious), antimicrobial agents in 18% (52% serious), cardiovascular drugs in 11% (50% serious), and excipients in 5.5% (41% serious) [54]. The nonsterile nebulized bronchodilator solutions contain preservatives that can induce concentration-dependent bronchospasm: sulfites, benzalkonium chloride, or ethylenediaminetetraacetic acid [55]. The critical care toxicologist should keep drug-induced bronchospasm in the differential in the ventilated patient who has a change in oxygenation.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) is associated with high mortality (47%) and is characterized by an exanthema with facial edema, enlarged lymph nodes, eosinophilia, and high-grade fever [56]. The severity depends on the organs involved (hepatitis, acute renal failure, pneumonitis, myocarditis, hemophagocytic syndrome, encephalitis, and/or multi-organ failure) [57]. DRESS can be easily missed as sometimes the eosinophilia is delayed and skin manifestations vary in severity from mild to severe [58]. Drugs associated with DRESS will usually have been prescribed for at least 2 weeks and include anticonvulsants (e.g., carbamazepine and lamotrigine), sulfonamides, and antibiotics (e.g., amoxicillin, ciprofloxacin, and minocycline) [59–61]. Discontinue all suspected drugs and treat supportively for organ failure and shock. Severe cases may require corticosteroids, intravenous immunoglobulins, and/or antiviral drugs (e.g., ganciclovir) because DRESS can closely resemble herpes

virus reactivation with eosinophilia and systemic symptoms (“VRESS”) [57, 58].

Dermatologic ADRs

Steven–Johnson Syndrome and Toxic Epidermal Necrolysis

Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe and potentially life-threatening systemic disorders characterized by skin and mucous membrane lesions, sometimes with necrosis. The extent of the surface area involved as well as the presence of necrosis helps to differentiate them. The lesions typically appear on extensor surfaces as well as the palms or the hands and soles of the feet. If there is epidermal and mucous membrane detachment and more than 30% of the body surface area is involved, TEN is implicated. Drugs implicated in SJS and/or TEN are pharmacologically diverse. Data mining implicates multiple pathways and suggests metabolizing enzymes, and transporters increase the intracellular tissue concentrations of reactive metabolites resulting in oxidative stress and the immunologic response. A disproportionate number of drugs associated with SJS were metabolized by cytochrome P450 3A4 and 2C9 and implicated transporters, multidrug resistance protein 1 (MRP-1), organic anion transporter 1 (OAT1), and PEPT2 [62]. Drug targets highly associated with SJS included cyclooxygenases 1 and 2, carbonic anhydrase 2, and sodium channel 2 alpha which overlaps with results of other studies implicating antiepileptic drugs [63]. See Table 7 for drugs identified by the US Food and Drug Administration’s (FDA) Adverse Event Reporting System (FAERS) as being highly associated with SJS. The FDA has issued post-marketing safety alerts for acetaminophen (warning), phenytoin (modified warning), and carbamazepine (boxed warning). Critical care patients often require treatment with drugs highly associated with SJS; treatment involves discontinuing the suspected

Table 7 MASE and FAERS ICU drugs highly associated with Steven–Johnson syndrome when $PRR \geq 2$ or EBGM ≥ 2 and $N > 30$

Analgesics: acetaminophen
Antiepileptics: carbamazepine, lamotrigine, phenytoin, zonisamide
Antimicrobials: amoxicillin, ampicillin/sulbactam, amphotericin B, azithromycin, cefdinir, cefepime, ceftriaxone, cefotaxime, cefuroxime, cephalexin, ciprofloxacin, clarithromycin, clindamycin, erythromycin, fluconazole, meropenem, piperacillin/tazobactam, rifampin, sulfamethoxazole, trimethoprim, vancomycin
Barbiturates: phenobarbital
Diuretics: furosemide, torsemide
Mucolytics: acetylcysteine
Proton pump inhibitors: pantoprazole
Vitamins: phytonadione

drug(s) and continuing care in facilities experienced in burn care.

Cardiovascular ADRs

Drug-Induced Arrhythmias and Conduction Disturbances

Arrhythmias and conduction disturbances range from bradycardia to tachycardia, can originate anywhere from the atria to the ventricles, can be regular or irregular, and can be mild or life threatening. Many of the toxin-induced arrhythmias are discussed throughout the medication chapters including cardiovascular digitalis glycosides, beta-receptor antagonists, cardiovascular calcium channel blocking agents, cyclic antidepressants, and lithium.

Drug-Induced QT Prolongation

This section discusses ADRs associated with QT prolongation; for additional details, refer to ► Chap. 22, “Toxicant-Induced Torsade de Pointes.” QT prolongation is highly prevalent in the ICU, and one prospective study found 24% of patients in a mixed ICU had QTc > 500 ms [64]. QT prolongation can result from hypokalemia, hypomagnesemia, hypocalcemia, genetic predisposition (ion channel polymorphisms),

tissue hypoxia, and/or the presence of one or more drugs with potassium-blocking properties. A nomogram exists and should be used to correct for heart rate [65]. For a reference list of QTc prolonging medications, the Arizona Center for Education and Research on Therapeutics (AZCERT) continually updates their list (www.crediblemeds.org). The concurrent use of drugs inhibiting cytochrome 3A4 or 2D6 should also be recognized in the setting of QT prolongation [66–69].

Torsades de pointes (TdP), a potentially fatal ventricular arrhythmia, is associated with QT prolongation but usually requires at least one other risk factor before emerging. One review of QTc prolongation and TdP found 92.2% of TdP cases had at least one additional risk factor for QTc prolongation [70]. In reviews of thorough QT studies, while drug-associated QTc prolongation is associated with and considered a surrogate for predicting TdP, other intrinsic and extrinsic factors modify this risk. Bradycardia may be a major risk factor for TdP; TdP rarely occurs when HR is above 105 beats per minute [65]. A large case-crossover study of more than 17,000 patients who were prescribed with antipsychotic drugs found a drug’s arrhythmogenic propensity was related to dose, blockade of potassium channel, and short-term usage [71]. For antipsychotic drugs, the strength of potassium blockade from lowest to highest was quetiapine, chlorpromazine and trifluoperazine, clozapine, aripiprazole, prochlorperazine, olanzapine, zotepine, risperidone, thioridazine, ziprasidone, and haloperidol [71]. Beside potassium channel blockade, tachycardia associated with muscarinic blockade may be a risk factor for cardiotoxicity [72]; however, another large retrospective review of antipsychotic ingestions admitted to a medical toxicology service demonstrated tachycardia may be protective [65]. ICU drugs associated with QTc as listed by AZCERT are highlighted in Table 8.

The treatment for QT prolongation includes discontinuing associated drugs and replacing associated electrolyte deficiencies. Resolution of prolongation will depend on the pharmacokinetics of implicated drugs. Sodium bicarbonate and

Table 8 ICU drugs associated with QTc prolongation as listed by Arizona Center for Education and Research (AZCERT)

Drug	AZCERT risk of TdP		
	Possible	Known	Conditional
Antiarrhythmics			
Amiodarone		X	
Disopyramide		X	
Dofetilide		X	
Dronedarone		X	
Flecainide		X	
Ibutilide		X	
Procainamide		X	
Quinidine		X	
Sotalol		X	
Anticonvulsant			
Felbamate	X		
Antidepressant: SARI, SSRI, tricyclic			
Amitriptyline			X
Citalopram		X	
Clomipramine	X		
Desipramine	X		
Doxepin			X
Escitalopram		X	
Fluoxetine			X
Imipramine	X		
Nortriptyline	X		
Paroxetine			X
Sertraline			X
Trimipramine	X		
Trazodone			X
Antiemetics			
Diphenhydramine			X
Dolasetron	X		
Granisetron	X		
Hydroxyzine			X
Metoclopramide			X
Ondansetron		X	
Promethazine	X		
Antihypertensive and/or diuretic			
Furosemide			X
Hydrochlorothiazide			X
Indapamide			X
Isradipine	X		
Nicardipine	X		
Torsemide			X
Antimicrobials			
Azithromycin		X	
Bedaquiline	X		
Chloroquine		X	
Ciprofloxacin		X	
Clarithromycin		X	

(continued)

Table 8 (continued)

Drug	AZCERT risk of TdP		
	Possible	Known	Conditional
Erythromycin		X	
Fluconazole		X	
Gemifloxacin	X		
Iloperidone	X		
Itraconazole			X
Ketoconazole			X
Levofloxacin		X	
Metronidazole			X
Moxifloxacin		X	
Norfloxacin	X		
Pentamidine		X	
Posaconazole			X
Telavancin	X		
Telithromycin	X		
Voriconazole			X
Antipsychotics			
Aripiprazole	X		
Clozapine	X		
Chlorpromazine		X	
Droperidol		X	
Haloperidol		X	
Iloperidone	X		
Mirtazapine	X		
Olanzapine	X		
Paliperidone	X		
Pimozide		X	
Quetiapine	X		
Risperidone	X		
Sulpiride		X	
Thioridazine		X	
Ziprasidone	X		
Drugs of abuse			
Cocaine		X	
GI prophylaxis			
Famotidine	X		
Pantoprazole			X
Ranitidine			
Immunosuppressant			
Hydroxychloroquine			X
Tacrolimus	X		
Muscle relaxant			
Solifenacin			X
Tizanidine	X		
Tolterodine	X		
Phosphodiesterase inhibitor			
Anagrelide		X	
Cilostazol		X	

(continued)

Table 8 (continued)

Drug	AZCERT risk of TdP		
	Possible	Known	Conditional
Vardenafil	X		
Sedative–analgesia–anesthetic			
Dexmedetomidine	X		
Chloral hydrate			X
Methadone		X	
Propofol		X	
Sevoflurane		X	
Others			
Perflutren lipid microspheres	X		
Ranolazine	X		
Apomorphine	X		
Oxytocin	X		
Amantadine			X

Table 9 Algorithm for the initial assessment of shock. When there are signs of tissue hypoperfusion (altered mental status, mottled/clammy skin, decreased urine output, tachycardia, and/or elevated lactate), an assessment of the

type of circulatory shock begins with estimating CO or SvO₂. Echocardiography can be used to differentiate circulatory shock

Type	CO or SvO ₂	CVP	Echocardiograph	
			Cardiac chambers	Cardiac contractility
Distributive	Normal or high		Normal	Normal
Hypovolemic	Low	Low	Small	Normal or high
Cardiogenic	Low	High	Large ventricles	Poor
Obstructive	Low	High	Small ventricle(s) depending on location of obstruction	

Modified from Vincent and Backer [76] *Abbreviations: CO* cardiac output, *CVP* central venous pressure, *SvO₂* mixed venous oxygen saturation

hyperventilation should be used in the setting of concurrent QRS prolongation; sodium bicarbonate is not known to change QTc [73, 74]; refer to ► [Chaps. 21, “Cardiac Conduction and Rate Disturbances”](#) and ► [22, “Toxicant-Induced Torsade de Pointes”](#) for further information on the management of these patients.

Drug-Induced Hypotension

This section discusses ADRs associated with hypotension; for additional details, refer to ► [Chap. 14, “The Assessment and Management of Hypotension and Shock in the Poisoned Patient”](#) Drug-induced hypotension can occur in up to 35% of ICU patients, and the most prevalent medications include cardiovascular medications, sedatives, and

analgesics [75]. Hypotension may be hypovolemic (intravascular volume loss), distributive (vasodilation or smooth muscle relaxation), cardiogenic (decreased cardiac output via decreased conduction velocity, contractility, and/or heart rate), and/or obstructive (e.g., pulmonary embolism, cardiac tamponade, or tension pneumothorax) [76]. Drug-induced hypotension often involves a combination of hypovolemic, distributive, and/or cardiogenic mechanisms. Table 9 is an overview of the initial assessment of shock, and Table 10 lists ICU drugs associated with hypotension with their known mechanism. For details of the treatment of hypotension, refer to ► [Chap. 14, “The Assessment and Management of Hypotension and Shock in the Poisoned Patient.”](#)

Table 10 ICU drugs associated with hypotension. Common ICU drug classes are listed with examples of generic drugs implicated. Mechanism of hypotension included hypovolemia, distributive (vasodilation), and/or cardiogenic (decreased CO)

Classification		Generic name	Mechanism		
			Hypovolemia	Vasodilation	Decreased CO
Beta-blockers	Selective	Atenolol, bisoprolol, esmolol, and metoprolol			B1B
	Nonselective	Carvedilol		A1B, B2B	B1B
		Labetalol		A1B, B2B	B1B
		Propranolol		B2B	B1B
		Nadolol		B2B	B1B
		Sotalol		B2B	B1B
CCB	Dihydropyridine	Amlodipine, nicardipine, and nifedipine		L-type CCB	
	Non-dihydropyridine	Diltiazem and verapamil		L-type CCB	L-type CCB
Diuretics	Thiazide	Hydrochlorothiazide	inh. Na/Cl symporter		
	Thiazide-like	Metolazone	inh. Na/Cl symporter		
	Potassium sparing	Spironolactone	inh. Na/K exchanger and competitive aldosterone ant.		
	Loop	Bumetanide and furosemide	inh. Na-K-2Cl symporter		
Imidazolines		Clonidine and dexmedetomidine		A2A	
Nitrates		Isosorbide dinitrate and nitroglycerine		NO	
Opioids		Morphine, codeine, hydromorphone, meperidine, fentanyl		Decrease sympathetic outflow, H2	Decreased sympathetic outflow
Renin-angiotensin antagonists	ACEI	Benazepril, fosinopril, lisinopril, and ramipril	Bradykinin natriuresis	Bradykinin	
	ARBs	Candesartan, irbesartan, losartan, and valsartan		ARB	
Sedative/hypnotics		Propofol		Decreased sympathetic outflow	Decreased sympathetic outflow
	Barbiturates	Phenobarbital and pentobarbital		Decreased sympathetic outflow	Decreased sympathetic outflow
	Benzodiazepines	Lorazepam and midazolam		Decreased sympathetic outflow	Decreased sympathetic outflow
Vasodilators		Hydralazine			

Abbreviations: ACEI angiotensin-converting enzyme inhibitor, *ant* antagonist, ARB angiotensin II receptor blocker, A1B alpha-1-adrenergic receptor blocker, A2A alpha-2-adrenergic receptor agonist, B1B beta-1-adrenergic receptor blocker, B2B beta-2-adrenergic receptor blocker, CCB calcium channel blocker, Cl chloride, CO cardiac output, inh inhibitor, K potassium, Na sodium, NO nitric oxide

Drug-Induced Cardiogenic Shock

Drugs associated with cardiogenic shock include β 1-adrenergic antagonists, muscarinic agonists, and L-type calcium channel antagonists. β 1-adrenergic antagonists decrease heart rate, conduction velocity, and contractility. Muscarinic receptor subtype M2 agonists decrease heart rate and cardiac conduction velocities [77, 78]. Calcium channel blockers acting at L-type channels decrease cardiac contractility, conduction velocity, and/or heart rate; dihydropyridine calcium channel blockers are associated with vasodilation, while nondihydropyridines are also associated with decreased cardiac output [79]. Sedatives and analgesics decrease sympathetic outflow that decreases norepinephrine and epinephrine release resulting in both vasodilation and decreased cardiac output.

Drug-Induced Distributive Shock

Vasodilation can result from L-type calcium channel antagonists, angiotensin receptor blockers (ARBs), α 1-adrenergic antagonists, α 2-adrenergic agonists, β 2-adrenergic antagonists, bradykinin receptor agonists, histamine H2 receptor agonists, muscarinic M3 antagonists, and/or prostaglandin E2, D2, and I2 agonists [77, 78, 80–83]. Drugs impacting NO signaling will cause vasodilation when concentrations of either NO or cyclic-guanosine monophosphate are increased. Histamine release can occur proportionately to drug dose and has been associated with drugs such as opioid analgesia and antibiotics such as vancomycin (see section on “[Infusion Reactions](#)” for additional drugs associated with histamine release). A double-blind study found meperidine was most frequently associated with histamine release, but morphine and codeine have also been implicated [84]. Opioids can also cause hypotension through vasodilation and vagal activation [85].

Opioids

Opioid receptors are located peripherally and centrally; they are involved in vascular regulation and decrease sympathetic neural regulation [86–88]. Mu-, delta-, and kappa-opioid receptors participate in the complex vasoregulatory process and when blocked centrally decrease hypotension

[89–93] and narrow the ability to autoregulate blood flow [94].

Propofol

Propofol is an anticonvulsant and amnestic with rapid onset and short duration of action [95]. Due to its faster recovery time and return of spontaneous respiration time, propofol has been favored by some over benzodiazepines for procedural sedation and for patients in the ICU [95–97]. Propofol is structurally unrelated to other sedative-hypnotics and produces its effects in a dose-dependent manner. Propofol causes hypotension and bradycardia with an average maximum mean arterial pressure (MAP) reduction of 29% after initiation, and severe hypotension develops in 26% of patients [97, 98]. Hypotension occurs through centrally mediated venodilation, sympatholysis and vagolysis [99, 100]. Pretreatment with ketamine, ephedrine, dopamine, or naloxone may decrease risk [101–105], as does the use of the lowest effective dose [106]. Intravenous fluid administration does not appear to be an effective prevention [107, 108].

Propofol is a mitochondrial toxin and can inhibit intracellular energy production resulting in propofol-related infusion syndrome (PRIS) [109]. Signs of PRIS include metabolic acidosis, lipemic serum, rhabdomyolysis, cardiac arrhythmias, acute renal failure, hepatomegaly, and cardiac arrest [109]. PRIS has been associated with longer duration of infusion (>48 h) and faster infusion rates; other risk factors include increased catecholamine and glucocorticoid serum levels, head injury, and respiratory failure [109, 110]. An increase in triglyceride concentration is the most widely accepted marker of PRIS and may be explained by the fat content of the propofol emulsion [109, 110]. PRIS occurs in less than 5% of critically ill patients receiving propofol [109, 111]. One large retrospective study found a mortality of up to 40% in persons with PRIS; a review of FDA MedWatch data found mortality increased to 30% [109, 112]. A predictive tool was created and assigns points based on the presence of six factors: age \leq 18, cardiac manifestations, metabolic acidosis, renal failure, hypotension, and rhabdomyolysis. Mortality increases with each point from 24% to 83% [112]. If PRIS is

suspected, propofol should be immediately discontinued. If the patient continues to decline, extracorporeal membrane oxygenation has successfully treated cardiac arrest [113, 114].

Treatment

The treatment for hypotension is based on the identified cause. The “VIP” approach guides first steps in therapy: ventilate (oxygenate), infuse (fluid administration), and pump (administration of vasoactive agents) [115]. Initially, resuscitation should be done with crystalloid fluids (Level of Evidence [LoE] I) followed by placement of a central venous catheter if refractory hypotension requires vasoactive agents. The end point for fluid resuscitation is when cardiac output is preload independent [76]. Measuring SvO₂ (LoEI) and serum lactate concentrations (LoE_I) can help guide therapy although additional technologies are evolving. Vasoactive agents include vasopressors and inotropes and should be initiated on a case by case basis, considering each drug’s potential adverse reaction profile. Vasopressors cause vasoconstriction from agonism at the β_2 - and α_1 -adrenergic receptors. Inotropes increase cardiac output through agonism at the β_1 -adrenergic receptor (increases heart rate, conduction velocity, and contractility). Adverse effects are related to dose, mechanism, potency, drug–drug, and/or drug–disease interactions.

Inotropic Agents

β -adrenergic agonists increase the heart rate and contractility which may increase the risk of myocardial ischemia in some circumstances [116]; however, a double-blind study found no difference in troponin elevation for treated patients with septic shock [117]. Dobutamine has predominantly beta-adrenergic properties and increases cardiac output and is a consideration when hypotension is mediated by cardiac pump dysfunction. Dobutamine has not demonstrated improved perfusion parameters in patients with septic shock without cardiac failure [118].

Vasopressors

By definition, vasopressors cause vasoconstriction, which can impair tissue perfusion.

Epinephrine’s range of effects is strongly dose dependent. At low doses (usual dosing range 0.01–0.1 microgram/(kg*min)), epinephrine predominantly targets β -adrenergic receptors; however, as the dose increases, more significant α -adrenergic effects appear [116]. Epinephrine has been associated with arrhythmias, decreased splanchnic blood flow, and increased blood lactate concentrations [119, 120]. Dopamine is an immediate precursor to norepinephrine in the synthetic catecholamine pathway [116]. Dopamine is an agonist at dopamine and β -adrenergic receptors at lower doses ($<10 \mu\text{g}/(\text{kg}\cdot\text{min})$), but with higher doses ($10\text{--}20 \mu\text{g}/(\text{kg}\cdot\text{min})$), α -adrenergic effects predominate [76]. The predominant dopaminergic effects observed with low doses of dopamine ($<3 \mu\text{g}/\text{kg}/\text{min}$) may preferentially dilate the hepatosplanchnic and renal circulations, but controlled trials have not shown clinically significant protection from renal dysfunction [121]. “Renally dosed” dopamine theoretically could worsen vasodilation resulting in hypotension, and many toxicology patients have minimal tolerance for worsened blood pressure. Dopamine may increase the incidence of arrhythmia when compared to norepinephrine [122]. Beta doses of dopamine ($<10 \mu\text{g}/(\text{kg}\cdot\text{min})$) may cause further vasodilation and worsen hypotension. Therefore, for critically ill patients, dopamine therapy should be initiated at alpha receptor active doses ($\geq 10 \mu\text{g}/\text{kg}/\text{min}$).

Norepinephrine should be considered as the first-line vasopressor. Several studies demonstrate no advantage of dopamine over norepinephrine, and dopamine is associated with increased rates of arrhythmias and 28-day mortality for patients with cardiogenic and/or septic shock [122, 123]. For tricyclic antidepressant poisoned patients with hypotension refractory to intravenous fluid and serum alkalinization, norepinephrine appeared superior to dopamine as a first-line vasopressor agent [124] (LoE II-3). Norepinephrine may be associated with greater risk for peripheral ischemia and necrosis; however, these effects can occur with other vasopressors including vasopressin, dopamine, and epinephrine; preexisting vascular disease, sepsis, and DIC may be risk factors [116, 125–131].

Hematologic ADRs

Drug-Induced Thrombocytopenia

Thrombocytopenia is a commonly encountered abnormality in the critically ill, occurring in up to 44% of patients. Between 10% and 25% of these cases are thought to be drug induced. Potential mechanisms for this are platelet consumption or destruction, impaired platelet production, and hemodilution [132]. Multifactorial etiology is usually suspected when drug-induced thrombocytopenia (DITP) has occurred; however, single agents are not excluded. Platelets become targeted for destruction when a drug causes an antibody response. Depending on the molecular weight of the drug, this could be hapten dependent (e.g., penicillin) via covalent bonds to platelet glycoproteins or drug dependent (e.g., sulfonamide antibiotics), forming a complex or conformational change [133]. Sometimes autoantibodies are produced that can persist long after drug exposure and result in chronic autoimmune destruction [133].

DITP typically occurs 1–2 weeks after beginning a new drug or suddenly after a single dose of a drug which has previously been taken [134, 135]. Exceptions include first doses of antithrombotic agents such as tirofiban [136–139]. Table 11 contains a list of ICU drugs associated with thrombocytopenia. Antibiotics are associated with thrombocytopenia and, because of their prevalent use in ICU patients, are commonly implicated. Case-control studies have associated quinolones and trimethoprim/sulfamethoxazole with thrombocytopenia [140, 141]. Sample size, exposure rates, and the potential effect of drug combinations likely limited their findings to only these drugs as there are over a thousand case reports of DITP. A database can be found online at <http://www.ouhsc.edu/platelets/ditp.html>. Other drugs to consider for ICU patients include antifungals, antivirals, anticonvulsants, and glycoprotein IIb/IIIa inhibitors and anticoagulants [141].

Heparin or low-molecular-weight heparin is frequently used in immobile ICU patients. These drugs require careful consideration when evaluating a patient for thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) type 2 occurs in 0.5–5% of patients receiving heparin products [142]. Typically this syndrome is characterized by a 50% or greater thrombocytopenia from baseline, occurring 5–15 days after initial heparin therapy. It can occur sooner if there was a prior exposure to heparin. Physiologically, IgG antibodies bind heparin and platelet factor 4 (PF4), forming complexes. These complexes bind platelets and result in thrombocytopenia. If thrombin is activated, thrombosis can occur. If HIT is considered, an HIT score should be calculated to guide therapy. If the HIT score is low (0–3 points), heparin therapy should be continued. For moderate or high scores, further testing is recommended, and the patient started on alternative anticoagulation until the diagnosis can be conclusively excluded. The absence of PF4 IgG antibodies has a high negative predictive value and rules out HIT; specificity is poor so positive tests require additional analysis [142–145]. Serotonin release assay has high specificity (95–100%) and positive predictive value for HIT; however, the availability is limited. Several days are often required for results. Once HIT has been confirmed, duration of therapy should be for 4 weeks or until baseline platelet counts are restored. In the presence of thrombosis, treatment should be continued for 4 months.

When other drugs are suspected, they should be discontinued and platelets monitored for recovery. Recovery time will depend on the pharmacokinetics of the offending drug and the implicated mechanism. Usually, recovery begins 1–2 days after the offending drug has been discontinued and is complete within 1 week [134]. Drug-dependent antibodies can persist for years; patients should be counseled to avoid the implicated drug. See ► Chap. 30, “Toxicant-Induced Hematologic Syndromes” for more detail.

Drug-Induced Methemoglobinemia

Methemoglobinemia is discussed in ► Chap. 30, “Toxicant-Induced Hematologic Syndromes.” Methemoglobinemia can be caused by dapsone

Table 11 ICU drug-induced thrombocytopenia (DITP). Drugs are grouped by drug class and mechanism with number of reports and probability score and if an antibody has been detected. University of Oklahoma Health Sciences Center's DITP database was referenced on May

6, 2015, for number of cases from individual and group patient reports. Drugs were added from recently published literature. Additional drugs, in parentheses, were added from recently published literature

Classification	Generic name	N ^a	Probability score ^b	Ab
Antibiotics				
Beta-lactamases	Amoxicillin	1	5	+
	Ampicillin	5	2	+
	Penicillin	6	1	
	Piperacillin/tazobactam	14	1	+
Carbapenems	Imipenem	4	2	
	Meropenem	11	2	
Cephalosporins	Cefazolin	1	5	+
	(Cefepime)	(1)	(2)	+
	Ceftriaxone	6	2	+
	Cefuroxime	1	3	
Dihydrofolate reductase inhibitor/sulfonamide	Trimethoprim/sulfamethoxazole	65	1	+/+
Fluoroquinolones	Ciprofloxacin	6	1	+
	Levofloxacin	2	2	+
	Moxifloxacin	2	2	
Glycopeptide	Vancomycin	27	1	+
Lincosamide	(Clindamycin)	(1)	(3)	+
Macrolide	Clarithromycin	3	2	
Oxazolidinone	Linezolid	221	5	
Antifungals	Amphotericin	3	1	
	Fluconazole	5	2	
	Itraconazole	1	2	
Antivirals	Acyclovir	2	2	
	Ganciclovir	23	4	
Anticonvulsants	Levetiracetam	35	2	
	Valproic acid	231	5	+
Glycoprotein IIb/IIIa inhibitor	Tirofiban	125	1	+
Anticoagulant	(Heparin)		(1)	+

^aNumber of total patients with DITP based on individual and group reports when specified^bHighest probability score from case reports: 1-thrombocytopenia definitely caused by drug, 2-probably, 3-possibly, 4-unlikely, 5-excluded (reasons included insufficient data and/or agents that cause thrombocytopenia due to marrow suppression)

or local anesthetics placed into the pharynx before nasogastric or orogastric tube placement or other procedures [146–157]. Local anesthetics associated with methemoglobinemia include benzocaine, cocaine, lidocaine, and prilocaine [146, 148, 149, 152, 154–157]. Benzocaine treatment may produce more methemoglobin than lidocaine [158]. Methylene blue is the antidote, but should be dosed carefully as logarithmic dosing errors or very high doses could worsen methemoglobinemia [159, 160].

Pulmonary ADRs

Drug-Induced Respiratory Disease

This section discusses ADRs associated with respiratory disease. For additional reference, see ► Chaps. 100, “Irritant and Toxic Pulmonary Injuries” and ► 16, “Treatment of Acute Respiratory Distress Syndrome in the Poisoned Patient.” Respiration requires the integration of multiple systems. Respiratory failure occurs when any part of this process becomes dysfunctional and is

unable to maintain normal pH and/or adequate tissue oxygenation. Types of drug-induced respiratory disease can be subdivided based on location: airway (small and/or large), parenchymal/interstitial/pleural lung disease, pulmonary vasculopathy (e.g., noncardiogenic pulmonary edema or pulmonary arterial hypertension), neuromuscular respiratory disease (e.g., decreased respiratory drive), and/or circulation (e.g., methemoglobinemia) [161–164]. Neurologic drug-induced respiratory disease is common in the ICU due to the number of sedatives and analgesics administered. When evaluating for drug-induced respiratory disease, initial attention to oxygenation, respiratory rate, and end tidal CO₂ is helpful to determine if respiratory depression is present. Hypercarbia is more sensitive than hypoxia for early respiratory depression, and occasionally respiratory depression occurs in the absence of moderate to severe neurologic abnormality; naloxone and/or other antidote(s) administered can confirm and treat. If cyanosis and low pulse oximetry (90%) are present, arterial co-oximetry should be performed to evaluate for methemoglobinemia.

After excluding hemoglobinopathies and drug-induced respiratory suppression, further evaluation may include white blood cell differential, bronchial-alveolar lavage, chest radiograph, and/or high-resolution computed tomography (HRCT). Eosinophilia on peripheral blood smear or bronchial-alveolar lavage may suggest a drug-induced eosinophilic pneumonia. HRCT can further characterize the pathology [162–164]. Some diagnoses require an echocardiography, right-heart catheterization, and/or biopsy for diagnosis or to exclude other diagnoses. Echocardiography can exclude left-sided congestive heart and evaluate for cardiac comorbidities. A list of drugs associated with respiratory disease is maintained online by the Department of Pulmonary and Intensive Care at a University Hospital in Dijon, France (www.pneumotox.com). Table 12 contains a list of ICU drugs associated with more than 50 reports of respiratory disease.

Drug-Induced Airway Dysfunction

Refer to allergic/hypersensitivity ADRs section within this chapter where drug-induced bronchospasm and angioedema are discussed in detail.

Drug-Induced Parenchymal and Interstitial Lung Disease (ILD)

Parenchymal lung disease includes many subtypes, but commonly associated ICU drugs include amiodarone, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and drugs of abuse (before ICU admission). Frequently encountered conditions include acute ILD, subacute ILD, eosinophilic pneumonia, diffuse alveolar damage, and ILD with a granulomatous component. Patients who previously received chemotherapy can have ADRs based on their previous outpatient treatment regimens. Many chemotherapeutic drugs are associated with ILD. For example, ILD is emerging as a class effect of tyrosine kinase inhibitors (TKIs), inhibiting oncologic drugs that inhibit the vascular endothelial growth factor (VEGF) receptor. Diffuse alveolar damage (DAD) may be the most common manifestation, although other etiologies occur [165].

Amiodarone-induced respiratory disease has a wide spectrum of manifestations that can develop acutely or after many years [166–168]. The elderly may have higher risk. Peak onset occurs after 6–12 months of therapy [169]. Higher doses may be associated with increased risk although toxicity can develop with any dose [167, 170]. Typical presentation includes malaise, cough, fever, and pleuritic chest pain, with imaging demonstrating patchy opacities and/or acute respiratory distress syndrome (ARDS). Sometimes only pulmonary fibrosis is present, but pathological manifestations can include eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia, or diffuse alveolar damage (DAD) [166]. DAD is a severe respiratory failure involving alveolar fibrin, hyaline membranes, reactive epithelial cells, and diffuse ground-glass opacities [166, 171]. If amiodarone-associated respiratory disease is suspected, the drug should be discontinued and alternative medications titrated to control heart rate.

Table 12 ICU drug-induced respiratory disease. Drugs from www.pneumotox.com were included if ≥ 50 cases reported for a drug–disease pattern. Pneumotox was referenced on May 17, 2015

Generic drug	Airway disease	Interstitial/parenchymal disease	Pleural disease	Pulmonary vasculopathy
Drugs of abuse (IV/inhaled)		Granulomatous ILD, mass(s), pneumoconiosis	PTX	PAH
Amiodarone		Acute/subacute ILD, PF, lung nodule(s), DAD	Fibrothorax, pleuritic chest pain	ARDS
Beta-2 agonists (parenteral)				NCPE
Beta-blockers	Bronchospasm			NCPE
Crack cocaine	Bronchospasm			
Dopamine agonists			Fibrothorax	
Ethanol				ARDS
Excipients (vehicle)				PAH
Hemotherapy (blood or platelet transfusion)				NCPE, ARDS, TRALI, TACO
Heroin (inhaled, insufflated, snorted)	Bronchospasm			
Heroin (injected)	Bronchospasm		PTX	NCPE, flash pulmonary edema
Hydrochlorothiazide				NCPE
Latex	Bronchospasm			
Minocycline		EP		
Nitrofurantoin		Acute pneumonitis/ILD, subacute pneumonitis/ILD, PF	Acute pleuritis	
NSAIDS	Bronchospasm	EP		
Salicylate	Bronchospasm			NCPE

Key: acute respiratory distress syndrome (*ARDS*), diffuse alveolar damage (*DAD*), dopamine (*DA*), eosinophilic pneumonia (*EP*), inhaled (*INH*), interstitial lung disease or pneumonitis (*ILD*), intravenous (*IV*), noncardiogenic pulmonary edema (*NCPE*), parenchymal lung disease (*PLD*), pneumothorax (*PTX*), pulmonary arterial hypertension (*PAH*), pulmonary fibrosis (*PF*), transfusion-associated circulatory overload (*TACO*), transfusion-related lung injury (*TRALI*)

Nitrofurantoin is associated with acute or subacute pneumonitis (ILD) characterized generally with bilateral and symmetric pulmonary opacities. Pulmonary fibrosis, eosinophilic pneumonia, or pleuropathy (discussed later) may be present with restrictive lung dysfunction and hypoxemia, which usually resolve after the drug is discontinued [172–174].

Eosinophilic pneumonias (EP) have been associated with a significant number of drugs; antibiotics and NSAIDS are the most commonly reported [175–184]. Historically, there have been epidemics of EP associated with exposure to a toxic-oil spill in 1981 and L-tryptophan ingestion in 1989. Minocycline was the antibiotic most

commonly reported by www.pneumotox.com (between 50 and 100 cases reported); daptomycin, nitrofurantoin, and sulfasalazine followed with 10–50 reported cases. The FDA has issued a warning regarding daptomycin and risk for eosinophilic pneumonia. Signs and symptoms of EP include fever, fatigue, dyspnea, wheezes with pulmonary infiltrates, and eosinophilia in blood, bronchial–alveolar lavage, and/or tissue [182]. Symptoms usually resolve after the implicated drug is discontinued; however, sometimes steroids are required.

ILD with a granulomatous component has been associated with drugs of abuse and mimics pulmonary and/or systemic sarcoidosis [185, 186].

The culprit could be a cutting agent such as levamisole or talc since the primary drug of abuse is more likely to cause other drug-induced respiratory disease (see Table 11). Heroin has been associated with bronchospasm, noncardiogenic pulmonary edema (NCPE), flash (fulminate) pulmonary edema, and/or pneumothorax [187, 188]. Crack cocaine has been associated with bronchospasm [189]. Other cutting agents such as clenbuterol, a beta-agonist, have been associated with NCPE [190], and topical anesthetics have been associated with methemoglobinemia [191]. Characteristically, ILD with a granulomatous component appears radiographically as sterile non-necrotizing granulomas and/or with a miliary appearance; lymphadenopathy may also be present [185, 186]. Patients may have granulomatous skin lesions.

Drug-Induced Pulmonary Edema and Vasculopathy

The lungs have an extensive vascular surface used for oxygenation and gas exchange, but this increases the risk for significant morbidity and mortality when endothelial and/or vascular injury occurs [192]. ARDS and noncardiogenic pulmonary edema (NCPE) are common clinical manifestations of drug-induced respiratory disease. Their clinical and radiographic features are difficult to distinguish from other causes of pulmonary edema; therefore, timing is an important consideration to determine etiology [193]. Patients may present with dyspnea, chest pain, tachypnea, and hypoxemia [193]. Chest imaging will demonstrate bilateral opacities not fully explained by effusions, atelectasis or nodules, and the absence of cardiomegaly and pulmonary vascular redistribution. Echocardiography or wedge pressure may be used to exclude cardiogenic causes, a requirement for the diagnosis of NCPE.

ARDS is defined and graded based on gas exchange abnormalities. The diagnosis is used interchangeably for mixed pathology but morphologically best characterized by DAD. ARDS is an acute, diffuse, inflammatory lung injury that increases pulmonary vascular permeability, hypoxemia, shunting, and pulmonary dead space. Using the Berlin definition, ARDS is defined

based on the degree of hypoxemia as mild ($\text{PaO}_2/\text{FIO}_2 \leq 300$ mmHg or $\text{P/F} \leq 300$), moderate ($100 < \text{P/F} \leq 200$), and severe ($\text{P/F} \leq 100$) [194]. Mortality increased for each stage, 27%, 32%, and 45%, respectively [194]. Duration of mechanical ventilation in survivors increased for each stage: 5, 7, and 9 days, respectively [194]. When an ADR is suspected, the drug should be immediately discontinued.

NCPE, or permeability edema, is associated with opioids [187, 188, 195–197]; the mechanism may involve histamine release with capillary leak [198]. These effects usually occur within hours of opioid use and may persist. Decreasing the doses of opioids and/or changing to less histaminergic opioids may be helpful. When pulmonary edema develops within minutes of drug administration, it is called flash (fulminate) pulmonary edema.

Transfusion-related acute lung injury (TRALI) is a type of drug-induced pulmonary edema associated with hemotherapy and should be differentiated from transfusion-associated circulatory overload (TACO). TRALI can occur with transfusion of blood, platelets, plasma, IVIG, or any blood product. TRALI has an incidence rate of 22.5 per 100,000 hospital stays; risk factors include continued platelet and plasma transfusions, amount transfused, female gender, white ethnicity, and 6-month histories of pulmonary fibrosis and/or tobacco use [199, 200]. Decreasing female donation of blood products significantly reduced the incidence but suggests there is both an immune and nonimmune mechanism [199, 201]. Symptoms of TRALI develop within 8 h of infusion and can be difficult to differentiate from TACO, a type of overload pulmonary edema. TACO can occur when the rate or amount of fluid infused is more than the circulatory system can accommodate. Assessing fluid balance and measurement of brain natriuretic peptide may suggest an etiology as TRALI and/or TACO [202].

Pulmonary Arterial Hypertension

Drugs increasing serotonin and/or norepinephrine levels may cause pulmonary arterial hypertension (PAH) because of the vasoconstrictive and growth-modulating effects on smooth muscle

cells, resulting in an increased pulmonary vascular resistance, right cardiac failure, and death. Another proposed mechanism includes endothelial dysfunction [203]. PAH associated with ICU drugs could occur through excipients (vehicle), as reported by Pneumotox. Other considerations include drugs of abuse such as amphetamines and cocaine, anorexic or appetite suppressants, and other over-the-counter drugs such as nasal decongestants [203–205]. Fenfluramine, an appetite suppressant, was withdrawn from the market and had been associated with PAH. Phenylpropanolamine, a nasal decongestant, was withdrawn because of an increased risk of hemorrhagic stroke and may have been a risk factor for PAH.

Drug-Induced Neuromuscular Respiratory Disease

Respiratory pump function is dependent on central respiratory drive, peripheral nerves, neuromuscular junctions, and respiratory muscles. Drug-induced neuromuscular respiratory disease is discussed in the neurologic ADR section.

Gastrointestinal ADRs

Drug-Induced Constipation/Ileus

Constipation is the irregular and/or infrequent evacuation of the bowels. Multiple causes have been identified including poor nutritional intake (low dietary fiber); emotional disturbances; systemic, structural, and infectious conditions; and drugs. Drug-induced constipation has been associated with drugs affecting muscarinic, opioid, and gamma-aminobutyric-acid (GABA) receptors. Opioids are the drug class most frequently associated with constipation, which occurs in up to 71% of patients with chronic non-cancer pain whom are prescribed with opioids [206].

Opioid-induced constipation has significant economic ramifications as it is associated with longer inpatient stays (3–5 days vs. 1–2 days) and higher costs (US\$16923–US\$23631 vs. US\$11117–US\$12652) [206]. For ICU patients, the costs could be even higher, and patients should be prescribed with bowel regimens to promote daily motility. When

conservative measures have failed, opioid antagonists may be considered (LoE_I). Cost is preclusive to widespread implementation. Naloxone, naltrexone, and nalmefene are opioid antagonists with low systemic bioavailability because of first-pass metabolism [61]. If given in sufficient doses, naloxone crosses the blood–brain barrier to reverse opioid analgesia; naloxone has a narrow therapeutic window when administered to treat opioid-induced constipation. Quaternary analogues of the opioid antagonists such as methylnaltrexone and alvimopan have greater polarity and lower lipid solubility; these analogues poorly cross the blood barrier. Methylnaltrexone is administered parenterally (0.15–0.3 mg/kg every other day) and alvimopan orally (0.5 or 1 mg once daily).

Delayed Absorption

Critically ill patients may already be at increased risk for delayed absorption of enteral medications. Some ICU drugs delay gastric emptying or slow motility and can interfere with the absorption of other drugs. Common drugs include anticholinergic, opioid agonists, anesthetics, and other sedatives. In the setting of overdose, absorption can continue longer than predicted by pharmacokinetics, especially for enteric coated or extended release medications, anticholinergics, and/or opioids [207–219].

Diarrhea

Many of the withdrawal states can be associated with diarrhea as can many antibiotics. Twenty-nine percent of 743 prospectively treated patients prescribed with inpatient antibiotics developed diarrhea during hospitalization, and four cases were confirmed of *Clostridium difficile* infection (CDI) [220]. Diarrhea started between 1 and 16 days after initiation with median onset on day 4. Potentially any antibiotic is associated with diarrhea, but cephalosporins, clindamycin, penicillins, and quinolones may carry a higher risk, especially for CDI [221]. Antibiotic-associated diarrhea was associated with increased age, proton pump inhibitor use, and being critically ill. The prevalence of CDI for ICU patients prescribed with antibiotics may be higher than other

Table 13 Clinical phenotypes for DILI associated with ICU drugs. Clinical phenotypes associated with ICU drugs with latency, initial bilirubin, and R value. R is calculated:

(ALT/ULN)/(ALP/ULN) (Source: <http://livertox.nlm.nih.gov> (Accessed 5/18/2015))

Clinical phenotype	Latency	Bilirubin (mg/dL)	R	Drugs
Acute hepatic necrosis	<2 weeks	<10	>5	Acetaminophen, amiodarone, aspirin, cocaine, methylenedioxymethamphetamine (MDMA, ecstasy), niacin
Acute hepatitis	2–24 weeks	>2.5	>5	Disulfiram, isoniazid (INH), nitrofurantoin, sulfonamides
Cholestatic hepatitis	2–12 weeks	>2.5	<2	Ceftriaxone, clavulanate, fluoroquinolones (ciprofloxacin, levofloxacin), macrolides, penicillins, rifampin, sulfonamides, sulfonylureas
Mixed hepatitis	4–24 weeks	>2.5	2–5	Aromatic antipsychotics (e.g., carbamazepine, phenytoin), lamotrigine, NSAIDs, sulfonamides

Abbreviations: alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin (BILI), upper limit of normal (ULN)

hospitalized patients and has been reported as 25% in patients with antibiotic-associated diarrhea [222]. CDI-associated mortality rate may be as high as 9% [223], and for ICU patients, the unadjusted rate may be as high as 23–37% [222, 224, 225]; however, other literature suggests early recognition and treatment of ICU-acquired CDI decreases the risk for mortality [226].

The development of antibiotic-induced diarrhea results in an additional hour of nursing care per day which decreases nurse time spent with other critically ill patients [220]. Patients who develop CDI have a longer length of stay of 2.2 ICU days, 4.5 hospital days [224]. Probiotics have been studied for the prevention of antibiotic-associated diarrhea and/or *Clostridium difficile* diarrhea; in older hospitalized patients, they may not be as helpful when compared to other age groups [227–229]. Decreasing hospital use of quinolones may decrease the overall incidence of *Clostridium difficile* [230–233]. Antimotility agents should be avoided until CDI is ruled out with a rapid screening ELISA test.

Drug-Induced Hepatotoxicity

This section briefly discusses ADRs associated with hepatotoxicity; for additional information refer to ► Chap. 17, “Toxicant-Induced Hepatic Injury.” Drug-induced liver injury (DILI) is the major reason for drug removal or restriction by regulatory agencies and is estimated to occur in 1 in 1,000,000 patient-years or 35 cases in 100,000 using EMR data [5, 234]. Fewer than

10% of DILI cases progress to drug-induced acute liver failure and up to 80% of these will die or require transplantation [235, 236].

DILI mimics many forms of liver disease and is usually a diagnosis of exclusion. Complicating the diagnosis is the latency period or the time from first dose of a new drug to the onset of hepatotoxicity. For hepatotoxic ADRs, the latency period is usually days to weeks after starting a new medication, but there are exceptions. The clinical signs and symptoms are usually nonspecific but temporally can be used to guide the differential. A good reference to published case reports is Livertox (<http://livertox.nlm.nih.gov>), which is continuously updated (Table 13) [234, 237]. Patterns of hepatic enzyme elevation can suggest hepatocellular, cholestatic, or mixed injury patterns (Table 14). These patterns of elevation also guide workup for alternative explanations (e.g., hepatocellular or mixed DILI should be tested for acute viral hepatitis, while a cholestatic pattern should be evaluated for biliary tract pathology).

The most common phenotype is serum enzyme elevation without jaundice or other symptoms. The most characteristic phenotype suggesting DILI is cholestatic and/or mixed hepatitis. Between 30% and 50% of DILI cases are described as acute hepatitis and resemble acute viral hepatitis. The most concerning phenotype is acute hepatic necrosis, characterized by many-fold elevations of ALT within days of drug exposure; however, the most likely phenotype to result in DIALF is acute hepatitis.

Table 14 Laboratory criteria for diagnosing and classifying drug-induced liver injury (DILI). DILI can be diagnosed when either ALT or ALP is elevated or when both

BILI and ALT are elevated. R is calculated (ALT/ULN)/(ALP/ULN) and patterned based on earliest identified liver chemistry available that qualifies as DILI

DILI diagnosis	ALT $\geq 5 \times$ ULN	ALP $\geq 2 \times$ ULN	Bilirubin $\geq 2 \times$ ULN and ALT $\geq 3 \times$ ULN
DILI classification	R		
Hepatocellular	≥ 5		
Mixed	$2 < R < 5$		
Cholestatic	≤ 2		

Abbreviations: alanine aminotransferase (ALT), alkaline phosphatase (ALP), upper limit of normal (ULN)

Drug properties and certain host factors increase risk for DILI. High lipophilicity ($\text{LogP} \geq 3$) and high daily dose (≥ 100 mg) predict DILI [238]. Patients with fatal outcomes are more likely to have chronic liver disease and satisfy Hy’s Law (ALT or AST $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN with no initial findings of elevated serum ALP or other reason for abnormal liver biochemistries) [239]. Mechanisms for DILI include the formation of toxic metabolites (e.g., *N*-acetyl-*p*-benzoquinone imine from metabolism of acetaminophen), mitochondrial dysfunction [240], modification of allergic mediators [242] and altered bile acid homeostasis [241]. Minocycline can induce an allergic or autoimmune injury with antinuclear antibodies (ANA) and perinuclear antineutrophil cytoplasmic antibodies, pANCA. Nitrofurantoin autoimmune hepatitis is associated with antinuclear and smooth muscle antibodies [243, 244]. DILI associated with amoxicillin–clavulanate has been associated with the HLA alleles A*02:01, DRB1*15:01-DQB1*06:02 [245]. Some drugs may cause DILI through hypotension and/or increased metabolic demand. Drugs that can cause hypoxia or hypotension, or increase metabolic demands, may worsen acute liver failure because each of these conditions by itself can cause ALF.

Causality can be difficult to determine, but the suspected drug(s) should be immediately discontinued and the liver biochemistries monitored; the liver has an amazing capacity to recover from injury [246]. Rechallenge is dangerous and should be avoided. Currently available biomarkers [247–252] (Table 15) are not specific enough and/or not widely available; a liver biopsy should be considered if signs of liver function

continue to decline or if peak ALT level has not fallen by $> 50\%$ at 30–60 or 180 days, respectively, for hepatocellular and cholestatic DILI [253]. Exceptions, or drugs to consider restarting, may include an immunomodulatory drug if no alternatives are available.

Drug-Induced Pancreatitis

Acute pancreatitis is a sudden inflammation of the pancreas and can be fatal; however, drug-induced acute pancreatitis is usually mild or moderate in intensity. The most commonly identified cause of acute pancreatitis is gallstone followed by ethanol, drugs, and cannabis [254]. Drug-induced acute pancreatitis (DIAP) occurs for less than 5% of patients with acute pancreatitis, and drugs with stronger causality are listed in Table 16 [255, 256]. Mechanisms for DIAP include pancreatic duct constriction, cytotoxic and metabolic effects, accumulation of a toxic metabolite, or intermediary and/or hypersensitivity reactions [257, 258].

There are many drugs possibly associated with pancreatitis but causality is not definitively established. There have been numerous reports of adverse effects with drugs such as the antipsychotics clozapine, olanzapine, and risperidone, but when a cause–effect relationship is scrutinized, the data is questionable [10, 259]. For glucagon-like peptide-1 drugs such as exenatide, pancreatitis was seen in the clinical trials but other studies have demonstrated mixed results [260]. Class labeling warnings have been added to the FDA labels. ICU drugs associated with acute pancreatitis with stronger causality (positive rechallenge and other causes excluded) include ace inhibitors (ACEI; enalapril), antiepileptics (divalproate), antimicrobials (dapstone,

Table 15 Liver biochemical and function tests. Most of these biomarkers are located intracellularly and released after hepatocyte injury

Biomarker	Clinical significance
Hepatocellular injury	
ALT	Remains elevated longer than AST (longer half-life)
AST	Less specific than ALT
APAP-CYS	Early and specific marker for APAP hepatotoxicity; remains elevated for days
GSTA	Centrilobular injury; more rapid assessment because of shorter half-life than ALT/AST
HMGB1	Associated with immune activation followed by apoptotic and necrotic hepatocytes; earlier marker of hepatotoxicity than ALT; prognostic marker
K18	Necrotic hepatocytes; prognostic marker
K18, cleaved	Apoptotic hepatocytes; prognostic marker
miR-122	Earlier marker of hepatotoxicity than ALT; can be used to predict injury
SDH	Earlier marker of hepatotoxicity than ALT
Biliary injury	
ALP	Nonspecific and can be elevated with bile duct obstruction, cholestasis, and hepatocellular injury as well as released from bone and placental tissue
GGT	More sensitive and specific marker of biliary injury than ALP
Mitochondrial injury	
GLDH	Earlier marker of hepatotoxicity than ALT, released from mitochondria
Hepatic biosynthetic capacity	
Albumin	Produced by the liver and decreased in chronic liver disease; decreased in nephrotic syndrome
Ammonia	Released by intestines and metabolized by liver
PT	Decreased production of hepatic coagulation factors increases PT
Hepatic regeneration	
AFP	May have value as prognostic marker
LECT2	May have value as prognostic marker; inversely proportional to ALT

Abbreviations: acetaminophen (*APAP*), acetaminophen–cysteine adducts (*APAP-CYS*), alanine aminotransferase (*ALT*), alkaline phosphatase (*ALP*), alpha-fetoprotein (*AFP*), alpha-glutathione-S-transferase (*GSTA*), aspartate aminotransferase (*AST*), gamma glutamyl-transpeptidase (*GGT*), glutamate dehydrogenase (*GLDH*), high-mobility group box-1 (*HMGB1*), keratin 18 full length (*K18*), leukocyte cell-derived chemotaxin-2 (*LECT2*), microRNA-122 (*MiR-122*), prothrombin time (protime, *PT*), sorbitol dehydrogenase (*SDH*)

metronidazole, tetracycline), cannabis, diuretics (furosemide), and statins (pravastatin, simvastatin) [256]. Drugs with positive rechallenge but without other causes excluded include amiodarone, antimicrobials (sulfamethoxazole/tazobactam), ARBs (losartan), and proton pump inhibitors (omeprazole) [256]. ICU drugs with more than four case reports of acute pancreatitis include acetaminophen, erythromycin, and propofol [256].

The proposed mechanism for pancreatitis caused by statins is via accumulation of a toxic metabolite or drug interactions through cytochrome P450 3A4 [261]. Valproic acid may cause pancreatitis by a direct toxic effect of free

radicals and depletion of superoxide dismutase, catalase, and glutathione peroxidase [261]. When drug-induced pancreatitis is suspected, the implicated agent should be discontinued [255].

Renal ADRs

Drug-Induced Acute Renal Failure

This section discusses ADRs associated with acute renal failure. For additional details, refer to ► [Chap. 18, “Toxicant-Induced Renal Injury.”](#) Drugs are a common cause of renal insufficiency because a major route for drug excretion occurs

Table 16 Drug-induced pancreatitis. Drugs are grouped by drug class and listed when stronger causality has been documented

Class	Drug(s)
ACEI/ARBs	Enalapril and losartan
Antiarrhythmics	Amiodarone
Antiepileptics	Divalproate
Antimicrobials	Dapsone, metronidazole, sulfamethoxazole/tazobactam, and tetracycline
Cannabis	
Diuretics	Furosemide
Ethanol	
Glucagon-like peptide-1 (GLP1) receptor agonists	Exenatide, liraglutide, albiglutide, dulaglutide
Proton pump inhibitors	Omeprazole
Statins	Pravastatin and simvastatin

renally. During this process, drugs concentrate in nephric tissues which increase the potential for local tissue toxicity [262]. The high renal rate of blood flow increases nephric tissue exposure to drugs when compared to tissue in organs with lower rates of blood flow.

Drug-induced nephrotoxicity should be considered when the serum concentration of creatinine rises temporally in relation to drug administration. Good ICU care noting a diminishing urine output should avoid this complication. Drug toxicity in the kidney can manifest through the same clinical syndromes associated with other kidney diseases (refer to Table 17 for common clinical syndromes matched with associated drugs). Antibiotics are the most common cause of drug-induced renal failure; aminoglycosides are the most common cause of acute tubular necrosis (ATN), with an incidence of at least 10% of all cases of acute renal failure [263]. Penicillins and sulfonamides are more commonly associated with acute interstitial nephritis (AIN). Some drugs such as cephalosporins, cocaine, and NSAIDs can be associated with multiple renal syndromes [264–267]. When considering drug-induced nephrotoxicity, consider the dose, timing, duration of exposure, concurrent use of nephrotoxic drugs, and individual patient

Table 17 Nephrotoxicity associated with ICU drugs

Clinical syndrome	Drug
Acute renal failure	
Prerenal/hemodynamic	Contrast, amphotericin B, ACEI, NSAIDs
Intrarenal	
ATN	Acetaminophen, aminoglycosides, amphotericin B, cephalosporins, cocaine
AIN	Penicillins, cephalosporins, cocaine, sulfonamides, NSAIDs
Postrenal/obstructive	Acyclovir, analgesic abuse
Nephrotic syndrome	NSAIDs
Chronic renal failure	Lithium, analgesic abuse

Abbreviations: acute tubular necrosis (ATN), acute interstitial nephritis (AIN)

risk factors (age, chronic kidney disease, sepsis, etc.) [262, 263, 268–271].

Prerenal Nephrotoxicity

Prerenal azotemia is a hemodynamically mediated renal insufficiency associated with low urine sodium excretion and is usually reversible when the offending agent is discontinued early. Some drugs, such as radiocontrast agents, cause vasoconstriction through increased production of endothelin and/or thromboxane A2 which reduces renal blood flow and glomerular perfusion [272]. Radiocontrast agents can impair renal blood flow by both vasodilation and vasoconstriction; contrast nephropathy usually develops within 24 h after administration [272]. Risk factors include preexisting renal impairment, severe congestive heart failure, volume depletion, age, dose, and concurrent use of other nephrotoxins; there was no statistical difference in the complication rate when changing the type of contrast prescribed (high/low osmolality or ionic/non-ionic) [272, 273].

NSAIDs inhibit cyclooxygenase and decrease the synthesis of vasodilating prostaglandins, which in patients with chronic renal disease can impair glomerular perfusion [270, 274]. ACEIs

inhibit the conversion of angiotensin I to II; angiotensin II is a potent vasoconstrictor which helps to maintain glomerular perfusion at the efferent arteriole when renal blood flow is compromised [274]. Azotemia initially occurred for 25% of patients receiving vancomycin, but when the impurities were addressed, the incidence of nephrotoxicity decreased to less than 7% and was associated with a significantly elevated vancomycin trough [275].

Intrarenal Nephrotoxicity

Drug-induced nephrotoxicity from intrarenal mechanisms occurs through ATN or AIN [262, 265, 276]. ATN is often a result of direct drug toxicity on the renal tubular cells; the urinalysis can demonstrate proteinuria, tubular epithelial cells, and noncellular casts. ATN outcomes may be predicted based on the number of cells and casts visualized on the urinalysis [277]. Aminoglycosides accumulate within the renal cortex tubular cells with nephrotoxicity occurring 5–7 days into the antibiotic course; rank order for nephrotoxicity from greatest to least includes gentamicin, amikacin, and tobramycin [278]. Acetaminophen has been associated with ATN with therapeutic doses or following overdose [279–281]. Cephalosporins can cause ATN and/or AIN; a rank order for potential tubular toxicity from animal studies suggests cephazolin has increased risk compared to cephalexin and ceftazidime [276, 282, 283]. AIN is a result of intrarenal inflammation and often has systemic signs of hypersensitivity such as fever or rash; urinalysis can contain proteinuria, red and/or white cells, and/or cellular casts [265].

Postrenal Nephrotoxicity and Nephrotic Syndrome

Postrenal or obstructive nephrotoxicity associated with ICU drugs can occur when insoluble drugs such as acyclovir precipitate into the renal tubular lumen [284]. Acyclovir has been associated with nephrotoxicity when administered intravenously and at high doses [284]. Urine sediment can contain red and/or white cells with needle-shaped birefringent crystals. Drug-induced nephrotic syndrome has occurred with NSAIDs and is

diagnosed when proteinuria, hypoalbuminemia, and edema are present [266, 285–287].

Treatment

Modalities such as therapeutic drug monitoring programs may decrease risk for nephrotoxicity [288]. Drugs such as vancomycin and gentamicin can be monitored with trough and/or peak blood concentrations; risk for nephrotoxicity is avoided with shorter courses of treatment and the use of the lowest effective drug concentration [275, 278]. Once nephrotoxicity has occurred, treatment is based on identifying potential nephrotoxins and avoidance of concurrent use of other nephrotoxic drugs [274, 289]. Intravenous hydration is beneficial in some circumstances, as are diuretics [271]. After the nephrotoxicity has resolved, the drug can be resumed with renal dosing in some circumstances, but in the setting of nephrotic syndrome or AIN, the drug should not be restarted.

Neurologic ADRs

Drug-Induced Delirium

This section discusses ADRs associated with delirium. For additional reference, see ► Chap. 19, “Toxicant-Induced Alterations in Consciousness.” ICU delirium has been referred to as ICU psychosis, acute brain dysfunction or failure, and acute encephalopathy, among other terms. ICU delirium can prolong mechanical ventilation and is associated with a threefold higher rate of re-intubation, an increased rate of ventilator-associated infections, prolonged hospital stays, and increased 1-year mortality [290, 291]. Delirium is defined as a fluctuating change in attention, cognition, consciousness, and/or perception and can be further categorized as hyperactive, hypoactive, and mixed [290, 292]. Vanderbilt University Medical Center maintains the website www.icudelirium.org as a resource for delirium and includes screening and management tools for emergency department, ICU and non-ICU patients. When assessing delirium, workup for toxicologic or pharmacologic causes should occur simultaneously with

Table 18 ICU drugs associated with delirium by class. ICU delirium can prolong mechanical ventilation and is associated with increased risk of infection, prolonged hospital stay, and 1-year mortality. Workup for toxicologic or pharmacologic causes should occur simultaneously with evaluation for other causes as delirium is often multifactorial. Some conditions not normally associated with delirium when occurring concurrently with other pathologies

Class	Generic name	Mechanism
Analgesic – opioid	Fentanyl	5HT, kappa-opioid agonist
	Meperidine	5HT, MAOI
	Hydromorphone	kappa-opioid agonist
Analgesic – dissociative hypnotic	Cyclohexanone–ketamine	NMDA antagonist
Antibiotic – aminoglycoside	Gentamicin	NMDA agonist, decrease ACh release and effect. Iron complexes inhibit mitochondria resulting in lipid peroxidation
Antibiotic – penicillins	Penicillin	GABA-A antagonism
Antibiotic – cephalosporin	Cefepime	GABA-A antagonism
Antibiotic – carbapenem	Imipenem	GABA-A antagonism
Antibiotic – fluoroquinolones	Moxifloxacin or levofloxacin	GABA-A antagonism and NMDA agonist
Antibiotic – oxazolidinones	Linezolid	MAOI
Anticholinergics	Some antiemetics, antihistamines, antipsychotics, and muscle relaxants	Muscarinic acetylcholine antagonist
Antiemetics	Diphenhydramine	Muscarinic acetylcholine antagonist
Antipsychotics	Haloperidol	Dopamine antagonism
	Olanzapine or quetiapine	Muscarinic acetylcholine antagonist
Benzodiazepines	Midazolam or lorazepam	GABA-A agonist
Corticosteroids	Solumedrol	Disturbances in the hypothalamo–pituitary–adrenal axis

Abbreviations: gamma-aminobutyric acid (GABA), monoamine oxidase inhibitor (MAOI), serotonin (5HT)

evaluation for other causes as delirium is often multifactorial [293]. Table 18 discusses drugs associated with delirium by class.

Consider the timing and progression of neurological symptoms in relation to all prescribed hospital drugs. Consider previous medications (prescribed or non-prescribed) that have been abruptly discontinued and their propensity to cause withdrawal (for additional information, refer to ► Chap. 27, “Withdrawal Syndromes”). Certain withdrawal states not normally associated with delirium, when occurring concurrently with certain pathologies, may be

may be considered. Consider drug or withdrawal states resulting in disturbances in the production, release, and/or effects of acetylcholine, endorphins, GABA, glutamate, 5HT, and dopamine neurotransmitters. Substance-induced psychosis is associated with the longer duration use of alcohol, amphetamines, cannabimimetic agonists, cocaine, and hallucinogens. Drug withdrawal delirium occurs classically with alcohol, benzodiazepine, and barbiturates

considered. Examples include nicotine, opioid, and cannabis withdrawal. Nicotine withdrawal in the setting of brain injury has been associated with delirium [294]; however, larger review studies have not clearly implicated nicotine withdrawal with delirium in hospitalized patients [295]. Opioid withdrawal is not normally associated with delirium but in the ICU should be considered as a contributor, as opioid withdrawal can occur after only 5 days of continuous opioid analgesia and by day 9 occurred in 100% of patients [296]. Cannabis withdrawal is associated with anger, aggression, and

irritability; performing urine drug screens at admission could help to identify patients at risk since this is the most common illicit drug used in the USA and withdrawal symptoms can persist for 3 or more weeks [297–301]. Synthetic cannabinoid withdrawal has been reported, but the propensity for delirium is not yet clear [302].

Consider previous medications (prescribed or non-prescribed) that may interact with currently prescribed ICU drugs; commonly implicated drugs include serotonergic, anticholinergic, and *N*-methyl-D-aspartate (NMDA) receptor antagonists [303–305]. Previous substance misuse should be considered, especially for dopaminergic drugs, as these drugs are associated with substance-induced psychosis and may be a function of the severity of use and dependence and persist for months after last use. Drugs implicated include alcohol, amphetamines, cannabimimetic agonists, cocaine, hallucinogens (e.g., methylenedioxymethamphetamine MDMA), and NMDA antagonists (e.g., phencyclidine and ketamine) [306]. Independent precipitating factors for delirium such as bladder catheters, fecal management systems, immobilizing therapies, and restraints should be avoided [290, 307, 308]. Major groups of ICU drugs associated with delirium that may be evaluated by a medical toxicologist include analgesics, antibiotics, antipsychotics, and sedative-hypnotics.

Analgesics

Analgesic-induced delirium could occur by interaction with other medications, opioids with serotonergic properties, and/or kappa-opioid agonism [309]. Fentanyl and/or methadone may interact with linezolid or other monoamine oxidase inhibitors (MAOI) or serotonergic medication resulting in serotonin syndrome [310–316]. A retrospective review of 4538 patients treated with fentanyl and concurrent serotonergic agents suggests the incidence of serotonin syndrome was low [311], but prospective studies are needed before ignoring this ADR as there are many case reports suggesting a higher incidence [310–312, 317–322].

Furthermore, the hospital stay and mortality among patients prescribed with serotonin

reuptake inhibitors prior to ICU admission are higher and may be related to an analgesic reaction [323]. Serotonin reuptake inhibitors may also increase risks secondary to platelet serotonin inhibition and increased bleeding risk or other mechanisms [324–328]. Propensity for kappa-opioid agonism may be another factor to consider when evaluating delirium after opioid administration; fentanyl and hydromorphone may have higher risk in animal studies [309].

When delirium is suspected to be drug mediated, the implicated drug(s) should be discontinued. If opioid-induced delirium is suspected, opioid avoidance or lower doses are recommended by one large prospective study [329]. If a patient has a history of prescription or illicit serotonergic substance use, consider avoiding serotonergic drugs such as fentanyl until more prospective data is available. For opioid withdrawal, initiating a long-acting full or partial opioid agonist may be best until the patient has been extubated and then further tapered and/or provided with symptomatic treatment.

Antibiotics

Major groups of antibiotics associated with delirium include aminoglycosides, beta-lactams (penicillins, cephalosporins, and carbapenems), fluoroquinolones, oxazolidinones (linezolid), and trimethoprim/sulfamethoxazole. Aminoglycosides activate NMDA receptors, inhibit presynaptic release of acetylcholine, and bind postsynaptic receptors. Chronic toxicity (increased trough levels) occurs when iron complexes inhibit mitochondria and cause lipid peroxidation. Aminoglycosides are associated with peripheral neuropathy and neuromuscular blockade; case reports have linked gentamicin to encephalopathy [330] (Table 19).

The beta-lactam ring itself is known to be neurotoxic and drugs containing this structure cause neurotoxicity by GABA-A antagonism. For beta-lactams, symptoms of neurotoxicity usually present 12–72 h after initial administration, but can occur later after increased dosing or when metabolic and/or elimination pathways are inhibited. Previous case reports have identified the following risk factors: being critically ill,

Table 19 Major antibiotic classes associated with neurotoxicity. The beta-lactam ring is epileptogenic with variability depending on side chains and other substitutions

Drug or class	Mechanism	Onset	Signs/symptoms
Penicillins and cephalosporins	Inhibit GABA binding to GABA-A receptor, blocks GABA-A chloride channel	12–72 h	Confusion, dysarthria/aphasia, agitation, lethargy/coma, myoclonus, seizures, and/or NCSE
Carbapenems	Affinity for GABA-A receptor complex	3–7 days	Focal and generalized seizures
Fluoroquinolones	Inhibit GABA binding to GABA-A receptor, NMDA agonist	1–4 days	brief tonic–clonic, sustained generalized myoclonus
Isoniazid	Inhibit pyridoxine kinase	30 min–2 h	Recurrent, generalized tonic–clonic seizures
Metronidazole	Increased hydroxy and 1-acetic acid metabolites	5–7 days	Seizures, peripheral neuropathy

Abbreviations: gamma-aminobutyric acid (*GABA*), nonconvulsive status epilepticus (*NCSE*)

reduced creatinine clearance, preexisting CNS conditions and/or damage to the blood–brain barrier, concurrent use of other neurotoxic drugs, and dosing errors [330–335]. Symptoms of beta-lactam neurotoxicity are secondary to impaired GABA-A transmission [335]. Cephalosporins with higher affinity for GABA-A receptors and those with higher CNS penetrance are more neurotoxic. Resulting clinical effects range from coma to agitation and can fluctuate with delirium, aphasia, myoclonus, seizures, and nonconvulsive status epilepticus. Cefazolin, cefepime, and ceftazidime may have higher risk for neurotoxicity, while cephalexin and ceftriaxone may be lower. A retrospective review of 100 patients prescribed with cefepime found the incidence of encephalopathy was 15% [336].

Fluoroquinolone's mechanism of toxicity includes inhibition of GABA-A receptors and activation of NMDA receptors. CNS reactions occurred for 3% of patients prescribed with gemifloxacin, but other quinolone derivatives implicated include gatifloxacin, moxifloxacin, ofloxacin, and, its levo-stereoisomer, levofloxacin. Neurotoxicity can be manifested as delirium associated with psychotic features including delusions and hallucinations as well as restlessness and seizures.

Antipsychotics

Literature suggests that quetiapine decreases the incidence of ICU delirium although other antipsychotics can be used to effectively treat ICU

delirium after it has occurred [337–340] (LoE 1). As with the initiation of any medication, the antipsychotic side-effect profile should be considered when prescribing an antipsychotic for delirium; haloperidol may be associated with extrapyramidal symptoms, while olanzapine was found to be the most sedating [341]. Combining the critical care and toxicology literature, antipsychotics with anticholinergic properties should be used at low doses when treating delirium not suspected to be anticholinergic; some antipsychotics such as olanzapine and quetiapine cause agitation because of anticholinergic mechanism. Anticholinergic toxicity from olanzapine and/or quetiapine (or any other anticholinergic medication) can be diagnosed and treated with appropriately dosed physostigmine [342–344].

Benzodiazepines

Benzodiazepine use increases the risk of delirium [308, 345–347]. This could be through a paradoxical reaction, after prolonged ICU use, or benzodiazepine withdrawal [348]. If benzodiazepine delirium is suspected, appropriately dosed flumazenil can diagnose and treat patients following intubation or after benzodiazepine overuse and following alcohol withdrawal with little if any risk for seizures or precipitating withdrawal [346, 349–355]. Historically, patients with benzodiazepine dependence has been used as a contraindication to flumazenil, and a meta-analysis warns against the use of flumazenil, but when patients who received an initial flumazenil dose

of 1 mg or more were excluded, there were no significant adverse events in either the placebo or flumazenil groups [356]. Benzodiazepine dependence is not an absolute contraindication to flumazenil (LoE II-1). Flumazenil, therefore, should be dosed at 0.2–0.3 mg if there are concerns about rapid awakening or, otherwise, 0.5 mg; if improvement is observed, discontinue benzodiazepines and repeat flumazenil as needed when symptoms recur (LoE II-1) [346]. If benzodiazepine withdrawal is suspected, replace with a longer-acting benzodiazepine such as diazepam or with phenobarbital (LoE III) [357]. Another option for patients at risk for benzodiazepine withdrawal is a phenobarbital taper [358]; this may be beneficial for patients who received benzodiazepines with extended duration while mechanically ventilated.

Steroids

Neuropsychiatric effects including agitation occur in about 6% of patients who receive steroids; dose is the most significant risk factor [359]. ICU patients may experience agitation, delirium, and/or failure to wean [360–364]. Treatment includes reducing or avoiding steroids; however, some studies have suggested steroid switching (LoE III) and treatment with antipsychotics such as risperidone [360, 362, 365–369] (LoE III).

Disturbances in Circadian Rhythm

ICU delirium is often multifactorial, and disturbances in circadian rhythm and sleep deprivation can contribute to hypoxia, infectious, metabolic, and ADRs. Risk factors may include age and existing dementia or cognitive impairment. Circadian rhythm disturbance is a diagnosis of exclusion. Melatonin can be used to facilitate circadian rhythm and can decrease need for sedation improving neurologic indicators although further study is needed [370, 371] (LoE I).

Treatment

Pharmacologic sedation should be titrated to the least effective dose with at least daily sedation holidays to minimize the incidence of delirium. Avoiding infusions is one method for titrating sedation to the least effective dose. Once delirium

has occurred, treatment is based on identifying and discontinuing potential causative medications. Consider previous medications (prescribed or non-prescribed) that have been abruptly discontinued and their propensity to cause withdrawal. Also, consider previous medications (prescribed or non-prescribed) that may interact with currently prescribed ICU drugs.

If benzodiazepine or anticholinergic delirium is high on the differential, flumazenil and/or physostigmine can be administered safely; positive results may avoid costly and unnecessary radiographic testing that place the patient at increased risk for morbidity and mortality (e.g., during transport and while outside of the ICU setting [372]). If opioid withdrawal is a suspected contributor, the administration of a long-acting opioid will ameliorate the delirium. The patient can later be treated symptomatically for opioid withdrawal if not a candidate for outpatient opioid maintenance therapy.

Dexmedetomidine is an imidazole alpha-2 agonist that increases days alive without delirium or coma while in the ICU when compared to lorazepam [373]. The incidence of delirium was 54% in dexmedetomidine vs 77% in midazolam-treated patients ($P < 0.001$). There was no significant difference in time at targeted sedation level for 375 patients located in 68 centers in five countries who were treated in a double-blind, randomized trial [374]. Dexmedetomidine has caused hypotension during the initial bolus in between 25% and 56% of patients and, compared to benzodiazepines, may be more likely to cause bradycardia, which is the most significant ADR [373, 374]. Since dexmedetomidine is not usually associated with respiratory depression, it can be used to treat withdrawal syndromes in non-ventilated patients [374–376]. Cost is a consideration when considering dexmedetomidine; compared to midazolam, dexmedetomidine lowered total ICU costs and decreased ventilator time and ICU length of stay [377]. However, for moderate to severe anticholinergic delirium, physostigmine would be expected to be a more cost-effective primary therapy; dexmedetomidine could be used as an adjunct to avoid higher doses of benzodiazepines, but additional studies are needed.

An alternative to dexmedetomidine for pharmacies who restrict its use may be clonidine, and one study proposed the use of a short course of dexmedetomidine before transitioning to sublingual or orally administered clonidine [378]. The mechanism of these drugs differs such that the ratio of alpha-1 to alpha-2 may predispose clonidine to more hypotension and bradycardia and less sedation compared to dexmedetomidine, but the cost savings are difficult to ignore.

Drug-Induced Seizures

This section discusses ADRs associated with seizures. For additional details refer to ► Chap. 20, “Toxicant-Induced Seizures.” Six percent of new-onset seizures and 9% of status epilepsy may be drug related [379]. Major classes of drugs associated with seizures include antidepressants, anticholinergics/antihistamines, and stimulants, but the clinician should also consider NSAIDs, beta-lactams, quinolones, and drug withdrawal [336, 380–385]. Consider drugs previously prescribed that have not been continued in the ICU such as baclofen, gabapentin, pregabalin, zolpidem, and zopiclone; any drug acting at the GABA complex should be considered [386–391]. ICU drugs cause seizures by inadequate inhibitory neurotransmitters (e.g., GABA), excessive excitatory neurotransmitters (e.g., glutamate), and/or interfering with sodium channels [385, 392]. Antimicrobials impair GABA-A transmission [335, 393]. Magnesium homeostasis may be associated with seizures as diuretics, proton pump inhibitor, and antimicrobials may decrease the seizure threshold [335, 393].

Seizures are treated with either benzodiazepines or barbiturates; generally barbiturates are considered to be a second-line therapy [385]. Antiepileptics are ineffective when the mechanism of toxicity is caused by metabolic abnormalities or drugs impairing GABA-A transmission. Antiepileptics could be considered if seizures persist despite first- and second-line treatment.

Strategies to Decrease ICU ADRs

Patients admitted to the ICU have a higher mortality compared to hospitalized patients; 30-day mortality ranges from 12% to 44% depending on

the ICU patient subtype [394]. Thirty-four to forty-five percent of ADRs are preventable and represent an opportunity for risk reduction and improved patient safety [5, 7, 395]. Prior studies have demonstrated that technology, multispecialty care teams, specialized treatment centers, and standardized treatment algorithms can assist with these goals.

Technology has facilitated the development of medication databases and systems to identify potential drug–drug interactions, and one study identified that 11% of ICU admissions have potential drug–drug interactions [396]. As with any technology with an alarm, there is potential for alarm fatigue and technology should be curtailed to the ICU population to minimize this [397]. Conversely, when an ICU ADR has been identified, technology can be used to identify medications potentially causing the condition, medications to avoid, and the appropriate medications to use.

Multispecialty care teams consist of admitting physicians, consulting physicians, pharmacists, nurses, specialty therapists, care coordinators, and social workers. In the ICU, the value of the pharmacist is especially important. Pharmacists obtain medication histories; develop and manage policies and protocols for optimal patient care, drug expenditures, and cost avoidance (i.e., analgesia, anticoagulation, delirium, pharmacokinetic, sedation, and transfusion guidelines); optimize antimicrobial stewardship; respond to resuscitation events; verify accuracy of computerized order entry; educate other ICU personnel; assist in discussing treatment modalities with patients and/or families; prospectively evaluate drug therapy; and monitor and identify ADRs [398–410]. The impact of the clinical pharmacist in the ICU has significantly decreased ADRs, antimicrobial resistance, medication costs, transfusions, hemorrhage, ventilator days, and length of stay. Unfortunately, pharmacist services are not directly reimbursable; pharmacy departments receive funds from a hospital’s general operating budget. Pharmacy departments are penalized when they increase the ratio of clinical pharmacists to occupied beds from 1/100 to 1/20, an increased expenditure which was shown to

decrease ADRs by 48% [410]. The optimal pharmacist to patient ratio is unclear, but considering the services of a medical toxicologist are reimbursable, could a medical toxicologist enable a group of clinical pharmacists, thereby increasing the reimbursement of the pharmacy? Medical toxicologists, when available, are experts in pharmacokinetics and toxicokinetics and should develop relationships with multidisciplinary teams to aid in the reduction of the incidence of ADRs, length of stay, and mortality.

In addition to pharmacist to patient ratio and their impact on ADRs and mortality, patient to physician and/or nurse ratios should be considered. When nurse to patient ratio was greater than 2.5, the risk of death increased by 3.5. When the physician to ICU patient ratio exceeded 14, the risk of death increased by two [411]. High patient turnover and a high volume of life-sustaining procedures were also predictive of increased mortality. Admissions during weekday rounds did not increase mortality [412]. High-intensity daytime staffing reduced mortality [413].

Specialized treatment centers have been shown to improve care, especially for ICUs. Medical toxicology admitting services are not widely available, but there is great need as demonstrated by one large study of 3581 patients cared for primarily by toxicologists and non-toxicologists within the same hospital system as well as a third group of patients cared for by non-toxicologists outside of the hospital system. During the 2-year study period, there was a median savings of 1483 hospital days and \$4.3 million dollars, as well as a significant decrease in mortality for patients cared for by toxicologists [414]. Extrapolating from other specialty data, when only specialists are allowed to admit and care for critically ill patients, length of stay and mortality in the ICU were shortened [413, 415]. All things considered, patients cared for by non-specialists have increased risk for extended length of stay and mortality, which suggests that medical toxicologists and critical care intensivists should remain involved in patient care potentially until hospital

discharge. On admission, general recommendations may include holding any nonessential medication potentially resulting in drug–drug or disease–drug interactions; for example, many ICU patients may be started on antimicrobials, calcium channel blockers, and/or amiodarone, and these drugs increase concentration of simvastatin by inhibiting CYP3A4, thereby increasing drug levels resulting in an increased risk for rhabdomyolysis, renal failure, and hepatotoxicity [416–424]. Medical toxicologists may also provide daily recommendations for restarting or modifying home medications, as well as querying potential medication interactions, substance use disorders, and drug withdrawal. Until there are more admitting toxicology physicians, consultants should provide daily recommendations directly to the care team until the day of patient discharge. Interactive audio–video telemedicine consultation may be an alternative when traditional bedside care is not possible as this service has been useful for other specialties [425].

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Medical errors and medication errors may cause patient harm and death and occur in all steps of the medication process and in all settings across healthcare. Some settings, such as the intensive care unit (ICU), involve higher risk of harm from such errors. This increased risk is due to many factors. Sicker patients with organ system(s) dysfunction and use of high-alert medications are two important factors for the risk of medication errors. Other risk factors such as age and comorbidities may also contribute. According to the Institute for Safe Medication Practices, a high-alert medication is “a drug that bears a heightened risk of patient harm when used in error” [1]. Medical toxicologists are sometimes consulted when a medication error occurs to provide expertise in management, to recommend treatment if necessary, and to offer mitigation strategies.

A medication error is defined as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer” [2]. An error can result in harm or may be intercepted prior to reaching the patient causing no harm (near miss). The medication use process, with functions such as prescription, transcription, dispensing, administration, and monitoring, lends itself to errors as each function can be broken into additional steps. Numerous strategies have been developed to mitigate errors at each of these functions to reduce harm to patients.

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This chapter will provide an overview and explore the epidemiology of medication errors and drug–drug interactions in the ICU. Factors that lend themselves to causing errors and prevention strategies for errors will also be discussed.

The ICU Setting

Particular areas of the hospital are at increased risk for errors and near misses due to the nature of the area, type of patients, and medications and procedures used as part of patient care. The ICU is one such high-risk area. ICU patients usually have organ dysfunction or multiple organ dysfunction and are routinely exposed to high-alert medications (e.g., adrenergic agonists and antagonists, opioids, insulins, sedation agents, and anticoagulants). In one study involving two medical centers, the strongest predictor or risk factor for an adverse drug event or medication error in an ICU was the patient's illness severity [3]. Another study, involving medical and surgical ICUs compared to general medical and surgical wards, found that patients in an ICU were prescribed twice as many drugs as patients on general wards and had a twofold preventable and potential adverse drug event rate [4]. Another risk factor is the use of weight-based dosing for many medications, including anti-infectives, vasopressors, and anticoagulants. Weights may be estimated which can lead to under- or overdosing of necessary medications. Mathematical calculations are prone to error with weight-based dosing as well [5].

Epidemiology

In 1999, the Institute of Medicine reported, "To Err is Human: Building a Safer Healthcare System." This report estimated between 44,000 and 98,000 patients experienced a medical error and died per year. These errors have an estimated cost of \$37.6–50 billion due to the need for extra care, lost income, and disability [6].

Multiple studies have tried to provide further epidemiologic data regarding medication errors in

the ICU. The lack of standard definitions for medication errors and adverse drug events and underreporting of these types of medication safety concerns make it difficult to give an exact number to the incidence [7]. Most of these studies are observational. One study, involving a medical ICU and a coronary care unit (CCU) at an academic medical center, found 78% of serious medical events involved medications. These errors were mainly related to medication ordering or executing a particular treatment associated with a medication. The most common medication error was ordering the wrong dose, and the most common medications involved were cardiovascular drugs, anticoagulants, and anti-infectives. The overall medication error rate in the medical ICU was 12.7% and 12.1% in the CCU [8]. A similar observational study also evaluated medical and cardiac ICUs for medication errors. It found that 65% of medication events (1183/1805) had the potential for harm. Some events had more than one error, either the actual order had more than one error or the event led to errors in more than one step of the medication use process (see below for discussion of the "[Medication Use Process](#)"). Thirty-eight events (38/1805, 2%) were considered preventable. Seven of these preventable events led to significant patient harm (i.e., diarrhea, nausea, vomiting), 13 lead to serious patient harm (i.e., gastrointestinal bleeding, allergic reaction but not anaphylaxis, or altered mental status), and 18 were considered life-threatening (anaphylaxis, respiratory failure, etc.). Antibiotics were most commonly involved at 26% (10/38) of the events, while diabetic medications were next at 20% (8/38). Most medication errors occurred during the administration (39%) and prescribing/ordering (32%) stages [9]. In a pediatric ICU, an observational study showed that 151 prescribing errors occurred in 1129 orders, with 104 of these errors requiring intervention or resulting in patient harm. Wrong dosage was the most common error followed by wrong drug selection and missing information from the order. The most commonly prescribed medications, analgesics and anti-infectives, had the most frequent errors, with infrequently prescribed drugs (e.g.,

antihypertensives and antimycotics) demonstrating higher errors rates [10]. While it is difficult to compare different types of ICUs, one study did show that medical ICU patients experienced higher rates of medication errors than do patients in surgical ICUs [4].

Medication Use Process

The medication use process is a complicated series of sequential functions leading to a patient receiving medication. Each function of the process has multiple steps to ensure that it is completed correctly. These functions include prescription, transcription, dispensing, administration, and monitoring. Errors can occur at each function of the process. The most error prone functions are prescription and administration [11]. A recent study of prescribing errors in the ICU identified 360 errors in 286 prescriptions out of 534 total prescriptions. The most common prescribing error was omitted information with computer prescriber order entry. Examples of the omitted information included route of administration or diluent needed [12].

Several studies have focused on medication administration in the ICU aimed at determining the epidemiology of administration errors. In one observational study, pharmacists observed nurses in the preparation and administration of medications. Of 2009 medications administered, 132 (6.5%) involved errors. The most common errors were wrong dose (31%, 41/132), wrong rate (22%, 29/132), and wrong preparation technique (18%, 24/132). Almost 20% (26/132) of the errors were potentially life-threatening, and 42% (55/132) of the errors were potentially significant (e.g., underdosing, time errors, and physicochemical incompatibility) [13]. Another observational ICU study for medication administration involved only 3.3% of errors compared to the above but had a multidisciplinary team including pharmacists in place at time of observation [14]. This study supports the use of a multidisciplinary team to reduce medication errors. See “[Prevention Strategies](#)” below.

Prevention Strategies

Many prevention techniques, including technological advances, have been developed over the years to try to mitigate medication errors and adverse drug events. These prevention strategies focus on different functions in the medication use process or cross all areas of the medication use process. In general, a comprehensive program to target all parts of medication use and to obtain information in different ways allows for a broader scope of information and highlights different concerns. In one study, a program assessing voluntary reporting, chart review, and computer-based monitoring included monitoring for specific orders (naloxone) and alerts. All of these methods identified different medication safety concerns with little overlap in the problems identified [15]. Another study showed that direct observation revealed a higher incidence of potential and actual events when compared to chart reviews and solicited incident reporting [16]. In one ICU in Australia, a Medication Error Minimization Scheme (MEMS) has been implemented as part of an ongoing quality improvement project. The overall research design uses “Plan-Do-Study-Act cycles” to achieve small steps toward improving medication safety. With this MEMS, the ICU has seen an increased number of reported medication problems from incident reporting, staff surveys, focus groups, and chart review [17]. Once these concerns are known, strategies for prevention can be targeted and tested using methodology such as “Plan-Do-Study-Act cycles.”

Prescription writing, or ordering of a medication, is one of the areas more prone to error. Poor handwriting has led to mistakes with transcription in the past. With the introduction of computerized prescriber order entry (CPOE), it is no longer necessary to interpret a prescriber’s handwriting. In one study, the error rate of handwritten prescription orders contained 6.7% compared to 4.8% with CPOE. The handwritten prescription errors included omission of key information such as dosing, unit, or frequency. Types of errors for the CPOE orders included dosing errors, omission of writing order for a required drug, and

prescriber's signature [18]. In one ICU, the initiation of CPOE reduced prescribing errors from 27% to 3% when compared to a paper-based unit in the same hospital. Both CPOE and paper-based ordering had errors most commonly with cardiovascular and antibiotic medications [19]. In another study, CPOE implementation in a cardiac care unit showed a decrease in errors from 44.8% with handwritten prescription orders to 0.8% in computerized orders after full implementation of the CPOE system [20]. The evidence supporting the benefit of CPOE in reducing medication errors is grade II-3.

Decision support is considered an essential part of CPOE. This technology incorporates tools into the ordering system to aid providers in appropriate prescribing. It allows providers to automatically check for drug interactions, appropriate medications for elderly patients, and appropriate dosing for renal function among other functions. Some hospitals have even implemented decision support into antibiotic prescribing to ensure quality metrics are met and treatment guidelines are followed. In one recent study, five anesthesia-run ICUs were studied pre- and post-implementation of antibiotic decision support. Prior to implementation, only 61% of antibiotic orders adhered to guidelines. Immediately after implementation, 92% adhered to guidelines. This study also showed more antibiotic free days and a decrease in mortality when antibiotic guidelines were followed [21].

Once medications have been ordered, they must get dispensed and administered. Barcode medication administration has been implemented throughout hospitals as a way to ensure the "rights" of medication administration (i.e., right patient, right medication, right dose, right route, right time, right documentation, right reason, and right response). Using barcodes, one ICU study showed an improvement in correct administration times. This study used a direct observation technique to monitor medication administration errors. Prior to barcode medication administration, 18.8% of were administered at a wrong time. After implementation of barcode administration, the error rate was 7.5% [22]. The evidence supporting the benefit barcodes is grade II-3.

Another technological advance in drug administration has been the use of intelligent infusion pumps for intravenous medications. These infusion pumps have programmable libraries with point-of-care decision support for infusion rates and doses and will alert the nurse to problems related to medication administration. These pumps evaluate dose, dosing unit, rate, and concentration and prevent free-flow or "runaway" medication administration [23]. At the initiation of using this technology, a prospective study found numerous ways that these intelligent pumps could prevent error. The study also showed numerous ways in which providers were bypassing these techniques, such as not using the preprogrammed drug library with correct infusion rates [24]. In one Pediatric Intensive Care Unit, after adapting the drug library to its specific needs and acceptance by nursing staff, smart pumps were found to be very effective in reducing IV medication administration errors [25]. These intelligent pumps have the ability to intercept and log medication errors as well. One study in Germany showed that there were 717 instances of an alert firing for potentially harmful overdosing [26]. These pumps when used with barcode medication administration aid to ensure the "rights" of IV medication administration are met [23]. The evidence supporting the benefit of intelligent infusion pumps is grade II-3.

An additional way to prevent medication errors in the ICU is to have clinical pharmacists as part of the care management team. Clinical pharmacists have been shown to reduce errors, reduce costs, improve individualized care, and serve an educational function in the ICU [27]. A study involving a medical ICU and a coronary care unit at a large teaching hospital showed that preventable prescribing errors were reduced by 66% when a senior pharmacist was a full member of the patient care team [28]. Another study in China showed that pharmacists in the ICU intervened in errors related to medication dosing (152/407 interventions) (e.g., patient with renal insufficiency or on renal replacement therapy), drug omission (83/403 interventions), and potential for an adverse drug reactions (54/407 interventions) over a 6-month observational study [29]. In a

Dutch hospital, clinical pharmacists in the ICU reduced the incidence of prescribing errors from 190.5 per 1000 patient days to 62.5 per 1000 patient days and reduced the number of preventable adverse drug events from 4 to 1 per 1000 patient days [30]. Clinical pharmacists can also develop a training program for providers working in the ICU to teach clinically relevant errors related to preparation and administration of IV medications. A study of a Vietnamese program showed a reduction from 64% to 49% following implementation of such a program, and any residual dosing errors were less likely to be clinically relevant [31]. In addition to reducing errors, pharmacists in the ICU can aid in improving the management of infections, anticoagulation therapy, sedation, and analgesia for ICU patients [32]. The evidence supporting the benefit of ICU-based pharmacists grade II-3.

Drug–Drug Interactions

Drug–drug interactions (DDIs) are common and can lead to patient harm. The severity and drugs involved may differ in the ICU compared to other clinical settings [33]. Similar to medication errors, patients in intensive care units may be at risk for more severe drug–drug interactions due to the complexity of their illness, medications administered and their number, disease severity, and organ system dysfunction [5]. In one Dutch study, a computerized algorithm was developed to determine the frequency of DDIs. The DDIs were classified based on surveys from nine pharmacists and intensivists. After a consensus was reached, the group studied admissions to an ICU. A total of 16,122 DDIs were identified. Most commonly, antithrombotic and antibacterial agents were involved [34]. In another Dutch retrospective observational medical ICU study, 54% of all ICU patients experienced a potential DDI. The most common consequences for the DDIs were increased risk of an adverse drug reaction/side effect or toxicity. Management for the DDIs seen in the ICU often involved increased monitoring of some type (e.g., vital signs, laboratory studies, clinical monitoring for toxicity or effectiveness,

or for changes on the electrocardiogram) [35]. DDIs were associated with prolonged lengths of stay, 12 days versus 5 days for patients without DDIs, in the ICU [36]. Another prospective, case–control study showed that 6.65 DDIs occurred per patient. Pharmacodynamic and pharmacokinetic DDIs were common. Risk factors associated with risk of DDIs included female gender, age >50 years, use of >10 drugs, and ICU stay >7 days [37]. One recent study showed that 37% (187/501) of patients in a cardiac ICU have documented QTc \geq 500 ms. While no patients developed torsades de pointes, 63 patients (34%) had atrial dysrhythmias and 37 patients (20%) had ventricular dysrhythmias [38]. This acquired prolonged QTc syndrome may be a potential serious consequence of ICU stay since critically ill patients are at risk for QTc prolongation in addition to these patients receiving multiple medications and having organ system dysfunction which may lead to electrolyte abnormalities or changes in metabolic function due to reduced renal and hepatic function [39].

In the cardiothoracic ICU, anti-infectives, central nervous system, and cardiovascular agents were the main drugs associated with major DDIs or contraindicated because of another drug present in the patient's medication regimen. The predicted consequences of the identified DDIs included altered GI absorption of antibiotics, inhibition/induction of enzymes for drug metabolism, and QTc prolongation [40]. Another study in a cardiothoracic ICU revealed that 17.7% of DDIs were considered major (i.e., life-threatening and/or require medical intervention to minimize or prevent serious adverse events) or were contraindicated for concurrent use. The most common interactions were drug metabolism and drug synergy effects. Azole antifungals and fluoroquinolones were the most common drugs involved [41]. In another prospective, observational study of a medical ICU, 5–9% of potential DDIs were major or contraindicated for concurrent use. The most common consequences were changes to blood coagulation profiles, QTc prolongation, and inhibition of cytochrome P450 enzymes [33].

Summary of Recommendations

Use *Computer Prescriber Order Entry* with *Decision Support* to Decrease Prescribing Errors

Use Other Technologies, such as *Barcode Medication Administration* and *Intelligent Infusion Pumps* to Decrease Administration Errors

Seek the Aid of *Pharmacists* to Reduce All Errors, Reduce Costs, and Provide Education on Best Medication Practices in the ICU

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Part IV

Medications: Cardiovascular

Alpha-2 Adrenergic and Imidazoline Receptor Agonists: Clonidine, Dexmedetomidine, and Related Antihypertensives, Decongestants, and Sedatives

35

Anthony J. Tomassoni

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Since the introduction of the imidazoline derivative clonidine, a topical nasal decongestant, in 1962, the number of agents in its class and the indications for their use have expanded greatly. Thousands of cases of clonidine exposure are reported to US poison centers annually (over 9700 exposures in 2014) with nearly 1 in 5 coded as resulting in moderate or major effect [1]. Exposures to guanfacine and other imidazolines increase the magnitude of the problem of alpha agonist exposures.

Xylazine, an analogue of clonidine, is used as a veterinary sedative, anesthetic, analgesic, muscle relaxant, and feline emetic agent (often in conjunction with ketamine) [2–4] and has been diverted as a drug of abuse [5] and adulterant of heroin [6, 7].

One might be tempted to discount the potential toxicity of medications in this class, but that would be shortsighted since interesting and useful agents continue to join this class, indications for some members of the class are expanding, and misadventures with these medications may have serious consequences. Dexmedetomidine is a recent addition to the class, approved by the US Food and Drug Administration in 1999. US Food and Drug Administration-labeled indications for dexmedetomidine were expanded to include procedural sedation in 2008.

The range of applications for these agents is ever broadening, and consequences of misuse may be severe. During its early use as a decongestant, the sedative and cardiovascular

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depressant effects of clonidine became apparent, sparking novel uses for this prototypical agent in the agonist/imidazoline group. Clonidine made its next debut in the treatment of hypertension and other applications followed. Clonidine and other imidazoline derivatives now have many indications, including the treatment of hypertension, mucous membrane congestion (naphazoline, oxymetazoline, tetrahydrozoline), sedation, anesthesia, pain control, migraine treatment, and muscle relaxation (tizanidine) [8], Tourette's syndrome [9], pediatric sleep disturbances [10], anxiety, attention-deficit hyperactivity disorder (ADHD) (guanfacine), treatment of menopausal hot flashes [11], glaucoma treatment (apraclonidine and brimonidine) [12], opioid detoxification [13], alcohol withdrawal [14], and smoking cessation [15]. In recent years, agents in this class have found application as adjuncts to anesthesia and to reduce anesthetic and analgesic requirements [16].

Biochemistry and Clinical Pharmacology

Clonidine and Related Agents

Clonidine is the most thoroughly studied of the centrally acting antihypertensive agents and is chemically and pharmacologically similar to other members of the imidazoline class, such as guanabenz and guanfacine. The development and clinical introduction of two newer oxazolines, moxonidine and rilmenidine, have led to better understanding of the mechanism of action of the imidazolines. These more recently developed agents are highly selective for the imidazoline receptor and have low affinity for α_2 -adrenergic receptors. They have improved side effect profiles compared with clonidine and are used primarily as antihypertensives. The initial introduction of clonidine as a mucous membrane decongestant was followed by the development and approval of several other imidazoline compounds for this indication, including naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline, which now are available over the counter or by prescription as decongestant solutions intended for nasal

or ocular use. As expected, based on their chemical and pharmacologic similarity, these agents have similar toxicity. Most reported cases of severe imidazoline intoxication pertain to clonidine.

Shortly after the initial introduction of clonidine, the compound's sympatholytic and hypotensive effects were noted [17], leading to its clinical application as an antihypertensive [18, 19] and subsequently to its use in the management of glaucoma [9, 15, 20–22], migraine headache [23], attention-deficit hyperactivity disorder [24], and, in conjunction with opioids or local anesthetics (or both) in epidural infusion, intractable cancer pain, postsurgical pain, and labor [25–28].

Knowledge of the existence of a central nonadrenergic binding sites responsible for the antihypertensive effect of clonidine was advanced in the 1980s after the investigation of structurally similar compounds synthesized to have fewer adverse effects [29]. Subsequently, the oxazoline compounds rilmenidine and moxonidine were approved for clinical application in several countries. These compounds have little α_2 -agonist potency compared with clonidine but nonetheless exert marked hypotensive effects. The study of these drugs has led to improved understanding of the imidazoline receptor concept, further described in the pathophysiology section. These compounds also possess antidysrhythmic activity [30]. Long-term use results in remodeling of the left ventricle. A hypoglycemic effect due to improved insulin sensitivity [31] without atherogenic effect also has been attributed to these agents [32–34]. The mechanism of action of clonidine and related agents is further summarized below in the discussion of the pathophysiology of toxic effects.

The activity of agents in this class is complex, and to understand them requires knowledge of both the centrally acting α_2 -agonist mechanism and the nature of imidazoline receptors. Three classes of imidazoline binding sites have been described and these are summarized in Table 1.

I₁-imidazoline binding sites meet important criteria associated with functional receptors: specificity in binding assays, linkage to physiologic functions, appropriate anatomic and cellular and subcellular localization, and binding affinities that

Table 1 Types of imidazoline receptors and their actions

Types of imidazoline receptors and their actions [161]	
I ₁ -receptor	Mediates sympathoinhibitory response to imidazolines to lower blood pressure
I ₂ -receptor	An allosteric binding site for monoamine oxidase, involved in pain modulation and neuroprotection
I ₃ -receptor	Regulates insulin secretion from pancreatic beta cells

correlate with functional drug responses. Additionally, I₁-imidazoline binding sites show physiologic regulation and endogenous ligands and are coupled to cellular signaling events. Activation of I₁ receptors causes choline phospholipid hydrolysis, leading to the generation of diacylglyceride, which in turn triggers the generation of second messengers including arachidonic acid and eicosanoids. Other cellular responses include inhibition of the Na⁺/H⁺ antiporter and the induction of catecholamine synthetic enzymes. Signaling pathways linked to the I₁-imidazoline receptor are reportedly similar to those of the interleukin family; therefore, I₁-receptors may be among the family of neurocytokine receptors [35].

Rilmenidine is an I₁-imidazoline receptor-selective antihypertensive agent. It acts both centrally and also in the kidney by inhibiting the Na⁺/H⁺ antiporter, providing antihypertensive action that has been compared with the efficacy of diuretics, beta-adrenergic blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors. While this agent is often used in addition to conventional agents, the tolerability and beneficial effects of this oxazoline (and moxonidine) warrant consideration of the oxazoline antihypertensives as first-line agents. Similar to moxonidine (discussed below) data support the role of this agent in the management of hypertension, suggesting important roles in special populations: patients with diabetes mellitus, dyslipidemia (due to beneficial effects on the metabolic syndrome), and chronic kidney disease (reduced microalbuminuria in patients with type 2 diabetes and hypertension). Rilmenidine has been reported to reduce left ventricular hypertrophy to a similar degree to other reference agents in patients at risk [36].

Moxonidine shares rilmenidine’s favorable effect in the face of insulin resistance.

Animal models suggest that moxonidine has a beneficial effect on insulin resistance and the metabolic syndrome resulting in improved glucose uptake and utilization and lowering lipid levels [37]. Metabolic and antihypertensive effects of moxonidine and moxonidine plus irbesartan in patients with type 2 diabetes mellitus and mild hypertension: a sequential, randomized, double-blind clinical trial [38]. Evidence also suggests that moxonidine may attenuate the sympathetic overactivity associated with the development and progression of chronic renal failure [39].

Dexmedetomidine and Etomidate

Dexmedetomidine is a selective adrenergic agonist that also possesses affinity for imidazoline receptors. Clinical studies have demonstrated that dexmedetomidine causes sedation and impairs memory [40]. This agent finds applications in critical care and operative care settings and should only be used where advanced airway and supportive care skills are available. Typical applications are for short-term perioperative and critical care sedation. Dexmedetomidine has been used as an adjuvant during anesthesia to augment sedation, anxiolysis, amnesia, and analgesia and reduce anesthetic and opioid requirements and particularly for its sympatholytic and cardiovascular stabilizing effects (similar to clonidine) in ventilated patients. Dexmedetomidine has been shown to blunt the sympathetic response to laryngoscopy, but impairs cognition and delays postanesthesia recovery [41]. The effect of dexmedetomidine on the adjuvant propofol requirement and intraoperative hemodynamics during remifentanyl-based anesthesia [42, 43]. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions [44]. While some anesthetic agents may increase the QT interval, a decrease in the QTc intervals has been measured after the administration of dexmedetomidine to pediatric patients undergoing sevoflurane anesthesia [45]. Since

dexmedetomidine does not affect the synthesis, storage, or metabolism of neurotransmitters or block receptors, its hemodynamic effects may be reversible with vasoactive drugs [46].

Adverse effects reported with dexmedetomidine use include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, and hypoxia [46–48]. First-degree or second-degree atrioventricular block has been observed in overdose. Adverse events associated with dexmedetomidine are usually observed during or briefly after loading of the drug [49].

Dexmedetomidine has found application in the management of alcohol withdrawal. Approaches to augmentation of therapy for patients with severe alcohol withdrawal after the failure of aggressive and symptom-guided benzodiazepine administration are not well standardized in the literature [50, 51]. In a small study of dexmedetomidine use as an adjunct to lorazepam and/or propofol, dexmedetomidine use was associated with less need for endotracheal intubation, quicker transfer to a lower level of care, and shorter hospital stays [52]. Other studies support the use of dexmedetomidine in severe alcohol withdrawal, citing reduced benzodiazepine requirements, low rates of mechanical ventilation, reduced alcohol withdrawal scores, and other benefits [53]. However, a single-site retrospective study comparing benzodiazepine use alone with dexmedetomidine *or* propofol therapy and adjusted for pneumonia or respiratory failure related to seizures prior to ICU admission suggests that adjunctive therapy with dexmedetomidine or propofol did not alter ICU course. The authors note that adjuncts to benzodiazepine therapy are usually selected in cases of severe withdrawal requiring high benzodiazepine doses and may reduce the amount of benzodiazepine required and facilitate the bedside titration of drugs to sedation goals, but did not have an appreciable effect on the course of patients with severe alcohol withdrawal syndrome [54].

Successful use of dexmedetomidine in the treatment of baclofen withdrawal after removal of an intrathecal baclofen pump from a 15-year-old patient with spastic quadriplegia and cerebral palsy has also been reported [55]. Expanded use

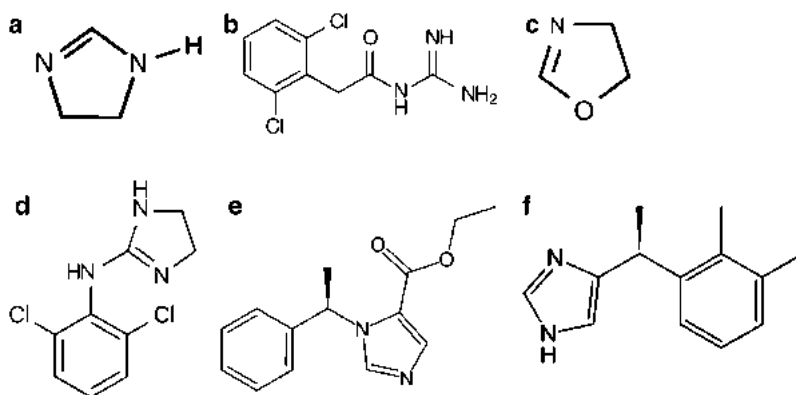
of dexmedetomidine on the generic market may facilitate broader application and future study of this agent.

Dexmedetomidine at a glance	
Indications, adults	Sedation of mechanically ventilated patients Procedural sedation of non-intubated patients Awake fiber-optic intubation
Administration	Continuous infusion with/without loading infusion
Precautions	Not recommended for use in those <18 years of age Reduce dosage in renal or hepatic impairment Heart block Ventricular dysfunction Increased risk of bradycardia and/or hypotension in patients with diabetes, chronic hypertension, hypovolemia, and the elderly Withdrawal symptoms in patients on infusion >24 h when discontinued abruptly Pregnancy category C
Drug interactions	Additive effects with vasodilators, negative chronotropic drugs, anesthetics, opioids, and sedatives. Consider dose reduction
Adverse effects	Hypotension, bradycardia, dry mouth, transient hypertension (upon loading), and sinus arrest

Many clinicians have experience with the imidazoline derivative etomidate, and some properties of dexmedetomidine may be better understood in that context. Etomidate, a predecessor of dexmedetomidine, is a widely used induction agent in emergency medicine and critical care, favored for its rapid onset, brief duration of action, cardiovascular stability (lack of hypotensive effect when compared with other imidazoline derivatives such as midazolam [56]), and lack of histamine release. Unfortunately, etomidate is also an inhibitor of 11-beta-hydroxylase, the enzyme responsible for the conversion of 11-deoxycortisol to cortisol [57–59]. Reports have long suggested that the use of etomidate may increase mortality in critically ill patients [60]. Meta-analyses of single-dose etomidate for rapid sequence induction in septic patients have further supported concern regarding adrenal

Fig. 1 Chemical structures of imidazoline, guanidine, and oxazoline compounds.

(a) A 2-Imidazoline. (b) Guanfacine. (c) Oxazoline ring. (d) Clonidine. (e) Etomidate. (f) Dexmedetomidine



suppression and potentially associated higher mortality rates [61]. While there may be some methodological issues with this and similar studies to date and while observed effects of etomidate on mortality may be multifactorial [62] and independent of glucocorticoid replacement [63, 64], the use of alternative agents may be well advised and further randomized controlled study is suggested.

Given the similarity between etomidate and dexmedetomidine, concern has been raised regarding the latter's potential to cause adrenal suppression and increase mortality. A three-arm study (control with conventional induction and anesthesia, etomidate bolus, and dexmedetomidine loading + maintenance infusion) that enrolled 99 pediatric patients scheduled for congenital heart disease corrective surgery found that suppression of the adrenal cortex occurred in all three groups, function returned to baseline within 24 h of anesthesia induction, and the adrenal cortex function inhibition produced by etomidate is much more significant than that found in the control and dexmedetomidine groups [65].

Clinical Pharmacology

The chemical structures of clonidine and other imidazoline and oxazoline compounds are shown in Fig. 1. Clonidine is absorbed completely and rapidly from the gastrointestinal tract with onset of action in 30–60 min and essentially 100% bioavailability. Peak effects have been

reported to occur at 2–3 h with a duration of 8 h when administered in therapeutic amounts [17]. Topical imidazolines are well absorbed through ocular and nasal mucosa and the gastrointestinal tract. Although clonidine is excreted predominantly unchanged through the kidney, other imidazolines, guanidine, and oxazoline compounds vary in terms of their clearance mechanisms [66–69].

As might be inferred from the diverse use of clonidine mentioned earlier, the drug has been available in a variety of doses and formulations ranging from tablets to drops, solutions for injection, transdermal patches, and ophthalmic rods [70]. Systemic effects may result from the topical use of imidazolines. The use of clonidine 0.5% eye drops intended to treat open-angle glaucoma has been noted to lower substantially the systemic blood pressure [71].

Transdermal delivery of imidazolines is effective, but the conversion from oral to transdermal dosing is not predictable, presumably because of interpatient variability in transdermal absorption. Transdermal dosing of clonidine always should begin with a patch designed to deliver 0.1 mg/24 h applied once every 7 days to avoid accidental hypotension or intoxication [72]. The rate of drug absorption from patches also varies with the site of application on any given individual [73]. The use of transdermal delivery systems has resulted in unintentional drug transfer. Used transdermal patches of clonidine contain large residual amounts of medication. The high concentration of clonidine in the patches is required to assure

steady-state delivery of clonidine over the life of the patch. For example, a 0.3 mg/24 h clonidine patch contains 7.5 mg/10.5 cm [2] of clonidine before use and may deliver approximately 2.1 mg clonidine after the recommended 1 week of use, theoretically leaving about 5.4 mg clonidine in the discarded patch [74].

Discarded patches may pose a particular hazard to toddlers, who might retrieve these after they are discarded and then wear the patch or, worse, swallow them or suck or chew on them, liberating toxic amounts of clonidine [75]. Inadvertent parent-to-child transfer of a transdermal clonidine patch resulting in toxic effects in the toddler also has been reported [76]. In addition, we have witnessed hypotension resulting from excess drug delivery when multiple transdermal patches were worn by a confused elderly patient who mistakenly placed new patches of medication without removing the old transparent patches, which she had difficulty locating once they were placed on her skin.

Dexmedetomidine is metabolized by the liver via glucuronidation and cytochrome P450 prior to renal clearance of metabolites; therefore, this drug should be used with caution in those with hepatic impairment [77]. Of note, no significant gender or geriatric differences in pharmacokinetics have been observed with dexmedetomidine use, and pharmacokinetics are similar to those in normal patients for patient with renal impairment (Cr Cl <30 mL/min) [78].

Pharmacokinetics of Selected Imidazoline and Guanidine Drugs

Clonidine

Volume of distribution: 3.2–5.6 L/kg; 0.96 L/kg in children [20]

Protein binding: 20–40%

Active metabolites: None reported

Mechanisms of clearance: 40–60% excreted unchanged via the kidney

Elimination half-life: 12–16 h

Dexmedetomidine (linear intravenous pharmacokinetics)

Volume of distribution: V_{ss} (steady state) 118 L

Distribution half-life: 6 min

Protein binding: 94% (predominantly serum albumin) with negligible displacement by fentanyl, ketorolac, theophylline, digoxin, and lidocaine

Active metabolites: NA

Mechanism of clearance: Hepatic (glucuronidation and p450 CYP2A6); 95% of metabolites excreted in urine

Elimination half-life: 2 h

Guanabenz

Volume of distribution: 7.4–13.4 L/kg

Protein binding: 90%

Active metabolites: None reported

Mechanisms of clearance: Hepatic (<1% excreted unchanged via kidney)

Elimination half-life: 12–14 h

Guanfacine, immediate release

Volume of distribution: 6.3 L/kg

Protein binding: human plasma 64%; also binds moderately to erythrocytes

Active metabolites: NA

Note: No appreciable first pass effect

Mechanism of clearance: p450 (CYP3A4), glucuronidation, sulfation, and hepatic and renal clearance

Elimination half-life: 16–21.4 h

Oxymetazoline

Volume of distribution: NA

Protein binding: NA

Active metabolites: None reported

Mechanisms of clearance: 30–72% renal, 10–22% fecal, and 40–50% excreted unchanged

Elimination half-life: 5–8 h

NA, no information available

Data (pharmacokinetics table) from references 68–71, 79–83

Pathophysiology of Toxic Effects

While death due to unintentional pediatric exposure to these agents is relatively uncommon, overdoses are common and sequelae may be

substantial. Although adverse effects may be expected to increase in magnitude with escalating doses of imidazolines, toxicity does not always correlate well with dose, and even 1–2 doses of an agent such as clonidine may produce severe effects in a pediatric patient [82–84]. Severe intoxication with clonidine may produce transient hypertension followed by hypotension, coma, bradycardia, apnea, hypothermia, and miosis secondary to sympatholysis.

Initial speculation regarding the mechanism of action attributed the sedation, oral hyposecretion, and antihypertensive effects of clonidine to its activation of brainstem α_2 -adrenergic receptors [85]. Stimulation of these receptors results in inhibition of the nucleus tractus solitarius and ultimately in decreased norepinephrine release. This reduced sympathetic outflow from the thoracolumbar spinal tracts to the periphery has been thought to be the primary basis for the cardiovascular and neurobehavioral effects of these drugs [86, 87]. Sedation is thought to result primarily from the α_2 -agonist actions of imidazolines and guanidines, such as clonidine and guanabenz, in the locus coeruleus where this action may stimulate gamma-aminobutyric acid release [88]. The peripheral sympathomimetic effects of clonidine and other α_2 -agonists in this class (e.g., transient vasoconstriction and initial rise in blood pressure) have been explained on the basis of postsynaptic α_2 -agonist actions in vascular smooth muscle [89]. The presynaptic α_2 -receptor agonist actions of these drugs at central and peripheral adrenergic synapses, resulting in suppression of norepinephrine release, also may contribute to the antihypertensive effects of clonidine. Some evidence suggests that endogenous opioid-like substances may contribute to the sedation caused by clonidine [90]. If true, this may provide a physiologic basis for the anecdotally reported amelioration of mental status and apnea associated with clonidine overdose in children by naloxone.

The hypotensive effect of clonidine has been associated with dose-dependent release of nitric oxide and resultant vascular relaxation. Animal studies have demonstrated reversal of this effect through nitric oxide synthase inhibition [91]. The role of NO contributing to hypotension after

administration of clonidine suggests a potential antidotal role for methylene blue in severe imidazoline poisoning.

The development of more potent α_2 -agonists did not yield compounds with improved antihypertensive properties, leading to the hypothesis that the central antihypertensive action of these agents may result in part from agonist actions at specific imidazoline receptors. As previously noted, investigations of structure–activity relationships of compounds synthesized in an effort to reduce or eliminate the adverse effects (e.g., sedation) of clonidine led to development of the oxazoline class of antihypertensives (e.g., rilmenidine).

Parallels between effects resulting from the stimulation of opiate receptors and central α_2 -adrenergic receptors have led to speculation about a potential relationship between these receptors. This speculation is reinforced by the successful use of clonidine in detoxification regimens for opiate dependence [92, 93] and as a spinal analgesic [25–28]. Current hypotheses regarding such a link between opiate receptors and central α_2 -adrenergic receptors remain unproven.

In summary, clonidine and related drugs are central α_2 -adrenoceptor agonists that also bind to specific imidazoline receptors. These agents stimulate postsynaptic α_2 -adrenergic receptors in the vasomotor center of the medulla enhancing activity of inhibitory neurons and resulting in decreased sympathetic outflow with apparent increase in parasympathetic tone (resulting in decreased heart rate and blood pressure – postulated to be the result of endogenous opioid release). Some agents may also act peripherally on α_1 -receptors to cause a pressor response that is usually overshadowed by the central effects in therapeutic doses, but which may cause significant hypertension early in overdose. It is thought that some agents may also cause a peripheral presynaptic α_2 -agonist effect decreasing norepinephrine release and further potentiating the hypotensive effect of these agents. Finally, clonidine is also considered a partial α -receptor agonist due to its ability to inhibit the effects of other α -agonists [94].

Clinical Toxicology of Dexmedetomidine

As a selective and specific agonist of central α_2 -receptors, the binding of dexmedetomidine to receptors in the brain and spinal cord may be expected to inhibit neuronal firing resulting in hypotension, sedation, bradycardia, and analgesia. Of note, dexmedetomidine is severalfold more specific for the α_2 -adrenoreceptor than clonidine, a compound for which richer overdose data exists, and dexmedetomidine might be expected to behave differently. Furthermore, dexmedetomidine has an $\alpha_2:\alpha_1$ activity ratio of 1620:1 compared with 220:1 for clonidine [95].

Medication errors with dexmedetomidine have been reported. Misadventures may have resulted from clerical/transcription errors, unfamiliarity with the medication (mcg/kg/min administered as with many critical care medications instead of mcg/kg/h), and high patient acuity and high patient/staff ratios. Dexmedetomidine administration at higher than currently recommended doses per the package insert has been studied and appears to be well tolerated. Some work has demonstrated a biphasic response to dexmedetomidine administration with hypotension at low doses and hypertension at higher doses (though this has not been noted in the illustrative overdoses discussed below). The hypertensive effect of dexmedetomidine seen in a fraction of patients is perhaps due to dexmedetomidine activity at peripheral vascular α_{2b} -receptors as opposed to the activity at central α_{2a} -receptors where sedation and analgesia are believed to be mediated [48, 96–99].

Dexmedetomidine overdose in three perioperative patients has been reported to result in no hemodynamic instability but in oversedation which resolved within the hour. Magnitudes of the doses administered were as follows: one intraoperatively as an adjunct to anesthesia (192 mcg over 20 min) and two postoperatively (4 and 2 mcg/kg/h instead of 0.4 and 0.2 mcg/kg/h; 0.5 mcg/kg/min instead of 0.5 mcg/kg/h). No other sequelae were reported during the patients' hospitalizations.

While dexmedetomidine is reputed to have a substantial safety margin, an erroneous ninefold overdose of dexmedetomidine administered to a 3-year-old child (loading bolus of 100 mcg administered instead of 11 mcg as intended) tells a cautionary tale. The overdose resulted in miosis, bradypnea, bradycardia, hypotension, and deep sedation. The patient rapidly became unconscious; vital signs shortly after the overdose were heart rate 65/min, respiratory rate (RR) 8–10/min, blood pressure 70/40 mm of Hg, and oxygen saturation (SpO₂) 85%. The patient's respiratory depression was successfully managed with the administration of oxygen by mask with RR and SpO₂ improving to 14–16/min and 98%, respectively, over about 10 min. Endotracheal intubation was avoided. Boluses of normal saline and epinephrine infusion (tapered over 7 h) were used for cardiovascular support. The patient became responsive to painful stimuli in 3 h and was oriented after the passage of 7 h. Blood glucose was reported to remain normal [100].

An overdose in a 21-month-old female undergoing sedation for MRI resulted from pump misprogramming at a rate of 1 mcg/kg/min instead of 1 mcg/kg/h and resulted in administration of 196 mcg more dexmedetomidine over 20 than actually ordered. Upon discontinuation of the infusion, all vital signs were monitored and remained within normal age-adjusted parameters, the toddler returning to an Aldrete score of 9 (sufficient for discharge from the recovery room) within 20 min and an Aldrete score of 10 (baseline neurologic function) within 2 h [101].

The teratogenicity of dexmedetomidine is not well studied. The drug is known to cross the placenta. Similarly, long-term use of the drug is not well studied, but one might speculate that a withdrawal syndrome similar to that seen with clonidine might result from withdrawal after extended use. Adverse effects of dexmedetomidine may include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, first- or second-degree atrioventricular block, and hypoxemia. Adverse effects are generally associated with loading doses or overdoses of dexmedetomidine, and dose reduction may minimize the adverse effects attributable to the use of this medication [46, 48].

Drug Interactions

The use of some imidazolines in conjunction with moderate or potent CYP1A2 inhibitors is contraindicated. For example, simultaneous use of tizanidine and fluvoxamine, a CYP1A2 inhibitor, resulted in a 33-fold increase in the tizanidine AUC (plasma drug concentration-time curve), potentially leading to exaggerated clinical effects [102]. Similarly, tizanidine should not be used in conjunction with fluoroquinolone antibiotics due to potential elevation of the serum tizanidine concentration [103].

The metabolism of clonidine is not well described, leaving some undocumented puzzles for the clinician regarding potential enzyme-mediated drug interactions. Current research suggests a major role for CYP2D6 in the metabolism and clearance of clonidine with relatively minor contributions by CYP1A2, CYP3A4, CYP1A1, and CYP3A5 [104]. Many hundreds of reported and potential drug interactions exist for clonidine. Among these are contraindications to the use of epidural clonidine in patients on blood thinners and cautions regarding amplification of the effects of sedative agents and agents with sedative side effects (increased sedation), beta-blockers and some calcium channel blockers (hypotension and bradycardia), digoxin (bradycardia), antidepressants (reduced antihypertensive effect), agents that promote orthostasis, and more [105]. Development of corneal lesions has been reported in rats treated with a combination of clonidine and amitriptyline within 5 days [106]. The combination of clonidine and high intravenous doses of haloperidol in patients with alcoholic delirium may lead to QT prolongation and arrhythmia [107].

Since a significant proportion of a guanfacine dose may be metabolized by CYP 3A4, inducers and inhibitors of this enzyme are best avoided during guanfacine therapy [79]. Although it has been suggested that dosage adjustments may be indicated when coadministering CYP3A4 inhibitors, it is likely safer to avoid concomitant administration of agents known to interact with guanfacine and other agents with similar metabolism. Interactions with cyclic antidepressants, azoles, MAOI, amphetamines, erythromycin,

and many other medications have been reported; clinicians are advised to check this extensive list.

Interestingly, a drug interaction between guanfacine and NSAIDs has been reported in a canine model. Indomethacin was reported to prolong the initial hypertensive response and to lessen the hypotensive effect of intravenously administered guanfacine. A less pronounced effect was noted with aspirin and ibuprofen [108]. Although the author is unaware of any trial of antidotal NSAID use in guanfacine or similar overdose, this finding suggests that such a future role may be plausible. On a cautionary note, administration of phenylbutazone decreases the pressor effect of guanfacine and enhances the hypotensive response in this same study. Accordingly, patients who use guanfacine and NSAIDs should be followed closely.

Clinical Presentation and Life-Threatening Complications

On the basis of numerous case reports and case series [109–116], the life-threatening effects of acute imidazoline intoxication may be characterized by initial hypertension and reflex bradycardia, followed by hypotension with bradycardia and a cyclical pattern of agitation alternating with coma/respiratory depression (bradypnea or apnea) that typically responds to vigorous physical stimulation. Syncope may result from the use or misuse of agents in this class. Peripheral vasoconstriction may manifest as skin pallor. Pupillary miosis is common (as a result of α_2 -receptor stimulation that decreases the prejunctional availability of norepinephrine leading in turn to reduced α_1 -sympathetic pupillary dilation and resulting in parasympathetically controlled miosis via muscarinic stimulation).

It is important to note that imidazoline ingestion may occasionally result in mydriasis [117] and that ocular administration of clonidine to patients with glaucoma may also result in mydriasis [118, 119]. Hypotonia, hyporeflexia, and hypothermia also may be present in severe intoxication. Bowel sounds may be reduced or absent, indicating gastrointestinal hypomotility.

Prominent α_2 -effects associated with imidazolines include sedation and reduced salivation. These common adverse effects of clonidine and guanabenz (compounds that possess strong α_2 -agonist properties) have limited their use at recommended doses by some patients. Although oral hyposalivation may be used to help characterize the toxidrome, this effect is less pronounced with oxazolines, such as moxonidine and rilmenidine, which have markedly reduced α_2 -agonist potency and higher selectivity for imidazoline receptors.

Abrupt cessation of clonidine has been associated with a hyperadrenergic syndrome characterized by what commonly is referred to as *rebound hypertension*. This effect may be dose dependent, may last up to a week, and has not been observed so far with the newer oxazoline group of antihypertensives [120, 121] although it may be prudent to taper these agents as is done with clonidine upon discontinuation. Clonidine doses are typically reduced over 2–4 days when discontinuing therapy in order to avoid rebound hypertension [106].

Diagnosis

A broad differential diagnosis should be considered in patients suspected of imidazoline, guanidine, or oxazoline drug toxicity, as for all patients presenting in coma (see ► Chap. 19, “Toxicant-Induced Alterations in Consciousness”).

The sympatholytic toxidrome may be characterized by an initial hypertensive phase followed by bradycardia, hypoventilation, sedation or coma, and miosis. Although uncommon, heart block may occur or SA nodal conduction may be affected. Hallucinations and seizures have been observed. The toxicologic differential diagnosis of central α_2 -agonist/imidazoline poisoning includes intoxication with opioids, β -blockers, calcium channel blockers, and digoxin (which may lead to increased automaticity/dysrhythmias unlikely with imidazolines). Like clonidine, each of these agents may be lethal, and each is potentially lethal to a toddler with a single dose. The differential diagnosis may extend to phenothiazines (e.g., chlorpromazine), true alpha blockers

(such as phentolamine, though this may often be distinguished by reflex tachycardia), acetylcholinesterase inhibitors (i.e., organophosphates or carbamates), barbiturates, and other sedative-hypnotic agents. Although routine toxicology immunoassay screens generally do not include imidazolines, these compounds can be identified in clinical specimens (e.g., urine) by gas chromatography/mass spectroscopy when clinically or forensically warranted. Where forensic concerns exist, it may be warranted to send specimens following chain-of-custody procedures.

Treatment

Compulsive supported care is the mainstay of alpha agonist toxicity. Because imidazoline compound-intoxicated or guanidine compound-intoxicated patients may develop light coma with or without apneic spells, special attention must be paid to airway and ventilatory status. Systemic oxygenation status and blood glucose concentration should be monitored early in the diagnostic evaluation. Given the potential for inhibition of glycogenolysis secondary to sympatholytic actions, the clinician should consider these patients to be at increased risk for hypoglycemia. Endotracheal intubation and mechanical ventilatory support are rarely required but may be warranted in severe intoxications. Successful management of imidazoline poisoning often has been limited to close observation with physical stimulation to terminate apneic episodes [111]. This may be especially true for unintentional pediatric exposures where the transient hypertension that follows ingestion does not require treatment.

Due to the potential for these agents to cause early central nervous system depression, many practitioners advise against the administration of activated charcoal. In the right setting, patients who present within 1 h of ingestion of clonidine or similar imidazoline tablets and those who have ingested clonidine transdermal patches might receive a single dose of activated charcoal (level of evidence III). However, this must be done cautiously and under close observation because

of the possibility of alterations in the patient's mental status and subsequent aspiration. Activated charcoal has not been shown to alter the outcome of patients poisoned by these agents. Whole-bowel irrigation may decrease gastrointestinal transit time of ingested transdermal patches and reduce absorption of the highly concentrated residual medication therein (level of evidence III) [75]. Completely expose all patients, examine for signs of trauma and injection sites, and remove any adherent clonidine patches.

Transient hypertension may be observed in patients who present early after overdose. This hypertension is generally of brief duration and often requires no therapy [122].

Severe hypertension following overdose can be treated (if necessary for signs of end-organ injury) only with short-acting, readily controlled vasodilator treatment (e.g., nitroprusside or nitroglycerin by intravenous infusion and titrated to effect) because it is likely to be transient and followed by hypotension as central sympatholytic effects become predominant.

Intravenous administration of crystalloid is the first-line therapy for hypotension in centrally acting antihypertensive overdose. The use of atropine for bradycardia in normotensive or hypertensive individuals may precipitate or prolong hypertensive crisis in individuals with a reflex increase in vagal tone secondary to peripheral vasoconstrictive effects. We recommend that atropine be avoided in imidazoline-poisoned patients except in the event of clinically significant bradycardia and hypotension (grade III recommendation). Intravenous norepinephrine, with or without atropine, is an appropriate choice of pressor in the treatment of hypotension associated with bradycardia [123].

Hypothermia can be managed with active or passive rewarming as indicated. Benzodiazepines are generally considered first-line therapy for imidazoline-induced seizures not caused by hypoxemia or hypoglycemia (grade III recommendation). Extracorporeal removal by hemodialysis has not been shown to be efficacious in enhancement of clonidine clearance [66], and neither is dialysis likely to be effective in cases of human overdose with xylazine due to its large volume of distribution [124].

There is no generally accepted specific antidotal therapy for imidazoline poisoning. Imidazoline-induced coma, respiratory depression, and miosis have suggested a role for intravenous naloxone as a means of reversing life-threatening clinical manifestations of toxicity, and there has been speculation regarding potential imidazoline-mediated release of an endogenous opioid-like substance without documentation. Reports of the efficacy of this treatment are inconsistent and are confounded by the typically cyclical course of the central nervous system effects of untreated poisoning [115, 116, 125–128]. It is possible that physical stimulation associated with the administration of this medication may be responsible for some reports of the efficacy of naloxone in reversing apnea and lightening sedation in some cases of imidazoline intoxication. Administration of naloxone to clonidine-poisoned children also has been reported to result in hypertension [129]. In cases in which naloxone has been suggested to have reversed clonidine-induced coma, the “response” has been transient and consistent with the untreated, cyclical course of the intoxication. The case of a 3-year-old child treated with naloxone after ingestion of 30 mL of 0.05% tetrahydrozoline solution reported by Holmes and Berman [130] illustrated this transient response. Two hours after the ingestion, incontinence of urine, hypotonia, and lethargy were noted. Naloxone (1.5 mg) was administered intravenously, followed by improvement in sensorium and increased heart rate and blood pressure. The effect was short-lived, however, and 10 min later the child again became somnolent with decreased pulse and blood pressure. The child subsequently was awake and alert approximately 8 h after ingestion without further administration of naloxone.

Despite the lack of convincing evidence that naloxone administration is beneficial in clonidine poisoning, its efficacy has not been excluded definitively by controlled clinical trials. If one is faced with the prospect of impending endotracheal intubation after the failure of vigorous stimulation to arouse an imidazoline-intoxicated patient in coma, it seems reasonable to proceed with an empirical trial of relatively high-dose naloxone (0.4–10 mg intravenously exercising

care to avoid precipitating withdrawal in opioid-dependent patients) as long as this intervention does not delay the institution of appropriate supportive care measures (level of evidence III). Perhaps the most appropriate empirical use of naloxone is in the setting of suspected or confirmed imidazoline intoxication to address the possibility of unrecognized or concomitant opioid toxicity.

Tolazoline, also an imidazoline compound, is a mixed central and peripheral α_2 -antagonist that has been used in the treatment of imidazoline intoxication, based on its theoretical potential for reversal of the central sympatholytic and peripheral sympathomimetic actions of imidazoline and guanidine drugs. Tolazoline use is not recommended, however, due to mixed clinical case experience and reported instances of hypertension, tachycardia, and arrhythmias after its administration [131]. Yohimbine, an indole derivative with central α_2 -antagonist actions, and idazoxan, an imidazoline and α_2 -adrenergic receptor antagonist, similarly lack sufficient supporting clinical evidence of efficacy and safety to recommend their use in the treatment of α_2 -agonist toxicity [132, 133].

Indications for ICU Admission in Clonidine and Other Imidazoline Derivative Poisoning

Coma/respiratory depression

Bradycardia/hypotension

Rebound hypertension from abrupt antihypertensive cessation

Ingestion of transdermal patch

Key Points in the Evaluation and Management of Clonidine and Other Imidazoline Derivative Poisoning

1. Severe toxicity, especially in young children, has resulted from the ingestion of small amounts (<15 mL) of over-the-counter topical and prescription imidazoline and guanidine preparations.
2. Clinical toxicity frequently presents as cyclical coma/respiratory depression alternating with agitation.

3. Appropriate treatment commonly is limited to routine supportive care and close observation, with physical stimulation as needed for episodes of apnea and intubation when required.
4. Although to date there is no convincing evidence that it reverses imidazoline-induced central nervous system depression, the empirical administration of high-dose intravenous naloxone in respiratory depression refractory to physical stimulation seems reasonable as long as it does not delay the provision of appropriately more aggressive supportive care (i.e., endotracheal intubation and mechanical ventilation).
5. Atropine use should be avoided in imidazoline-poisoned patients except in patients with clinically significant bradycardia and hypotension.
6. There is currently no antidote for centrally acting α_2 -agonist poisoning that has proved safe and effective, and the use of existing α_2 -adrenergic antagonists is not recommended.

Disposition

All symptomatic patients with clonidine or similar imidazoline exposures and all those who ingest clonidine transdermal patches should be admitted to a setting capable of close observation and critical care response. The onset of symptoms following the ingestion of transdermal clonidine patches may be delayed, and observation for a minimum of 24 h has been recommended since there are relatively few data regarding these ingestions and the amount of drug contained in a single patch is substantial (grade III recommendation) [134]. Whole-bowel irrigation with PEG-ELS may decrease GI transit time for ingested patches; however, insufficient data exist regarding benefits to clinical course and outcome. Those who present without symptoms shortly after ingestion must be observed in a setting capable of managing airway and hemodynamic

emergencies (emergency department, intensive care unit) due to the potential for decompensation within a few hours of overdose. In a study of 47 young children aged 9–84 months presenting with clonidine overdose, bradycardia occurred in 25, and apnea or depressed respiration was noted in 18. Thirty-four patients had symptoms within 1 h of presentation, but no patient was reported to have further clinical deterioration more than 4 h post-presentation [116].

An acetaminophen level should be obtained for all patients with suicidal ingestions, other coingestions should be considered, and psychiatric consultation is indicated. If a patient who has ingested a non-transdermal patch form of clonidine/imidazoline remains asymptomatic for 6 or more hours and is not suicidal, they may be discharged. Conservative practice suggests that those so discharged should be provided with return precautions and should have a reliable mechanism for return to the hospital in case of any unlikely delayed adverse effect.

<p>Criteria for ICU Discharge in Clonidine and Other Imidazoline Derivative Poisoning</p> <p>Intact sensorium</p> <p>Stable hemodynamic status</p>

Special Populations

Pregnant Patients

The teratogenicity of common prescription and over-the-counter imidazolines has not been studied completely. Given the relatively high fetoplacental penetration of imidazolines, developing fetuses are at potential risk of toxicity. Clonidine crosses the placenta readily with cord blood levels similar to maternal blood levels at delivery [135]. Maternal hypotension and hypoxia resulting from severe imidazoline intoxication also might result in reproductive toxicity. Fetal bradycardia is reported to occur with increased frequency in women who are administered epidural clonidine concomitantly with an

epidural anesthetic in labor [136, 137]. Infants born to women treated with oral clonidine late in pregnancy uncommonly may experience transient neonatal hypertension [138, 139]. Although high-dose animal studies of clonidine revealed effects on uterine blood flow, intra-amniotic pressure, and fetal oxygenation [140, 141], clonidine generally does not seem to be associated with significant adverse effects at doses that are nontoxic to the mother [142–144]. A case report of an infant with multiple severe birth defects (Roberts syndrome) born to a mother treated with 0.3 mg/day of clonidine throughout pregnancy for hypertension suggests, however, the preferable use of an alternative agent for the treatment of hypertension during pregnancy [145], with clonidine considered relatively contraindicated in this context. Clonidine crosses the placenta and is also secreted in breast milk [146].

Epidemiologic studies have not revealed definitive evidence of associations between the use of oxymetazoline and birth defects, despite one study in which maternal use of oxymetazoline, phenylpropanolamine, and pseudoephedrine revealed an association with gastroschisis. Pseudoephedrine and phenylpropanolamine apparently accounted for the major portion of this association [147–150]. A nonreactive nonstress test and late decelerations have been reported, however, in a patient presenting at 41 weeks' gestation. The fetus was delivered due to late decelerations and term pregnancy. The mother reportedly had overused an oxymetazoline-containing nasal spray before examination. Fetal heart rate changes were thought to result indirectly from decreased uterine perfusion or perhaps through a direct effect on the fetal central nervous system [151]. The safest policy is to advise against the use of imidazolines during pregnancy.

Pediatric Patients

Infants and young children are relatively susceptible to systemic effects from topical imidazoline use [152]. Pediatric patients also are at relatively high risk for poisoning due to their smaller body mass and greater likelihood of ingesting

imidazolines intended for topical use from containers supplied with dropper-type or spray-type dispensers resembling baby bottle nipples. Abundant case experience suggests that younger children are at particularly high risk for imidazoline-induced central nervous system depression and respiratory failure [109, 110, 113–116, 152, 153]. Clonidine has been found in human breast milk at concentrations about twice those in maternal blood, but the significance of this finding to nursing infants is unknown [135, 154].

Geriatric Patients

The elderly seem to be at increased risk of systemic adverse effects from topical imidazoline use. Bradycardia and hypotension have been reported in an elderly patient [155]. Some caution against the use of these drugs in the elderly seems appropriate.

Other Special Populations

Clonidine may be used to relieve symptoms in patients withdrawing from opioids, alcohol, or nicotine. Clonidine is used best in conjunction with other agents in the process of opioid or alcohol detoxification [156, 157]. Monotherapy with clonidine is not recommended, and clonidine alone does not reduce the incidence of seizures or delirium. Alcohol-dependent patients also should receive benzodiazepines [158]. Care must be exercised in treating opioid-dependent patients with possible polysubstance abuse because clonidine may mask symptoms of life-threatening sedative-hypnotic or ethanol withdrawal [159].

Exposures and Poison Prevention

Tetrahydrozoline, naphazoline, oxymetazoline, and xylometazoline currently are used in nasal and ocular decongestants. These are available in a wide variety of sprays and drops available by prescription and over the counter. Ingestion of 2.5 mL of 0.05% tetrahydrozoline (1.25 mg) has

resulted in respiratory depression. Drowsiness, sweating, marked hypotension, and shock resulting from the inadvertent ingestion of small amounts of these agents by children were recognized and reported by the mid-1960s [109, 153].

While the use of topical or systemic imidazolines in children younger than age 6 years has not been recommended in the Western English language literature for many years, such indications may persist in the literature of other regions. Aside from the age of the patient, some factors suggested as contributors to the intoxication of young children with “therapeutic” use of imidazoline decongestants include the difficulty of administering drops to children and packaging inadequate for proper dosing of children [110]. Recent child-resistant packaging of some imidazoline delivery devices promises to reduce unintentional exposure to these products.

Despite numerous reports of imidazoline intoxication after ingestion of 2.5 mL of solution, availability of over-the-counter imidazoline-containing nasal and ocular decongestants remains widespread.¹¹¹² Poison-prevention efforts should focus on increasing public and professional awareness of the hazard posed by imidazolines and on the selection of safe packaging, use, and storage of these agents.

Adult intoxication with clonidine may result from patient’s efforts to treat opioid or alcohol withdrawal with clonidine. Several reports of intentional ingestion of clonidine patches to ameliorate withdrawal symptoms may be found in the literature [134, 160]. Patients should be instructed in the safe use of imidazolines upon prescription, and compliance with safe handling of these medications should play a role in patient selection for imidazoline therapy.

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Introduction

Beta receptor antagonists, or β -blockers, are used therapeutically for numerous conditions, including the long-term management of congestive heart failure, hypertension, migraine prophylaxis, and glaucoma. They can also be used for treatment of various movement disorders, social phobias, hyperthyroidism, and acute management of tachydysrhythmias. Toxicity from β -receptor antagonists is one of the most commonly encountered cardiac medications toxicologists encounter [1].

Clinically significant toxicity can occur when β -receptor antagonists can occur with therapeutic doses, drug-drug interactions, or overdoses. Toxicity at therapeutic doses typically occurs as a result of an adverse drug effect deriving from the normal physiologic properties of the drug, or from excessive systemic absorption after ocular instillation. One such example of the former would be the development of bronchospasm as a result of antagonism of pulmonary β -receptors in susceptible individuals. Drug interactions can cause serious toxicity with β -receptor antagonists, particularly bradycardia or heart block, resulting from the simultaneous use of a β -receptor antagonist with a cardioactive calcium channel blocker, such as verapamil or diltiazem. Some of the most serious manifestations of β -receptor antagonist toxicity occurs following intentional overdose or the administration of excessive doses.

Biochemistry and Clinical Pharmacology

Structurally, β -receptor antagonists are typically ethers of an aromatic group with a propylamine moiety bound to an isopropyl or similar group via the nitrogen terminus of the propylamine (Fig. 1). These agents share considerable structural similarity to the phenylethylamine β -receptor agonists. Beta receptor antagonists comprise a group of structurally related agents that act as antagonist at the β_1 -receptor, the β_2 -receptor, or both. In addition, these drugs are thought to exert varying degrees of antagonisms at β_3 - and β_4 -receptors, although the clinical relevance of this blockade is not entirely clear.

The β -receptor antagonists can be classified via several unique methods. Perhaps the most common method of classifying this class of drugs is based on their selectivity for the β_1 -receptor. Virtually all of the β -receptor antagonists used clinically are either selective for the β_1 -receptor or nonselective at both the β_1 - and β_2 -receptors (Table 1). It should be noted, however, that in overdose, selectivity is often lost and agents that are designed to provide antagonism exclusively at the β_1 -receptor may also inhibit the β_2 -receptor at supraphysiologic doses. Several of the β -receptor antagonists have unique pharmacologic properties, such as sodium channel blockade (also referred to as membrane stabilizing activity [MSA]), potassium efflux channel blockade, nitric oxide production, or intrinsic sympathomimetic activity (Table 1). Agents with intrinsic sympathomimetic activity have the potential for producing sympathomimetic effects during poisoning, which may limit the severity of the overdose. Lastly, β -receptor antagonists can be classified as being either lipophilic or hydrophilic. Those that are particularly lipophilic (e.g., propranolol) can readily cross the blood-brain barrier, thereby inducing central nervous system toxicity.

Pharmacokinetics

While there is variation among the different β -receptor antagonists, as a class most are

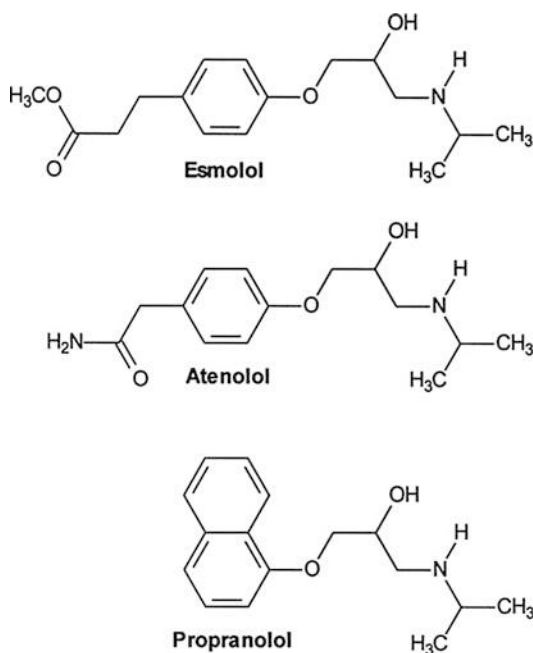


Fig. 1 Chemical structures of some common β -adrenergic antagonists. Note that the chemical side chain is widely conserved throughout this group

absorbed orally with a modest volume of distribution. However, some agents such as propranolol or carvedilol have an oral bioavailability of only 30%, whereas others, such as penbutolol or pindolol, have an oral bioavailability of nearly 100%. Certain β -receptor antagonists may be well absorbed following ocular application and result in high systemic concentrations [2–4]. Absorption after ocular administration is through the nasolacrimal duct and directly into the systemic circulation. Normal first-pass hepatic metabolism, a prominent feature of the oral administration of these agents, is thus bypassed.

Protein binding is quite variable, ranging from less than 10% for timolol to 98% for carvedilol. Most hepatically cleared β -receptor antagonists are metabolized by cytochrome P-450 2D6, an isoenzyme well known for its genetic polymorphism, as originally was shown for its role in debrisoquine oxidation [5, 6]. Although various 2D6 phenotypes have been described, they have not been shown to significantly influence the clinical course of β -receptor antagonist intoxication.

Table 1 β -Receptor antagonists

Agent	B1 selective	ISA	MSA	α -Receptor antagonist	Log D	Comments
Acebutolol	Yes	Slight	Slight	No	0.52	Most activity attributed to metabolite diacetolol
Alprenolol	No	Yes	Yes	No	0.68	
Atenolol	Yes	No	No	No	-2.03	
Betaxolol	Yes	No	Slight	No	0.56	
Bevantolol	Yes	No	No	Weak	1.07	
Bisoprolol	Yes	No	No	No	0.11	
Bopindolol	No	Yes	No	No	2.81	Nitric oxide production
Bucindolol	No	Slight	No	Yes	1.37	Nitric oxide production
Carteolol	No	Yes	No	No	-0.42	
Carvedilol	No	No	No	Yes	3.16	
Celiprolol	Yes	Slight	No	Yes	-0.07	
Esmolol	Yes	No	No	No	-0.22	
Labetalol	No	No	No	Yes	0.99	
Levobunolol	No	No	No	No	0.77	Nitric oxide production
Metipranolol	No	No	No	No	0.53	
Metoprolol	Yes	No	No	No	-0.34	
Nadolol	No	No	No	No	-0.84	
Nebivolol	Yes	No	No	No	2.36	
Oxprenolol	No	Yes	Slight	No	0.19	
Penbutolol	No	Slight	Slight	No	2.05	Serotonin release through 5HT _{1A}
Pindolol	No	Yes	Slight	No	-0.19	
Practolol	Yes	Yes	No	No	-1.26	Causes ocular and skin injury and sclerosing peritonitis
Propranolol	No	No	Yes	No	0.99	
Sotalol	No	No	No	No	-1.82	
Timolol	No	Minimal	No	No	-1.99	

Pathophysiology

Beta Receptors

Beta adrenergic receptors comprise a group of interrelated receptors, which have a guanine nucleotide binding protein (G protein) – linked ligand binding sites. These transmembrane receptors have varying affinities for a variety of agonists and antagonists. There are four subtypes of β -receptors (β_{1-4}) [7].

The β_1 -receptor is found primarily in the heart, where it is the most abundant type of adrenergic receptor. It is widely distributed throughout the heart and, when stimulated, results in increased chronotropy, inotropy, automaticity, and action

potential conduction velocity. Most of the clinically significant effects from β -receptor antagonist intoxication occur as a result of blocking the cardiac β_1 -receptor. In addition to the heart, the β_1 -receptors are also found in the bowel, kidney, posterior pituitary, and adipocytes. In healthy individuals, nearly 80% of the β -receptors in the body are β_1 , while 20% are β_2 . The β_3 -receptors account for a very small number of total β -receptors [8].

Like the β_1 -receptor, the β_2 -receptor is also found in cardiac tissue, although in a considerably lower density than the β_1 -subtype. The β_2 -receptors are also found on arterioles and veins, where they cause vasodilation, and on smooth muscles of the airways, where they cause relaxation.

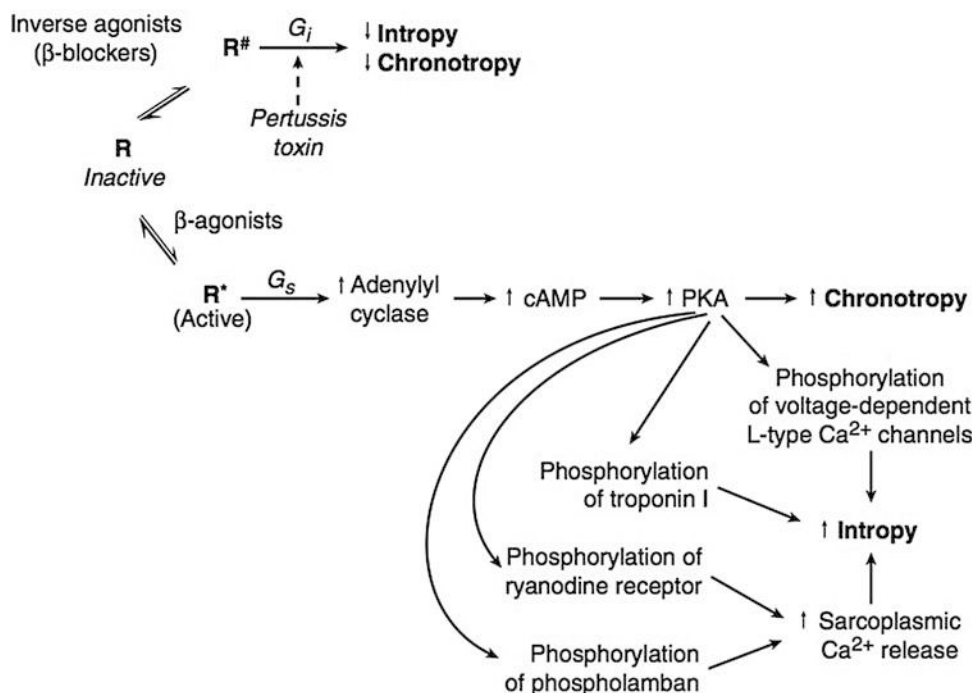


Fig. 2 Summary of where specific agents act in the cell. Isoforms of the β -adrenergic receptor and effects of their agonism. See text for further details. *cAMP* cyclic adenosine monophosphate, *PKA* protein kinase A

Most of the relevant toxicologic effects of the β_2 -receptor are due to the effects on the heart, arterioles, and airways. Beta₂ receptors are also found in the eye, uterus, skeletal muscle, pancreas, urinary bladder, spleen, liver, and intestines and throughout the gastrointestinal system.

The β_3 -receptor is best known for its action on adipocytes, in which the β_3 -receptors stimulate lipolysis. This receptor is also important in modulating the mast cell degranulatory response to immune system stimulation. The toxicologic significance of this receptor derives from its existence on the heart, however, where it may have a cardioinhibitory effect. The effects of the β_3 -receptor are most marked in patients with heart failure; however, as described subsequently, they may be important in the clinical manifestations of β -receptor antagonist intoxication and have a potentially significant influence on the response to therapy with adrenergic agents [7]. The β_4 -receptor is postulated to exist based on cardiostimulatory effects of β -receptor agonists that can be shown when the β_1 -, β_2 -, and β_3 -receptors are inhibited [7].

The physiology of β -receptors is complex [9, 10]. The β_1 -receptor (Fig. 2) exists in two forms – the active (R^*) and inactive (R) state, which exist in equilibrium. When a β -agonist binds to and stabilizes the R^* state, the equilibrium is shifted to an increased proportion of R^* . Agonist binding to R^* activates the stimulatory guanine nucleotide binding protein (G_s), which binds to and activates adenylyl cyclase, the enzyme responsible for the formation of cyclic adenosine monophosphate (cAMP), thereby activating protein kinase A. Protein kinase A subsequently induces phosphorylation of many proteins, including the voltage-gated L-type calcium channel. When these L-type calcium channels are phosphorylated, calcium influx occurs into the myocardium during phase II of the action potential. Phosphorylation of troponin I enhances muscle contraction by actinomycin. Phosphorylation of the ryanodine receptor and phospholamban on the sarcoplasmic reticulum enhances calcium release, which further stimulates excitation-contraction coupling. The β -receptor antagonists

bind to the R moiety, resulting in stabilization of the inactive form with a resultant shift in the equilibrium away from the activated receptor.

The β_2 -receptor also mediates several cardiac functions. While both the β_1 - and β_2 -receptors can be stimulated in a similar manner by β -antagonists, the β_2 -receptor can exist in a third isoform ($R^\#$) which acts primarily through an inhibitory protein, G_i [9]. Agents that bind to and stabilize $R^\#$ and mediate the β_2 -receptor-induced cardioinhibitory effects are known as inverse agonists. Most β -receptor antagonists function, to various degrees, as inverse agonists at this receptor, explaining the potential effects of these agents beyond that which would be expected from simple removal of the β_1 -receptor-mediated adrenergic tone.

The β_3 -adrenergic receptors constitute only a small fraction of the β -receptors on the heart and are cardioinhibitors, at least partially by a nitric oxide-mediated pathway, which seems to be independent of the pathways for the β_2 -receptor [10, 11]. The β_3 -receptor seems to be cardiostimulatory in the R^* state and may be cardioinhibitory in a G_i protein-linked manner via an $R^\#$ state analogous to that of the β_2 -receptor [7]. It appears that all β -receptor antagonists bind to the β_3 -receptor [7], although it is unclear which isoform of this receptor (R or $R^\#$) these agents stabilize.

When a β -receptor antagonist and a β -receptor agonist are pharmacologically present, there is a competition between them for binding to the various isoforms of β -receptors. The end result is a much greater dose of agonist required for a pharmacologic effect. The avid binding of the β -receptor antagonists to β -receptor means that the amount of agonist required to overcome the inhibition may be enormous.

Effects of β -Receptor Blockade

Airways

Agonism of the β_2 -receptor is associated with relaxation of smooth muscles of the airways and bronchodilation. In susceptible individuals, antagonism of the β_2 -receptor may result in significant

bronchoconstriction. It is not known to what degree, if any, inverse agonism at the β_2 -receptor causes bronchoconstriction.

Cardiac

There are many mechanisms by which β -receptor antagonists may exert negative inotropic and chronotropic effects on the heart, including β_1 -antagonism, inverse agonism at both the β_2 - and β_3 -receptors, membrane stabilization, and metabolic derangements. Agents with membrane stabilizing activity exert their effects via unique, non- β -receptor-mediated mechanisms. There also are certain uniquely individual properties of individual agents, the most prominent of which is associated with sotalol and described later.

Although normal human heart contains a large predominance of β_1 -receptors [12], there is a significant increase in the proportion of the β_2 -receptors in patients with heart failure [13]. It is, therefore, theoretically possible that the greater expression of inverse agonism that would occur with an increased proportion of β_2 -receptors may make the failing heart hypersusceptible to poisoning with these agents.

There is a theory that β -receptor antagonists, by virtue of their modulation of ion channels, cause hyperpolarization of the cell membrane and decreased inotropy and chronotropy [14].

Sotalol is a Vaughan Williams class III antiarrhythmic that increases the duration of the myocardial action potential and causes prolongation of the QT interval. Because QT interval prolongation is due to an increase in the duration of phase 2 of the action potential, as opposed to increased duration of repolarization, it is unclear whether sotalol predisposes to torsades de pointes; however, cases of this arrhythmia have been reported after intoxication with sotalol [15–17].

Membrane Stabilizing Activity

Agents with membrane stabilizing activity, such as propranolol, exert not only β -receptor antagonism but also sodium channel-blocking antiarrhythmic

effects characteristic of the Vaughan Williams class I agents. Clinically, this blockade manifests as QRS widening and may produce other myocardial effects similar to quinidine [18, 19]. Agents with membrane stabilizing activity may be characterized as class Ia antiarrhythmics in electrophysiologic action and toxicity (see ► Chap. 39, “Sodium Channel-Blocking Antidysrhythmics”). Treatment of the membrane stabilizing effects should include therapy targeting the sodium channel-blocking effects with sodium bicarbonate (see ► Chap. 39, “Sodium Channel-Blocking Antidysrhythmics”), in addition to therapy aimed at beta antagonists.

Blood Vessels

Stimulation of the β_2 -receptor causes vasodilation. It is anticipated that isolated β -receptor antagonist effects on vasculature allow for unopposed α -receptor-mediated vasoconstriction. However, the clinical manifestation is often difficult to appreciate due to the difficulty in separating the cardiac from the peripheral vascular effects.

Metabolic Effects

During routine physiologic conditions, the beta oxidation of fatty acids accounts for 60–80% of the myocardial energy substrate [20]. In therapeutic [21] or toxic [22] conditions, β -receptor antagonists cause a shift in the substrate preference of myocardium from free fatty acids to carbohydrates. Associated with this shift is a reduction in myocardial metabolic rate. This reduction may create an energy deficit from the heart. In an animal model involving therapeutic administration of a β -receptor antagonist, the administration of metoprolol resulted in inhibition of carnitine palmitoyltransferase I, suggesting reduction of fatty acid oxidation [20].

Clinical Presentation

Patients intoxicated with β -receptor antagonists present primarily with hypotension and cardiac bradydysrhythmias. In major intoxications,

a variety of additional effects may manifest. The clinical picture depends on the dose ingested, the underlying physiologic status of the patient, and the particular agent involved. Propranolol is one the most common agent implicated in severe or fatal ingestions [23].

Cardiac

The cardiovascular manifestations of β -antagonist poisoning typically are bradydysrhythmias, cardiac conduction defects, hypotension, and circulatory shock. Those agents with intrinsic sympathomimetic activity may cause hypertension. Severe β -antagonist poisoning may cause ventricular arrhythmias, including torsades de pointes and cardiac arrest. Sotalol is one such agent that has been associated with torsades de pointes in overdose [24]. Those beta blockers with sodium channel-blocking properties, such as propranolol, have been associated with intraventricular conduction delay [25].

Bradydysrhythmias

Because the heart has an intrinsic rhythm, the removal of β_2 -stimulation primarily prevents adrenergic stimulatory tone. This action by itself would not be expected to cause severe bradycardia in the absence of heightened vagal tone. However, inverse agonism, as described earlier, can theoretically worsen bradydysrhythmias. Those β -receptor antagonists with membrane stabilizing activity, particularly propranolol or oxprenolol, seem to be the primary cause of bradydysrhythmias [26], although they have been reported with other β -receptor antagonists as well [25, 27, 28].

Hemodynamically significant bradydysrhythmias may occur from the ocular administration of β -receptor antagonists, even at therapeutic dose [29–31]. Although bradydysrhythmias are less to occur in otherwise healthy patients, those with compromised cardiovascular function seem to be at greater risk of adverse events. These effects have been observed most frequently after the ocular administration of timolol [30–32], which is the agent often used to treat glaucoma. It has been described when timolol has been used

topically in the treatment of other conditions, such as hereditary telangiectasias [33]. Hypotension has also been described following ocular administration [4, 31].

Cardiac Conduction Defects

There have been many case reports of various dysrhythmias, including all forms of heart block, bundle branch blocks, junctional escape rhythms, and asystole associated with poisoning by many different β -receptor antagonists.

Pump Failure

Broadly speaking, pump failure following an overdose can be divided into three main categories: hypovolemic shock, distributive shock, and cardiogenic shock [34]. Cardiac pump failure from intoxication from β -receptor antagonists specifically may be due to hemodynamically significant arrhythmias, a decrease in inotropy, or both. This distinction is important, as the mechanisms have different therapeutic implications. Pump failure not attributable to bradydysrhythmias should be further characterized through measurement of hemodynamic parameters and echocardiography, unless it resolves with empirical treatment.

Hypotension

Hypotension has been associated with ingestions of nearly every β -receptor antagonists. The relative frequency of this effect has not been determined in a large case series, and it has not been associated with any particular β -receptor antagonists or pharmacologic characteristic. A study comparing the lipophilic, membrane stabilizing agent propranolol with atenolol, a β -receptor antagonists lacking these properties, showed no difference in the incidence of either systolic or diastolic hypotension after poisonings [25].

Pulmonary

Many pulmonary complications may be anticipated with poisoning from β -receptor antagonists. Patients with a depressed level of consciousness may develop hypoventilatory respiratory failure and should be considered at increased risk for

aspiration. The blockade of the pulmonary β_2 -receptors can result in increased airflow resistance, manifesting clinically as bronchospasm. Patients with severe cardiovascular dysfunction may develop adult respiratory distress syndrome.

Respiratory Depression

There have been multiple reports of respiratory depression after overdose with β -receptor antagonists. Respiratory failure seems to be secondary to cardiovascular or central nervous system depression and would not be expected independent of these effects. A clinical study comparing the propensity to cause bradypnea between atenolol and propranolol did not show any difference [25].

Neurologic

The two primary neurologic manifestations of β -receptor antagonist intoxication are central nervous system depression and seizures. The former may be secondary to cardiovascular depression and decreased cerebral perfusion. Lipophilic agents, such as propranolol, may have a more direct effect on the central nervous system.

Seizures have been reported with a variety of β -receptor antagonists in overdose. Propranolol, however, is disproportionately affected. Most of these patients have hemodynamic instability and intraventricular conduction delay [25]. In one series, two-thirds of patients ingesting more than 2 g of propranolol experienced a seizure [25]. Seizures are not clearly associated with a Glasgow Coma Scale score less than 15 or QT prolongation [25].

Miscellaneous

Intoxication with β -receptor antagonist can be expected to produce other effects that can complicate therapy, including hypoglycemia, rhabdomyolysis, metabolic acidosis, and acute kidney injury, the latter of which is most likely due to hypoperfusion.

Diagnosis

The diagnosis of β -receptor antagonist poisoning is a clinical diagnosis that should be suspected on the basis of the history and physical exam

findings. Relative or absolute hypoglycemia may be an important diagnostic clue. Most drugs of abuse screens will not be abnormal on the basis of β -receptor antagonist toxicity. Comprehensive drug testing, however, can confirm the exposure. Quantitative serum drug concentrations, while helpful in confirming the toxicity, are usually not routinely available and can be useful only for retrospective verification of the diagnosis. Confirmatory testing is not required to make the diagnosis of β -receptor antagonist toxicity.

Treatment

As with all poisonings, the treatment of β -receptor antagonist often relies on appropriate and aggressive supportive care, including airway support for standard indications, and monitoring for potential complications.

Decontamination

The administration of activated charcoal may reduce blood concentrations of ingested β -receptor antagonist. In a volunteer study of eight healthy subjects who ingested nadolol and then consumed 3 g of charcoal over 9 h, the area under the curve decreased after charcoal administration [35]. However, there are no studies demonstrating beneficial effect of activated charcoal following β -receptor antagonist overdose. If a patient presents following an ingestion of a β -receptor antagonist and presents within 1 h, it is reasonable to consider a single dose of activated charcoal. However, the clinical utility of this intervention is debatable because the effect on outcome is unknown and there is a risk aspiration from a declining mental status that may occur during activated charcoal administration.

Whole bowel irrigation with electrolyte-balanced polyethylene glycol solutions has been touted as an alternative to activated charcoal. There are no data supporting the use of this technique in the treatment of β -receptor antagonist toxicity, and its use is not recommended. The most recent position paper from the American

Table 2 Pharmacokinetics of β -receptor antagonists that are amenable to extracorporeal removal

Agent	Volume of distribution (L/kg)	Protein binding (%)
Acebutolol	1.2	26%
Atenolol	1.1	6–16%
Sotalol	1.2–2.4	0

Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) concludes there is insufficient evidence to routinely recommend whole bowel irrigation, but acknowledging its use can be considered in potentially toxic ingestions of sustained release preparations [36].

Patients who have β -receptor antagonist toxicity secondary to ocular administration may benefit from eye irrigation, although there are no randomized trials demonstrating benefit of ocular irrigation.

Most of these agents have a high volume of distribution. Consequently, it is unlikely that enhanced elimination techniques are likely to be beneficial in the treatment of most acute β -receptor antagonists. However, acebutolol, atenolol, and sotalol may be amenable to extracorporeal removal (Table 2).

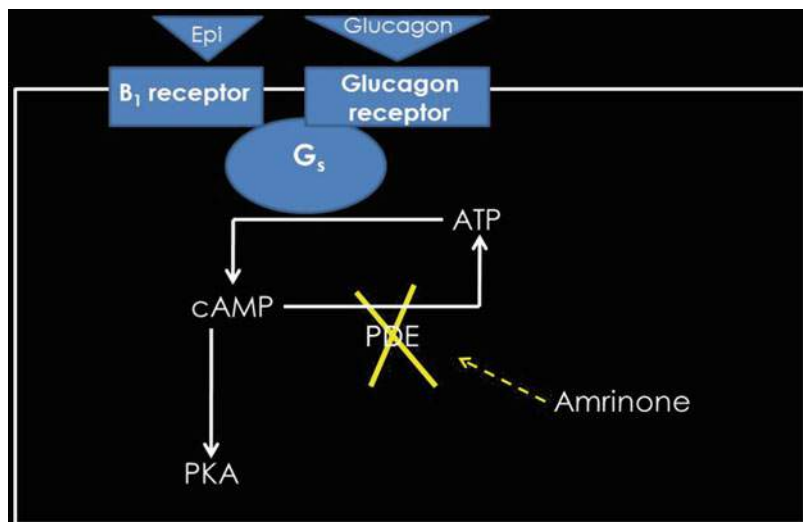
Cardiovascular Effects

Bradydysrhythmias

The various treatment modalities available for β -receptor antagonist-induced bradydysrhythmias have not been studied in individual or comparative trials. There is published case experience with the use of atropine, glucagon, β -receptor agonists, phosphodiesterase inhibitors, insulin, lipids, electrical pacing, intra-aortic balloon counterpulsation, and extracorporeal circulatory support for this indication.

Atropine, a muscarinic anticholinergic agent, increases the heart rate through its vagal-lytic effects. Although atropine may provide a transient increase in the cardiac rate, its effect is variable and short lived. Repeated doses may produce both central and peripheral anticholinergic toxicities.

Fig. 3 Sites of action of pharmacologic therapies that may be used in the management of β -receptor antagonists



Its primary use is limited to the initial stabilization of a bradycardic, hemodynamically unstable patient.

Glucagon has been widely suggested as an antidote for β -receptor antagonist poisoning. There have been multiple case reports, although generally these were in uncontrolled clinical cases involving several pharmacologic therapies. Several recent meta-analyses have found inadequate evidence to support its use [37, 38]. Nonetheless, many review articles continue to recommend its use as a possible treatment modality for the treatment of β -receptor antagonist toxicity [39–43]. The reported action of glucagon stems from its ability to stimulate adenylate cyclase independently of the β -receptor (Fig. 3). When used for the treatment of poisoning, glucagon is typically administered as a 5–10 mg intravenous bolus for adults, followed by a continuous infusion. The pediatric bolus dose is 50–150 mg/kg. Some preparations of glucagon have been packaged with a phenol-containing diluent. Because the doses of glucagon are higher than doses for other purposes, patients may receive an excess amount of phenol if the diluent is used. If the diluent is phenol, it should be replaced with normal saline or dextrose in water to reduce the risk of phenol toxicity. One of the major adverse effects with glucagon is vomiting. Prior to administration of glucagon, patients should receive a liberal dose of

antiemetics, as retching and vomiting can increase vagal tone, theoretically worsening bradycardia.

The use of β -receptor agonists, aimed at overcoming receptor blockade competitively, may be attempted in cases of hemodynamically significant cardiac bradydysrhythmias. The available options include isoproterenol, dobutamine, norepinephrine, epinephrine, and prenalterol. There are few data to rely on for assessing the effects of β -agonists in the treatment of these bradycardias. For patients who are refractory to simple supportive therapy, an empirical trial with a dobutamine or isoproterenol infusion can be attempted. As described subsequently, isoproterenol or dobutamine may worsen hypotension or cause cardiac dysrhythmias and should be used cautiously and only in a well-monitored patient. The typical adult dose of isoproterenol for conditions not related to β -blocker poisoning is 2–10 μ g/min. Because of the potential adverse effects of this therapy, the lowest effective dose should be used. The typical pediatric dose is 0.1–1.5 μ g/kg/min, with the lowest effective dose suggested. As described subsequently, however, it is unlikely that conventional doses of isoproterenol or dobutamine (typical doses of 0–20 mcg/kg/min) would be effective in a patient with serious β -blocker poisoning.

There are few published data on the use of dobutamine or epinephrine as a β -adrenergic agonist in patients poisoned by these agents. Because

of the high binding affinity of β -antagonists to the β -receptor, it is likely that high doses of receptor agonists would be required to overcome the blockade competitively. This likelihood may explain some cases where adrenergic agents fail. It has been calculated that a 10,000 times increase over standard isoproterenol dosing would be required to overcome the blockade induced by an overdose of propranolol [26]. For β -adrenergic agents that have any α -agonist properties, the administration of high doses may increase afterload to the point of causing adverse effects on cardiac hemodynamics or coronary perfusion or both, in part due to the unopposed α -adrenergic agonism that occurs as a consequence of β -receptor antagonist intoxication.

Cardiac pacing may be attempted for the treatment of bradyarrhythmias, although there is little clinical experience with this in the management of β -receptor antagonist intoxication. Successful use of the intra-aortic balloon pump has been reported in isolated β -receptor antagonist intoxication [44]. Similarly, in patients unresponsive to all other measures, extracorporeal cardiac support could be attempted [45, 46].

Phosphodiesterase inhibitors such as inamrinone or milrinone theoretically should have a positive chronotropic effect on the myocardium because the β -receptor exerts its effect by increasing intracellular cAMP, a molecule-metabolized phosphodiesterase. Phosphodiesterase is bound to the sarcoplasm in the heart. By inhibiting this enzyme, there is enhanced release of calcium from the sarcoplasm [10]. There is animal data demonstrating increased cardiac index with these agents [47, 48]. However, in other canine models of propranolol toxicity, the combination of glucagon with a phosphodiesterase inhibitor proved inferior to glucagon alone [47, 49, 50].

If inamrinone is utilized, the typical loading dose is 0.75 mg/kg as a bolus given over 2–3 min, followed by an infusion of 5–40 mcg/kg/min. Milrinone typically is administered as a loading dose of 50 mcg/kg over 10 min, followed by an infusion of 0.375–1 mcg/kg/min. These dosing protocols should be adjusted in patients with significant renal insufficiency.

Intravenous lipid emulsion therapy has emerged as a novel therapy for treatment of lipophilic drug toxicities. While various theories exist, one such theory, the so-called “lipid sink” theory, suggests that the administration of a high concentration of fat into the vasculature results in a redistribution of a lipophilic drug out of the periphery and into the vascular compartment [51]. However, it should be noted that this theory may not fully account for the clinical effects [52].

There are no randomized trials of intravenous lipid emulsion therapy in the treatment of β -receptor antagonist toxicity. Animal studies have examined intravenous lipid emulsion therapy for the treatment of propranolol, atenolol, and metoprolol toxicities. This data demonstrate equivocal efficacy with in some studies showing some benefit [53, 54] and others failing to confirm any benefit to its use [55, 56]. Numerous human case reports have described its use for the treatment β -antagonist toxicity [57–62]. While numerous dosing recommendations have been suggested, one involves the administration of 1.5 mL/kg as an intravenous bolus, followed by 0.25 mL/kg/min for 30 min [63].

Cardiac Conduction Defects

As described earlier, various degrees of cardiac conduction defects have been observed after intoxication with β -receptor antagonists, including agents with and without membrane stabilizing activity. There has been no systematic study of this phenomenon, and few data are available in the published literature on its treatment. Nonetheless, it is recommended that any intraventricular conduction delay be treated with intravenous boluses of sodium bicarbonate (e.g., 1–2 mEq/kg with additional therapy based on response). Minor degrees of heart block in an otherwise hemodynamically stable patient can be managed expectantly. If the heart block is associated with significant bradycardia, it is possible that it may resolve with treatment of the latter, as described earlier. The fluid and electrolyte status of the patient also should be optimized. If the heart block is significant enough to cause pump failure, treatment should be initiated as described in the following section.

Pump Failure

There have been no randomized clinical trials to date addressing the optimal therapy of β -antagonist-induced reduction in myocardial contractility. Pump failure due to hemodynamically significant bradycardias should be treated initially as described earlier. Pump failure that is not solely rate related can be managed, however, by the administration of inotropes, glucagon, or possibly insulin or phosphodiesterase inhibitors.

Pump failure resistant to pharmacologic interventions and optimal management of fluid status may require the use of a left ventricular assist device or extracorporeal circulation. If pump failure is refractory to initial therapeutic approaches, it may be helpful to obtain precise hemodynamic parameters through invasive monitoring (grade III). The clinical benefits and risks of this intervention have not been studied, however.

Some inotropic agents (e.g., dobutamine) act by stimulating cardiac β_1 -receptors and are expected to be antagonized competitively by the β -blocker. These agents may not be clinically effective, although a cautious empirical trial of this approach cannot be criticized. Theoretically, much higher doses of β -agonists may be necessary than doses typically used in the absence of β -receptor antagonist poisoning. Of the various options for β_1 -specific inotropes, dobutamine is the most appropriate based on theoretical considerations (evidence grade III). These effects may be magnified at higher doses. An emerging concern regarding the use of β -antagonists in the presence of a β -receptor antagonist relates to the cardioinhibitory β_3 -receptor. It is possible that blockade of the cardiac β_1 -receptor and β_2 -receptor could cause adrenergic inotropes preferentially to agonize the β_3 -receptor. In the presence of nadolol, isoproterenol exerts an inhibitory effect on dP/dt in the human myocardium [7].

The use of glucagon in the management of β -receptor antagonist toxicity was described earlier. Several animal studies have demonstrated beneficial effects following the use of glucagon in the treatment of β -antagonist toxicity (evidence grade IIb) [39–43]. One porcine study compared

vasopressin at 0.0028 units/kg/min titrated up to 0.014 units/kg/min with glucagon (0.05 mg/kg bolus followed by an infusion at 0.15 mg/kg/h). There was no difference in survival or hemodynamic parameters between the groups [64].

High-dose insulin has been postulated to improve hemodynamics via multiple different mechanisms, including increased inotrope, improved carbohydrate uptake by cardiac myocytes, and inhibition of free fatty acid [65]. However, it should be noted that supraphysiologic doses can produce vasodilation [66]. Based on several dog studies, hyperinsulinemic euglycemia therapy has been suggested as a possible treatment [40, 66]. Several non-randomized case reports and case series have been published, with the majority reporting benefit [67–70]. When used in this setting, however, hypokalemia and hypoglycemia are common. Many patients required prolonged concentrated dextrose infusions after insulin was discontinued [67]. While dose recommendations vary, one recommended dose involves an intravenous bolus of 1 unit/kg of regular insulin, followed by a continuous infusion of 1–10 units/kg/h (evidence grade IIc–III) [68]. There are no randomized trials in humans comparing insulin therapy with vasopressors for the treatment of β -receptor antagonist toxicity. The clinical pharmacology of high-dose insulin therapy is discussed in more detail in the chapter devoted to that antidotal treatment in the antidote section.

Vasopressors may be beneficial in the treatment of vasodilation secondary to β -receptor antagonist stimulation of the β_2 -receptors (grade IIc–III). Dopamine, norepinephrine, and epinephrine are commonly used. None of these agents have been systematically studied in this setting, however. An appropriate approach to using vasopressors in these patients is to start them at standard doses and quickly titrate the dose upward, while monitoring their efficacy in the particular patient by assessment of hemodynamic response. It should be noted that when treating toxicity from combined α - and β -blocker (e.g., labetalol, carvedilol, and celiprolol), the use of dopamine may theoretically exacerbate hypotension (grade III).

Noncardiovascular Effects

Respiratory depression, bronchoconstriction, central nervous system depression, seizures, hypoglycemia, and secondary complications such as acute kidney injury and rhabdomyolysis should be treated by standard measures for the approach to these complications in the intensive care unit. It should be anticipated, however, based on theoretical considerations, that attempts to treat bronchospasm with β -agonists may be unsuccessful due to the blockade of β -receptors. Similarly, because this bronchospasm is due to loss of β -adrenergic tone and not inflammation, it is unlikely that corticosteroids would offer significant therapeutic effects. Alternative bronchodilator approaches with greater potential efficacy include anticholinergic agents (e.g., ipratropium, glycopyrrolate), phosphodiesterase inhibitors (e.g., aminophylline), and possibly glucagon. Seizure secondary to β -receptor antagonist poisoning, seen most commonly with propranolol, should be treated in the same manner as other toxicant-induced convulsions (grade III) (see ► [Chap. 20, “Toxicant-Induced Seizures”](#)).

Special Population

Pediatric Patients

There is little information concerning significant differences in the pathophysiology, presentation, or treatment of β -receptor antagonist intoxication in children compared with adults. Among more than 10,000 β -receptor antagonist intoxications reported to US poison centers, more than 3,000 involved children age 12 or under [23]. A 7-year retrospective study of cases reported to a regional poison center in the United States evaluated children younger than 7 years old with β -receptor antagonist ingestions. As is typical for ingestions in children of this age, most involved either a small number of pills or only the suspicion of ingestion [69]. Only 8 of the 378 children evaluated developed any significant signs of toxicity. The toxicities that did occur

were bradycardias, lethargy, and hypotension. These were manifest at a median of 3 h post ingestion, with a maximal time from ingestion of 3.5 h. This study did not have enough cases with sustained release preparations to reach any conclusions regarding ingestion of these formulations. A different poison control center-based study examined 208 pediatric patients aged 6 months to 6 years with unintentional β -receptor antagonist. In that study, the majority of patients consumed one or two β -receptor antagonists. No cases of serious toxicity due to the β -receptor antagonist were developed, but one child did have a charcoal aspiration following gastrointestinal decontamination [71]. From the limited information available, it seems that the clinical presentation of β -receptor antagonist intoxication in children is similar to that in adults, and with the exception of sustained release preparations, children who will become symptomatic tend to do so within several hours. Patients who are asymptomatic but who have ingested sustained release preparations should be observed for a longer time. Asymptomatic pediatric patients who present following a β -receptor antagonist ingestion should be observed for 6 h for immediate release preparations and 8 h for sustained release preparations [72]. Asymptomatic patients who ingest sotalol should be observed for 12 h. Symptomatic patients should be admitted.

Elderly Patients

Patients with impaired cardiopulmonary reserve are more likely to develop clinical effects following an ingestion compared with those patients with normal physiologic reserve. In one study of patients with unintentional, supratherapeutic ingestion of their own β -receptor antagonist or calcium channel antagonists, 10% of patients developed signs of toxicity and 7% required hospital admission [73]. The management of patients should not differ based on age, although elderly patients may be more predisposed to develop severe effects.

Pregnant Patients

Most of the adverse experiences associated with β -receptor antagonist in pregnancy involve propranolol, which seems to cross the placenta and may concentrate in the fetus [74]. Bradydysrhythmias, hypoglycemia, respiratory depression (and even neonatal apnea), and circulatory collapse have been described in women who received propranolol before delivery [74–76].

A case of neonatal respiratory depression, hypotonia, and circulatory collapse was reported in a 33-week-gestation neonate delivered by cesarean section whose mother received intravenous labetalol before surgery [75]. A case report of a major overdose of metoprolol in a woman in her 20th week of pregnancy described cardiac arrest in the mother. Despite successful resuscitation, the event led to fetal demise [73].

Breast-Feeding Patients

Most β -receptor antagonists that have been studied in regard to breast-feeding are excreted in breast milk. A case report described an infant with β -receptor antagonist intoxication from breast-feeding by a mother who was treated with atenolol [77].

Indication for ICU Admission in β -Receptor Antagonist Poisoning

Hemodynamic instability
Coma or seizures
Bronchoconstriction not responsive to initial bronchodilator therapy
Dysrhythmias

Common Errors in β -Blocker Poisoning

Not realizing that therapeutic use of β -receptor antagonist-containing eye drops can cause significant toxicity
Failing to provide aggressive supportive care
Failure to continue titrating infusions due to reaching a predefined “maximal” dose

Key Points in β -Blocker Poisoning

β -Blockers may cause the following:

Bradydysrhythmia
Intraventricular conduction delay
Atrioventricular blocks
Hypotension
Central nervous system depression and seizures
Bronchoconstriction
Secondary complications deriving from the above, including renal failure

Therapeutic options beyond supportive care comprise

Gastrointestinal decontamination
Atropine
Phosphodiesterase inhibitors
Glucagon
Insulin
Lipid resuscitation therapy
Cardiac pacing
Left ventricular assist
Extracorporeal membrane oxygenation
Extracorporeal drug removal for certain agent

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The role of calcium in physiologic processes has long been recognized. In about 1960, it was first noted that calcium channel antagonists, which were being developed as vasodilators, had negative inotropic and chronotropic effects [1]. This observation gave rise to the concept that reducing calcium influx into myocardial cells and arterial vascular smooth muscle could negatively modulate excitation–contraction coupling, accounting for their vasodilating and negative inotropic effects [2]. Subsequently, it was recognized that inhibiting the inward calcium flux decreased the rate of spontaneous depolarization of cardiac pacemaker cells. Because this inward calcium current is slow compared with the fast sodium channel of cardiac myocytes, the former has been called the *slow calcium channel*, frequently referred to as simply the *calcium channel* [3].

The vasodilating and negative chronotropic effects of calcium channel antagonists have led to their development for many important indications, such as the treatment of hypertension, cardiac tachyarrhythmias, arterial vasospasm, angina pectoris, hypertrophic cardiomyopathy, congestive heart failure, premature labor, and pulmonary hypertension [4].

Several classes of calcium channel antagonists are in use. These classes vary in their effects on arterial smooth muscle and the heart. The pharmacologic actions of the various agents on these two organs account for their major clinical effects, as well as their toxicity, when used therapeutically [2].

The major calcium channel antagonists in clinical use around the world are verapamil, nifedipine, diltiazem, and amlodipine. As described in this chapter, the first three of these drugs are prototypes of the three major distinct classes of calcium channel antagonists; most of the data concerning the toxicity of these respective classes come from observations on these three specific agents. To the extent that information is available on the toxic effects of the other calcium channel antagonists, these are described as well [2].

Biochemistry and Clinical Pharmacology

Five classes of calcium channel antagonists are in clinical use (Table 1), although verapamil, diltiazem, and members of the dihydropyridine class have been the most frequently employed.

Table 1 Calcium channel antagonists

Class	Agent(s)	Class effects		
		Heart rate	Peripheral arterial tone	Cardiac contractility
Phenylalkylamine	Verapamil	↓	↓	↓↓
Dihydropyridine	Amlodipine	↑	↓↓↓	±
	Felodipine			
	Isradipine			
	Nicardipine			
	Nifedipine			
	Nimodipine			
	Nitrendipine			
	Nisoldipine			
Benzothiazepine	Diltiazem	–/↓	↓↓	↓↓
Diphenylpiperazine or tetralene	Mibefradil ^a	↓	↓↓	–/↓
Diarylaminopropylamine or diarylaminopropylether	Bepridil	↓	↓	↓

^aWithdrawn from the market in many countries because of numerous severe cytochrome P-450/P-450-related drug interactions. Mibefradil was unique among calcium channel antagonists in that it blocks the T and L calcium channels

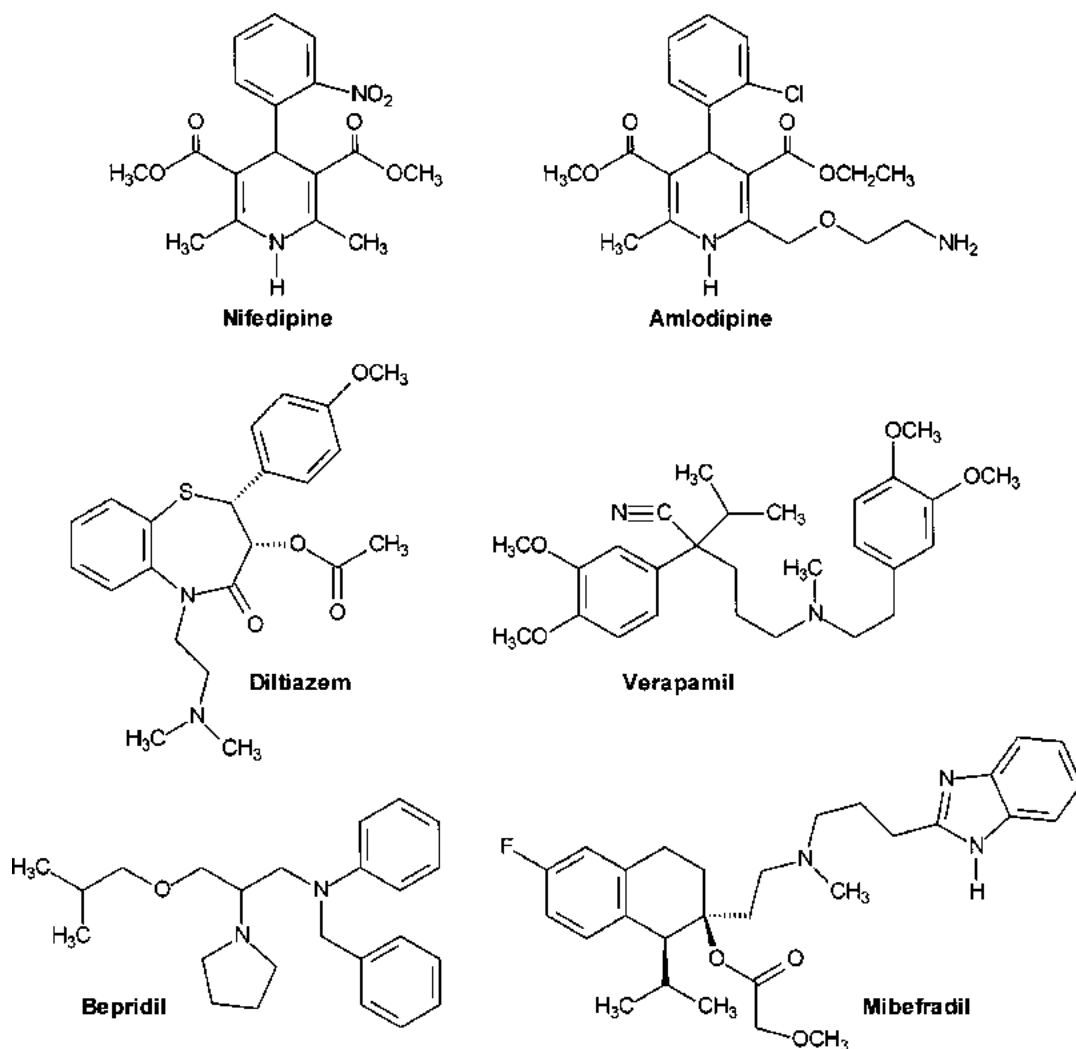


Fig. 1 Chemical structures of representative calcium channel antagonists, including the dihydropyridines, nifedipine and amlodipine; the benzothiazepine, diltiazem;

the phenylalkylamine, verapamil; the diarylamino compound, bepridil; and the tetrahydroisoquinoline, mibefradil.

Examples of the structures of these agents are shown in Fig. 1. All share the common property of antagonizing the slow, or so-called L-type, calcium channel. Further discussion of calcium channels follows in the pathophysiology section. Most of these agents have volumes of distribution greater than 2 L/kg, making clinically significant enhanced clearance of these drugs by extracorporeal techniques unfeasible. Exceptions are nifedipine (volume of distribution

0.64–1.4 L/kg) and possibly nifedipine (volume of distribution 0.6–2.21 L/kg) and nimodipine (volume of distribution 0.94–2.5 L/kg). However, because these and all other calcium channel antagonists are highly protein bound, they are not cleared to any significant degree by hemodialysis. Isolated case reports have shown conflicting results with the use of hemodialysis, charcoal hemoperfusion, and the molecular adsorbent recirculating system (MARS) [5].

Pharmacokinetics of Calcium Channel**Antagonists**

Volume of distribution: generally large*

Protein binding: extensive

Removal by extracorporeal techniques: minimal*

Mode of clearance: hepatic metabolism

Active metabolites: generally none[†]

*See text for exceptions.

[†]Verapamil and diltiazem have active metabolites, norverapamil and desacetyl diltiazem, respectively. These metabolites are significantly less active than are the parent molecules.

The pharmacokinetic features of calcium channel blockers vary. Moreover, it is difficult to estimate the half-life in an overdose situation, as the pharmacokinetics may be altered by the coingestants, presence of an ileus or decreased gut perfusion due to shock, or vasopressor administration. Pharmacobezoars have been reported, notably with certain formulations of extended release nifedipine [6–8]. In addition, calcium channel blockers are metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. In pharmacokinetic studies, coadministration of various inhibitors of this enzyme raised plasma calcium channel-blocker concentrations by up to 500% [9]. One well-conducted pharmacokinetic investigation of two cases of verapamil overdose found that despite markedly elevated plasma concentrations, the elimination of the parent drug and its primary metabolite, norverapamil, followed first-order kinetics, suggesting that their metabolism was not saturated during overdose [10]. However, despite the apparent first-order kinetics, the half-life of the elimination of verapamil was prolonged [11, 12].

Pathophysiology of Toxic Effects

Although there are a prodigious number of effects of calcium channel antagonists, the target organs of greatest importance to their clinical toxicity are the heart and the arterial vasculature. The effects of calcium channel antagonists on these two

organs differ among the various classes of agents (see Table 1). The selectivity of the various agents, in terms of their clinical effects, may derive from their tissue-dependent differential binding to L-type channels [12, 13]. Verapamil and diltiazem tend to bind nonselectively to vascular and cardiac tissue L-type calcium channels, whereas the dihydropyridine class binds primarily to L-type calcium channels in vascular tissue.

There are five different types of voltage-gated calcium channels, designated *L*, *T*, *P*, *Q*, and *N*. The L-type (or long lasting) channel is found primarily in the heart, arterial smooth muscle, and pancreatic beta cells, although it is present in a diverse group of other organs [14]. It is the largest channel and the slowest to undergo inactivation when opened—hence the designation *slow* calcium channel. The T-type (or transient) calcium channel is the fastest to become inactivated, and it is found on cardiac nodal and conducting cells. The P-type channel is found on cerebellar Purkinje cells. Q-type channels are similar to P channels. The N-type (or neuronal) calcium channel is found on neurons. The calcium channel antagonists inhibit calcium influx through the L-type channel, of which there are at least five subclasses.

Normally, there is an enormous concentration gradient of calcium across cell membranes, with serum concentrations in the millimolar range and an intracellular free calcium concentration of less than 10^{-7} M. The cell maintains this gradient by allowing calcium influx only through voltage-gated calcium channels, sequestering free calcium in the sarcoplasmic reticulum of muscle cells and maintaining an adenosine triphosphate (ATP)-driven calcium export pump (Fig. 2). When activated by membrane depolarization, the opening of the L-type channel results in an increase in the intracellular calcium concentration to the micromolar, or higher, range [16].

Pharmaceutical calcium channel antagonists act by binding to the α_{1c} subunit on the L-type calcium channel (Fig. 3). The exact binding site of the α_{1c} subunit for the various classes of calcium channel antagonists varies [14].

In cardiac myocytes or smooth muscle cells, the resulting increased intracellular calcium concentration initiates a cascade that results in muscle

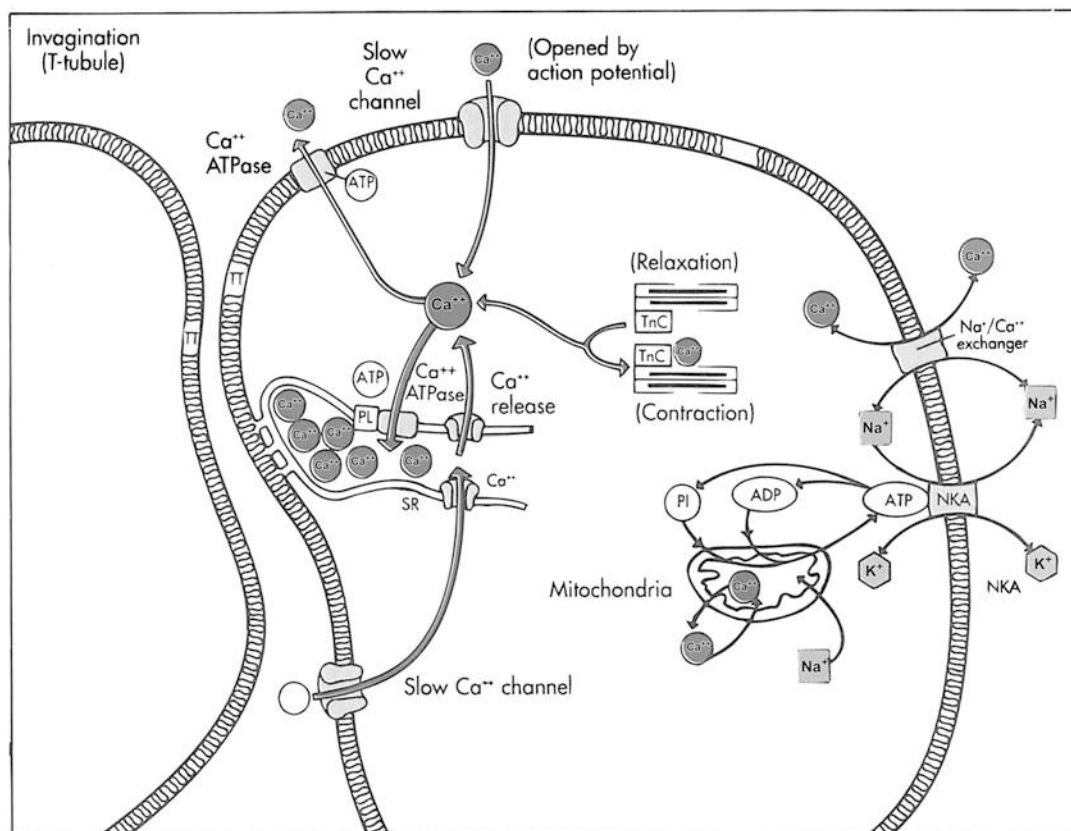


Fig. 2 Ca^{2+} influx through the L-type (or slow) calcium channel results in excitation–contraction coupling in myocardial and arterial smooth muscle. *NKA* Na^+/K^+ -ATPase,

PL phospholamban, *SR* sarcoplasmic reticulum, *TT* T-tubule, *TnC* troponin complex (From [15])

concentration (see Fig. 2). This process is reversed by the active reuptake of calcium into the sarcoplasmic reticulum. In contrast to skeletal muscle, most of the calcium for cardiac myocyte or smooth muscle relaxation comes from an influx through the L-type calcium channel [17]. Calcium channel antagonists have little effect on skeletal muscle.

The L-type calcium channel is activated when phosphorylated by intracellular protein kinases (Fig. 4), which are stimulated by cyclic adenosine monophosphate (cAMP), the mediator of effects caused by agonism at cardiac β -receptors (see Fig. 35.2, ► Chap. 36, “Beta-Receptor Antagonists”). Phosphorylation of the calcium channel occurs with each depolarization. The site of phosphorylation is the regulatory subunit of the calcium channel, called *phospholamban* [16].

In contrast to cardiac myocytes, the nodal cell’s resting potential is due to a calcium gradient, not a sodium gradient. The spontaneous depolarization of the sinoatrial and atrioventricular nodes is due to slow calcium influx through L-type channels [18].

Cardiac Effects

Calcium channel antagonists affect both the myocardium and cardiac pacemaker cells. These effects are seen primarily with the phenylalkylamine and benzothiazepine classes of agents and less commonly as a result of the toxicity of the dihydropyridines. The effects of the cardioactive calcium channel antagonists are exerted on the cardiac pacemaker cells and on the

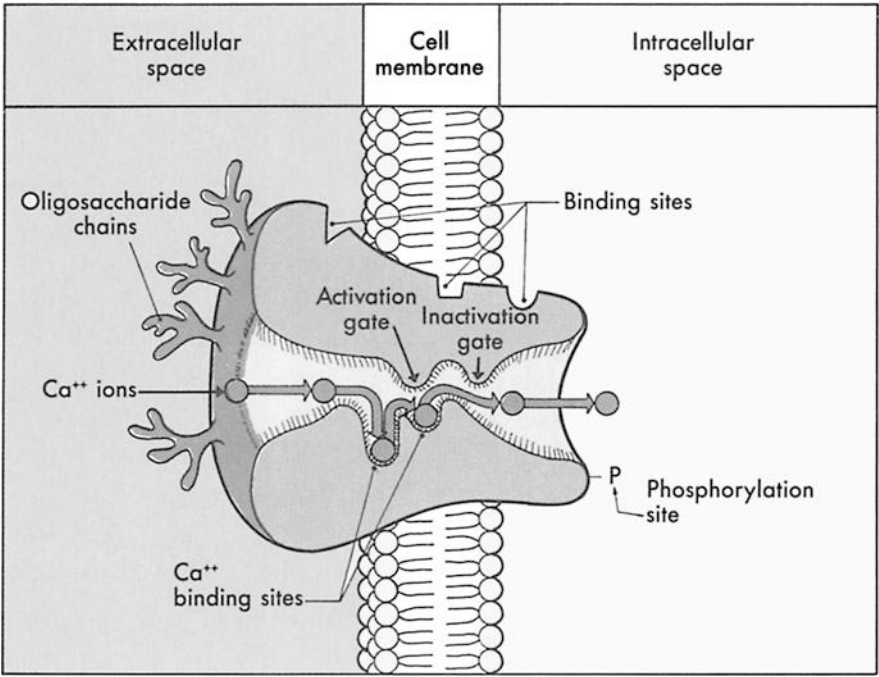
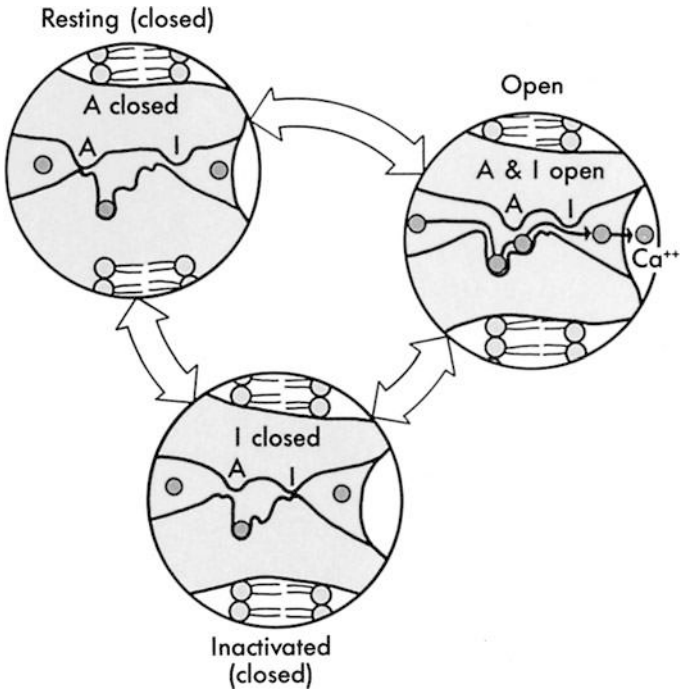


Fig. 3 Schematic L-type Ca^{2+} channel spanning the sarcolemmal membrane. The activation and inactivation gates control the flux of calcium through this channel. Binding sites for calcium channel antagonists, which decrease Ca^{2+} flux through the pore, are depicted. The actions of these

channels also are regulated by changes in electrochemical gradient across the sarcolemma. As shown in Fig. 4, the calcium channel can exist in open, resting, or inactivated states (From [15])

Fig. 4 Depiction of the three states of the calcium channel. In the open state, the activation and inactivation sites (see Fig. 3) are open. If either of these two sites is closed, the channel does not permit Ca^{2+} flux (From [15])



myocardium itself. As described earlier, cardiac pacemaker cells, such as those that make up the atrioventricular node, spontaneously depolarize as a result of a slow inward calcium flux. Inhibition of this calcium influx by calcium channel antagonists reduces the rate of pacemaker cell depolarization and, in cases of severe toxicity, can cause a complete arrest of this process [2].

The myocardium itself uses calcium through the action of voltage-dependent calcium channels that allow for calcium influx during phase II of the myocardial action potential, which is necessary for myocardial excitation–contraction coupling (see Fig. 2). The calcium influx that occurs at this time triggers further increases in intracellular free calcium concentrations by stimulating the sodium–calcium exchange pump on the myocardial cell membrane and by causing the release of stored sarcolemmal calcium. The combined result is a sharp increase in the intracellular calcium concentration, which leads to increased calcium binding to tropomyosin. Tropomyosin, a negative modulator of excitation–contraction coupling, acts by inhibiting the interaction of actin and myosin filaments. After calcium-induced activation of tropomyosin, the actin and myosin filaments are free to interact, causing muscle contraction. Inhibition of calcium influx results in decreased excitation–contraction coupling, which is manifested clinically by reduced cardiac inotropy.

Arterial Vasculature

In contrast to skeletal muscle and venous smooth muscle, arterial smooth muscle is highly dependent on external calcium for contraction. Calcium enters arterial myocytes via voltage-gated calcium channels, which, in a manner analogous to that in the heart, causes excitation–contraction coupling and increased arterial vascular tone. Inhibition of arterial smooth muscle calcium channels causes vasodilation. This effect is most evident with the dihydropyridine calcium channel antagonists (e.g., nifedipine).

Pancreatic Effects

Pancreatic insulin release is under the influence of the L-type calcium channel, which may become inhibited at high concentrations of channel blockers, thereby leading to hyperglycemia. A theoretical concern regarding hypoinsulinemia in patients with calcium channel antagonist poisoning is that in shock states the myocardium shifts its substrate preference from free fatty acids to glucose [19, 20]. Hypoinsulinemia adversely affects cardiac myocyte glucose uptake, which may be crucial to meeting its energy requirements under these conditions [21].

Metabolic Effects

Calcium channel antagonism can cause a decrease in mitochondrial calcium intake [20, 22], resulting in a reduction in pyruvate dehydrogenase activity and lactate accumulation [23]. This enzyme is required for pyruvate oxidation and subsequent Krebs cycle metabolism. Inhibition of pyruvate dehydrogenase causes hyperlactatemia.

Clinical Presentation and Life-Threatening Complications

Although there are major differences in the effects of the different classes of calcium channel antagonists when used therapeutically, some of these distinctions may be lost during overdose [24], wherein various pharmacologic actions tend to become clinically amplified. In general, the clinical presentation of calcium channel antagonist toxicity is one of hypotension, sinus node and myocardial depression, atrioventricular block, dysrhythmias, and hyperglycemia [25]. Other effects that commonly have been described with these agents are acute kidney injury, metabolic acidosis, and acute pulmonary edema [21, 25–29]. Effects of intoxication with these agents may be delayed (>6 h) and prolonged (>24 h) after the ingestion of sustained-release preparations [29].

Hypotension

In a prospective case series of 113 hospitalized patients with calcium channel antagonist overdose, hypotension (defined as systolic blood pressure <100 mmHg) was present in 43% of patients. Systolic blood pressure less than 60 mmHg was reported in 8% (nine) of patients [27]. Hypotension can be caused by either decreased peripheral resistance or cardiac pump failure in all calcium channel antagonists [24]. Other parameters of tissue–organ hypoperfusion (e.g., urine output, acid–base status) should be monitored closely in these patients.

Cardiac Conduction Deficits

Sinus node depression, all degrees of heart block, and junctional rhythms have been reported after calcium channel antagonist intoxication, more frequently after verapamil or diltiazem overdoses [29]. Most often, these conditions resolve within the first 48 h, but they have been reported to persist for 7 days [27, 30].

Cardiac Dysrhythmias

In the major series addressing cardiac dysrhythmias, bradycardia has been reported to occur in 29% of verapamil and diltiazem overdoses and in 14% of nifedipine overdoses. One-half to two-thirds of patients poisoned with the former two agents had heart rates less than 40 beats/min. There were no such cases reported in the same series in nifedipine-poisoned patients [27].

Sinus tachycardia is a common feature of poisonings by vasodilating (primarily dihydropyridine) calcium channel antagonists, occurring in one series in 57% of nifedipine overdoses, 26% of diltiazem overdoses, and 18% of verapamil poisonings [27]. Tachycardia also has been reported in several case reports of amlodipine overdose [31, 32], possibly secondary to carotid sinus reflex stimulation.

Noncardiogenic Pulmonary Edema

Although it is the impression of medical toxicologists that severe calcium channel antagonist poisoning may be accompanied by noncardiogenic pulmonary edema, the true incidence of this complication has not been formally studied, and documentation of its occurrence exists primarily in the form of case reports [33–37]. Several of these cases may in fact represent cardiogenic pulmonary edema related to aggressive fluid resuscitation in patients who have calcium channel antagonist-induced pump failure. However, there has been little published documentation of hemodynamic parameters, such as cardiac output, cardiac index, or pulmonary capillary wedge pressure, in these patients. It is hypothesized that dilation of a prepulmonary capillary or a drug-induced change in alveolar membrane permeability may contribute to noncardiogenic pulmonary edema [38–41].

Diagnosis

The determination of calcium channel antagonist toxicity generally starts with a history of the ingestion of these substances. In the absence of such a history, suspicion of toxicity by these medications should arise in a patient who presents with hypotension and other signs of toxic effects of these agents, as described earlier, which may be complicated by the diversity of presentation provoked by the different classes and pharmacokinetic formulations of agents. It is important to note that serum glucose concentrations correlate directly with the severity of verapamil and diltiazem intoxications. In fact, in a retrospective study conducted by Levine et al., the percentage increase of the peak glucose concentration was a better predictor of severity of illness than hemodynamic derangements [42]. In addition, Megarbane et al. have shown that a verapamil cutoff point of 5.0 μ M (2.2 ug/ml) was 100% sensitive and 91% specific to show a 2.76-times increase in the odds of fatality [43]. However, quantitative calcium channel antagonist determinations are generally available only from

commercial reference laboratories, and routine drug screens typically do not detect calcium channel antagonists.

Calcium channel antagonists generally are not considered to be radiopaque, although one case report has suggested that sustained-release verapamil may be detected radiologically [44]. Another case report of a fatal overdose with a sustained-release verapamil preparation found a large concretion of this material at autopsy, although it was not seen in abdominal radiographs obtained before death [45].

Treatment

As with all serious poisonings, the initial approach to the treatment of patients who ingested a potentially toxic amount of a calcium channel antagonist should be focused on preventing toxicity, maintaining adequate airway ventilation, oxygenation, and hemodynamic support. Based on the evidence documented in a systematic review [5] that predated the establishment of a working group, in 2015 representatives from 12 international critical care, emergency medicine, and toxicology associations proposed a stepwise approach for the in-hospital treatment of calcium channel-blocker poisoning (see Fig. 5) [46]. This section will discuss the treatments considered at each step, as well as other therapies that have been studied, but that are not included in these recommendations.

Asymptomatic Patients

It is recommended to observe asymptomatic patients who ingested a potentially toxic amount of a sustained-release calcium channel antagonist for approximately 24 h and to intervene with other treatments if they develop signs of toxicity (level II-3 evidence) [47]. No specific recommendation has been made by the international working group concerning decontamination. Activated charcoal may be efficient to prevent or decrease toxicity if it is administered soon after ingestion (level II-3

evidence) [48, 49]. However, there are no studies that indicate that the administration of activated charcoal significantly alters the outcome in these patients. The administration of activated charcoal should be done with great caution in patients who may develop alterations in mental status or seizures secondary to their ingestions.

Gastric lavage [50–52] or whole-bowel irrigation [53–55] are not recommended by the authors. Some hemodynamically unstable patients may not tolerate the vagal stimulation induced by the two latest decontamination modalities. Moreover, in a human volunteer study of sustained-release verapamil ingestion, whole-bowel irrigation did not reduce drug absorption significantly [51].

Symptomatic Patients: First-Line Treatments

Because these patients may have depressed mentation or evolving pulmonary edema, serious poisonings with these agents often warrant endotracheal intubation and mechanical ventilation. Intubation and mechanical ventilation is warranted in the presence of cardiovascular dysfunction requiring significant doses of pressors. Close monitoring of cardiac rhythm, vital signs, respiratory status, and urine output is fundamental to intensive care unit (ICU) management.

Indications for ICU Admission in Calcium Channel Antagonist Poisoning

Patient is mechanically ventilated or is anticipated to require it.

Hemodynamic instability is anticipated to become unstable.

Hyperglycemia of 188 mg/dL or more.

Coingestions requiring ICU care.

Because some of the manifestations of calcium channel antagonist intoxication may be caused by different mechanisms, additional monitoring and diagnostic modalities may be indicated. Hypotension caused by these poisonings may be the result of either decreased cardiac

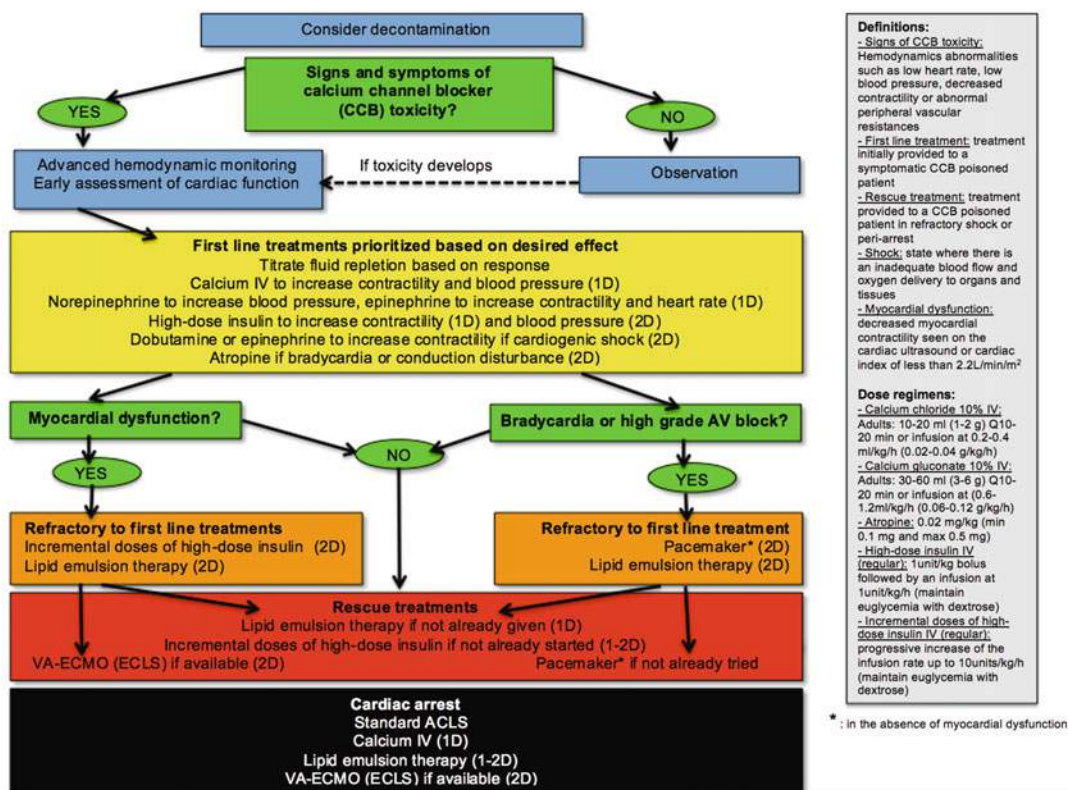


Fig. 5 Treatment algorithm suggested by an international working group building recommendations for the treatment of calcium channel-blocker poisoning [46]

output, systemic vascular resistance (SVR), or both. Therefore, it is preferable to assess myocardial function with a bedside echocardiogram or with more invasive hemodynamic monitoring techniques to identify the etiology of hypotension, to choose the appropriate therapeutic modalities, and to monitor the efficacy of these treatments (level III evidence). Fluid administration should also be titrated based on the patient's response (level III evidence).

As a first-line treatment in symptomatic patients, the international working group recommends the use of calcium IV, high-dose insulin, vasopressors such as norepinephrine or epinephrine, and to consider dobutamine if the patient presents with cardiogenic shock, or atropine if the patient presents with bradycardia [46].

Calcium (Level II-3 Evidence)

Given that the fundamental pathophysiology of calcium channel antagonist toxicity is an inhibition of calcium flux into target tissues, it seems intuitive that calcium supplementation would be an effective treatment, and to a significant degree, relevant data bear this out. The majority of animal studies using calcium demonstrated a reduced mortality, as well as hemodynamic improvement. However, not every patient predictably responded to calcium in human case series and case reports [5]. It is likely that patients who are severely poisoned and patients in whom therapy is started late constitute the population that may be refractory to calcium therapy of their hypotension [56]. Insufficient doses of calcium are another potential explanation for apparent nonresponders [57].

Calcium concentrations typically are expressed in mg/dL or mmol/L; 1 mg/dL is equivalent to 0.25 mmol/L. Because calcium is a divalent cation, 1 mmol is equivalent to 2 mEq. The use of calcium chloride (CaCl_2) in the treatment of calcium channel antagonist toxicity is preferable to calcium gluconate because the former has approximately three times the molar calcium concentration of the latter. There are 13.6 mEq (or 270 mg) of calcium in 10 mL of 10% CaCl_2 compared with 4.6 mEq (90 mg) in an equivalent ampule of calcium gluconate; 10 mL of 10% CaCl_2 or calcium gluconate contains 1 g of the respective salt. The 13.6 mEq/L of CaCl_2 means that calcium constitutes 27% of the chloride versus 9% in the 4.6 mEq of calcium gluconate.

There are no uniformly accepted infusion protocols for calcium administration in this setting. In a systematic review looking at treatments for calcium channel-blocker poisoning [5], the dose employed was typically an intravenous (IV) single dose of calcium chloride (1–5 g), sometimes followed by an infusion, or the equivalent dose in calcium gluconate. The international working group proposed 0.1–0.2 mL/kg of calcium chloride 10% IV Q10–20 min or an infusion of 0.2 mL/kg/h [46]. Adverse effects, such as hypercalcemia, were rare. Nevertheless, patients who are receiving calcium infusions should be monitored for hypotension, bradydysrhythmias, and conduction disturbances, and it may be imprudent to allow the ionized calcium to exceed 2 mmol/L [58]. Because of the caustic nature of CaCl_2 , it is preferable that it be administered through a large and ideally central line.

High-Dose Insulin (Level II-2 Evidence)

Three mechanisms of action have been proposed for high-dose insulin: (1) it increases inotropy by enhancing coronary blood flow (without increasing oxygen requirements) and by improving calcium handling and glucose transport, (2) it increases intracellular glucose transport by affecting phosphatidylinositol 3-kinase (a major insulin intracellular signaling pathway), and (3) it decreases vascular resistance by increasing endothelial nitric oxide synthase activity

[59]. Therefore, insulin is a potential inotrope, particularly when the myocardium is depressed [60, 61]. Normally, free fatty acids are the preferred myocardial energy substrate. In a canine model of verapamil toxicity [19], the change in myocardial preference for carbohydrates as an energy substrate is accompanied by the development of relative insulin resistance [62, 63]. After supplemental insulin infusion, the suppressed phosphodiesterase III activity was enhanced, preventing lactate formation and allowing for more efficient myocardial carbohydrate use to meet the demand for ATP production.

Insulin also enhances the influx of potassium into the intracellular space, causing hypokalemia and prolonging phase II of the myocardial action potential. During phase II, there is a calcium influx, and the prolongation of this phase increases intracellular calcium concentrations, promoting increased contractility [64]. In this way, the hypokalemia associated with insulin administration may be beneficial, and it has been suggested that it should not be treated unless it is severe [21].

High-dose insulin (IV bolus of 1.0 unit/kg followed by a 0.5–2.0 unit/kg/h infusion) resulted in an improvement in hemodynamics in one of two human observational studies, all five human case series, and in all four animal studies reported in a systematic review, but only animal studies could demonstrate a survival benefit [5]. Therefore, the international working group recommended a bolus of 1 U/kg followed by an infusion of 1 U/kg/h as a single therapy in the presence of myocardial dysfunction or even in the absence of documented myocardial dysfunction if used in combination with fluids, calcium, and vasopressors [46]. Euglycemia should be maintained with dextrose infusion if needed. Considering that incremental doses of high-dose insulin up to 10 U/kg/h are supported by little evidence [65], the international working group suggested this regimen only for patients with evidence of myocardial dysfunction who do not respond to first-line therapies or as a rescue treatment [46]. Based on these recommendations, we suggest a more detailed regimen to initiate, maintain, and terminate the high-dose insulin regimen (Table 2).

Table 2 Suggested regimen for high-dose insulin therapy

Set up D ₅₀ IV ^a (D ₂₅ for small children ^a)
Treat initial hypokalemia, if present
Rapid bedside capillary blood glucose determination. If <200 mg/dL (11 mmol/L):
<i>Adults:</i> administer bolus of 25 g of glucose (50 mL D ₅₀)
<i>Small children:</i> administer bolus of 0.25 g/kg of glucose (1 mL/kg)
Prepare 1 U/mL IV solution of regular insulin
Give initial insulin bolus of 1 U/kg insulin IV
Followed by an infusion of 1 U/kg/hr
Adjust infusion rate based on hemodynamical response
Rapid bedside capillary blood glucose determination at least after 0.5 hour and hourly thereafter
Infuse D ₅₀ (D ₂₅ for small children) at a rate such that blood glucose is maintained in the 150–200 mg/dL range (5.5–11 mmol/L)
Determine serum potassium concentrations hourly for at least 4 hr and then every 2 hr if it has been stable
Continue high-dose insulin therapy until vasopressors are weaned off
If incremental doses of high-dose insulin (level II-3 evidence) is considered:
Concentrate the regular insulin solution (10 U/ml) to avoid fluid overload
Titrate the insulin infusion by 1–2 U/kg/h every 15 min up to 10 U/kg/h based on the hemodynamical response
Rapid bedside capillary blood glucose determination at least every 0.5 hr when titrating up or down and hourly thereafter
Infuse D ₅₀ (D ₂₅ for small children) at a rate such that blood glucose maintained in the 150–200 mg/dL range (5.5–11 mmol/L)
Determine serum potassium concentrations hourly during titration and then every 2 hr if it has been stable
When the patient is improving hemodynamically and the glycemia is decreasing, titrate down the insulin infusion to 1 U/kg/h
Continue high-dose insulin therapy until vasopressors are weaned off

D₅₀ 50% dextrose, D₂₅ 25% dextrose

^aPreferentially in a central line because of its high concentration

Hypoglycemia and hypokalemia were reported as adverse effects [5]. In the series by Yuan and coworkers [21], the mean maximal dextrose requirement was 28.4 g/h (range 10–75 g/h). A total of 100 mL of 50% dextrose solution contains 50 g of glucose. Because of its osmolar effects at

this concentration, dextrose infusion in this setting should be administered through a central venous line. Given the hyperglycemia that may occur as an associated effect of calcium channel antagonist intoxication, not all patients receiving insulin therapy require dextrose supplementation [66, 67].

The clinical pharmacology of high-dose insulin therapy is discussed in greater detail in ► Chap. 147, “Euglycemic Insulin Therapy.”

Norepinephrine or Epinephrine (Level II-3 Evidence)

Vasopressors and inotropes constitute a diverse group of agents, consisting primarily of vasopressin, phenylephrine, norepinephrine, epinephrine, dopamine, dobutamine, isoproterenol, and milrinone. Each has its unique physiologic properties, which render it potentially useful under various clinical circumstances. Ideally, it is advantageous to determine whether the hypotension after calcium channel-blocker intoxication is due to myocardial depression or vasodilation. In a systematic review, norepinephrine infusion showed improved survival and hemodynamics in animal studies and case series [5]. Epinephrine was associated with increased cardiac output in animal studies, but hyperglycemia and increasing lactate were noted as adverse effects [5]. Therefore, the international working group recommended the use of norepinephrine and/or epinephrine in the presence of shock and preferentially norepinephrine in the presence of vasodilatory shock [46]. To be noted, Levine et al. reported a maximal infusion rate up to 100 µg/min for norepinephrine and 150 µg/min for epinephrine without significant ischemic complications [68]. Dopamine was not suggested by the international working group, as it yielded variable results [46].

Other Vasopressors and Inotropes

Patients with myocardial depression seem to benefit most from agents with β-adrenergic activity, such as dobutamine (level II-3 evidence) [46]. However, given the risk of hypotension, this therapy would not be suggested in other circumstances [68]. Isoproterenol, the most potent

β -agonist of this group, has been used successfully in animal models [69], although evidence for its efficacy in humans is only anecdotal. There is concern for the arrhythmogenic and myocardial ischemic effects of isoproterenol. Inamrinone is an inhibitor of phosphodiesterase III that is thought to prevent the degradation of cAMP, theoretically resulting in an enhanced flux of calcium into the cell. The inhibition of this enzyme may be insufficient, however, to increase cAMP concentrations above the threshold required for an inotropic myocardial response [70], and there is the theoretical concern that because inamrinone may upregulate the dihydropyridine receptor, the potential for antagonism of the calcium channel is increased [71]. Animal studies have shown variable results [72–76].

Patients with significantly reduced SVR may benefit from the α_1 -agonist actions of norepinephrine [5]. However, in one animal study of calcium channel antagonist intoxication, increasing SVR with phenylephrine, a pure α_1 -agonist, appeared to worsen myocardial depression by increasing afterload [77]. Vasopressin was also reported as potentially harmful in one blinded, randomized controlled trial using a swine model of verapamil poisoning [78], although one case series of two patients [79] and one case report [80] showed blood pressure improvement when added to other vasopressors.

In summary, concerning the use of vasopressors and inotropes, the international working group recommended the use of norepinephrine and epinephrine for the treatment of calcium channel-blocker poisoning and considered the use of dobutamine if the patient presents with cardiogenic shock. To be noted, atropine is also considered as a first-line treatment if the patient presents with bradycardia, considering that the systematic review revealed occasional improvements [46].

Symptomatic Patients: Refractory to First-Line Treatments

In cases refractory to first-line treatment, the international working group suggested the use

of incremental doses of high-dose insulin, up to 10 U/kg/h, as described previously in patients presenting with myocardial dysfunction [46]. In patients presenting with bradycardia or high-grade atrioventricular block, the working group suggested the use of a pacemaker [46]. Lipid emulsion therapy was also suggested [46].

Cardiac Pacing (Level II-3 Evidence)

Cardiac pacing has been reported to be effective in patients with bradydysrhythmias induced by calcium channel antagonists [27, 81]. However, it has been reported in some patients with high-degree atrioventricular nodal block that pacemaker capture may not occur [27]. Therefore, the international working group proposed trying transcutaneous pacing attempts first to avoid spending time on a therapy that involves risk and may not be effective [46].

Lipid Emulsion (Level II-3 Evidence)

Concerning the use of lipid emulsion therapy, it is hypothesized that this creates a separate intravascular compartment within which lipophilic drugs are sequestered from their sites of action [82]. This treatment also provides fatty acids that may be used by the myocardium and may increase intracellular calcium [83].

In animal models of IV verapamil toxicity and several case reports, the administration of a 20% lipid emulsion was associated with improvement in hemodynamics and survival [5]. However, there was no significant improvement or an increased mortality in two animal studies using an oral verapamil toxicity model (abstract available only) [84, 85]. In one case report [86], adverse effects, such as hypertriglyceridemia and hypoxemia, were observed with lipid emulsions when used at exceptionally high doses (2 L). Hyponatremia, extreme lipemia, and an inability to obtain reliable complete blood count, arterial blood gas, or electrolyte levels were also noted. The most commonly recommended dose is 1.5 mL/kg of 20% lipid emulsion administered as a bolus, repeated up to two times, as needed, until clinical stability is achieved, followed by an infusion of 0.25 mL/kg/min for 30–60 min [87].

The clinical pharmacology of lipid emulsion therapy is discussed in greater detail in ► [Chap. 152, “Lipid Resuscitation Therapy.”](#)

Symptomatic Patients: Refractory Shock or Peri-arrest

In refractory shock or peri-arrest patients, the international working group recommended the use of incremental doses of high-dose insulin, up to 10 U/kg/h, and lipid emulsion therapy, as previously described, if not already tried. In the presence of myocardial dysfunction, the working group members also added the consideration of extracorporeal life support in centers where the therapy is available.

Extracorporeal Life Support (Level II-3 Evidence)

In an observational study conducted by Masson et al., extracorporeal life support was associated with a lower mortality when initiated in a group of 14 patients compared with conventional therapies provided to a group of 48 patients (48% vs. 86%, respectively) after adjustment for the Simplified Acute Physiology Score (SAPS) II and beta-blocker intoxication [88]. Most human case series reported positive functional outcomes in the majority of survivors, but some patients experienced limb ischemia, thrombosis, or hemorrhage [89–91]. It is important to note that a Canadian cost-effectiveness analysis assessing the use of this therapy in patients in shock or cardiac arrest secondary to cardiotoxicant poisoning concluded that cost was not an argument against providing extracorporeal life support in centers where the therapy is available [92].

Patients in Cardiac Arrest

For a patient who sustains a cardiac arrest, the pathophysiologic changes induced by calcium channel antagonists are potentially completely reversible despite prolonged resuscitations, as exemplified by one patient who was in cardiac

arrest for 2.5 h and recovered fully [93, 94]. A patient in cardiac or circulatory arrest should be treated aggressively using calcium IV (level II-3 evidence) and lipid emulsion therapy (level II-3 evidence) in addition to standard advanced cardiac life support. [46] The use of extracorporeal life support should also be considered in centers where the therapy is available (level II-2 evidence) [46].

Other Treatments

Glucagon

Glucagon is a 29-amino acid polypeptide hormone secreted by pancreatic beta cells. It has a molecular weight of 3485 daltons (Da), and its volume of distribution is 0.04 L/kg. Well known for its biologic actions of increasing blood glucose and glycogenolysis, glucagon is also a potentially powerful cardiac inotrope and chronotrope [95, 96], acting at specific cardiac G protein-coupled receptors [97]. When bound to its receptor, glucagon stimulates an increase in cAMP, which leads to an increase in myocardial calcium influx [98, 99].

A study in isolated rat hearts, using a Langendorff preparation poisoned with various calcium channel blockers, showed that glucagon can reverse the depression of the rate of pressure change in the ventricle, dP/dt, by these agents. A clinically achievable serum glucagon concentration of 0.5 mmol was required [99]. Similarly, several animal studies with rodents [72, 100] and dogs [60, 77, 101, 102] reported that glucagon reverses verapamil-induced bradycardias. However, four of five studies employing canine models of verapamil intoxication failed to show a beneficial effect of glucagon on mean arterial pressure [60, 101–103]. Only one of the three human case series documented by the systematic review reported clinical improvement, and side effects, such as hyperglycemia and vomiting, have been reported [5]. Based on variable effects, possible side effects, and the availability of more effective alternatives, the international working group suggested not to use glucagon in calcium channel-blocker poisonings [46].

Methylene Blue

Case reports of amlodipine poisoning describe hemodynamic improvement after the administration of methylene blue (1–2 mg/kg bolus followed by infusions) [104–106]. In amlodipine poisoning, vasodilation occurs through the stimulation of nitric oxide release with increased cyclic guanosine monophosphate (cGMP) production. Methylene blue inhibits guanylate cyclase, the enzyme responsible for the production of cGMP, and it also has the ability to scavenge nitric oxide, as well as to inhibit nitric oxide synthase [105]. However, this therapy has only been documented by case reports thus far.

Other Therapies

As underlined by the systematic review published in 2014 [5], the use of 4-aminopyridine, levosimendan, L-carnitine, plasma exchange, albumin dialysis, charcoal hemoperfusion, continuous venovenous hemodiafiltration, intra-aortic balloon pump, left ventricular assist devices, and an Impella have been reported in humans without sufficient positive evidence available to recommend these interventions. The use of bay K8644, CGP28932, cyclodextrin, sugammadex, liposomes, fructose 1,6-diphosphate, PK11195, triiodothyronine, digoxin, and bicarbonate has only been studied in animals [5].

Criteria for ICU Discharge in Calcium Channel Antagonist Poisoning

No requirement for mechanical ventilation
Stable hemodynamic status

Special Populations

Pediatric Patients

There have been two retrospective case series of pediatric calcium channel antagonist ingestions. One involved only 29 cases [107]. The second study comprised 283 patients with a mean age of 27 months (range 8 months to 6 years) [48]. The first study called attention to the potential

seriousness of sustained-release calcium channel antagonist ingestions in children. In the larger study, 61% of the cases involved this type of formulation. Even the larger study by Belson and colleagues [48] is limited, however, in the amount of information available, as it was simply an analysis of data available to one poison control center over a 6-year period. Much about patient history, presentation, and clinical course is unknown. Little information can be gleaned about therapeutic options in children based on these studies, and in the absence of other data, they should be treated in the same fashion as adults. However, in the absence of evidence that children respond differently than adults to CCB poisoning, it may be reasonable to apply adult recommendations to the pediatric population.

Common Errors in Calcium Channel Antagonist Poisoning

Resorting to whole-bowel irrigation or gastric lavage despite its lack of documented efficacy for reducing calcium channel antagonist absorption

Failing to recognize when invasive hemodynamic monitoring is indicated

Administering fluids despite the absence of fluid responsiveness

Discontinuing high-dose insulin therapy when the patient is hypoglycemic, but is still hemodynamically unstable

Key Points in Calcium Channel Antagonist Poisoning

1. Calcium channel antagonists induce a syndrome primarily characterized by
Hypotension
Bradycardia and cardiac conduction disturbances
Hyperglycemia
2. The above triad may not be present in all patients.
3. Presentations may be delayed with sustained-release preparations.

(continued)

4. Treatment options are the following:
 - First line: fluids, calcium IV, high-dose insulin, norepinephrine/epinephrine, dobutamine if in cardiogenic shock, and atropine if bradycardia is present.
 - When refractory to first-line treatments: incremental doses of high-dose insulin, lipid emulsion therapy, and cardiac pacing if bradycardic.
 - When refractory shock or peri-arrest: consider extracorporeal life support if evidence of myocardial dysfunction.
 - In cardiac arrest: administer calcium IV and lipid emulsion therapy in addition to standard advanced cardiac life support and initiate extracorporeal life support in centers where the therapy is available.
5. Calcium channel blockers are not removed effectively by hemodialysis.
6. Be vigilant for ischemic complications that may result from protracted hypotension and its treatment.

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The medical use of cardiac glycosides began in 1785 with the publication of Withering's monograph on the therapeutic efficacy and toxicity of the leaves of the common foxglove plant, *Digitalis purpurea*. Various glycosides including digitoxin and ouabain were then extracted from plants, and digitalis glycosides have been widely prescribed for more than 230 years.

Digitalis still remains an important and useful therapy for patients with heart failure and/or atrial fibrillation [1]. However, despite a pertinent contribution of their pharmacological properties combining positive inotropic and negative chronotropic effects to reduce symptoms and hospital admissions in heart failure patients, meta-analyses showed neutral effect on all-cause mortality and robust trial data are lacking in patients with atrial fibrillation [2, 3]. Following the availability of therapies providing proved prognostic benefits in these patients including angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, and cardiac resynchronization therapy, prescription rates of digoxin have fallen substantially [4]. Their use is now restricted to the treatment of heart failure due to reduced ejection fraction with or without supraventricular dysrhythmias including atrial fibrillation.

Digitalis poisoning may result from either acute suicidal massive ingestion or more frequently from chronic toxicity in patients with cardiac diseases and renal failure. Digitalis overdose may lead to life-threatening toxicity. In 1976,

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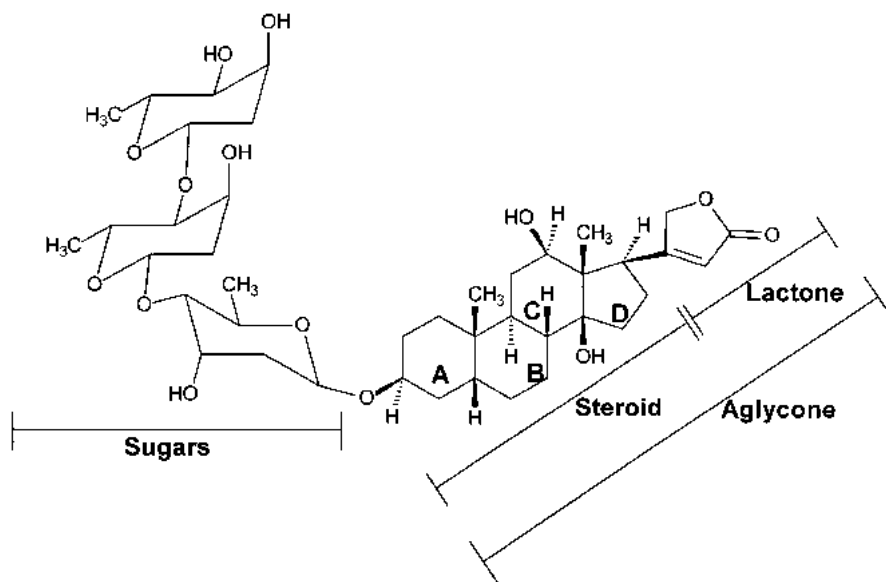


Fig. 1 Chemical structure of digoxin. Digitoxin lacks a hydroxyl group on the C ring, resulting in greater lipophilicity

Smith and colleagues reported the first case of human digoxin poisoning treated with anti-digoxin-specific Fab fragments, unveiling the modern era of treatment of cardiac glycoside toxicity [5].

Biochemistry of Digitalis Glycosides

Cardiac glycosides of therapeutic interest share a common steroid nucleus structure with one or more glycosidic residues bound at its C3 (Fig. 1). Their potent and selective properties to inhibit the membrane Na^+/K^+ -ATPase are due to the β -hydroxyl group at its C14 and the unsaturated lactone at its C17. Removal of the glycoside moieties (forming the genin or aglycone part) only minimally affects their pharmacological properties. The absence of a hydroxyl group at the C12 of the nucleus distinguishes digitoxin from digoxin. In addition to foxglove (*Digitalis*), other cardiac glycosides are divided in two subclasses, the cardenolides and the bufadienolides [6]. Cardenolides are present in *Antiaris toxicaria* (antiarin), *Nerium oleander* called common oleander (oleandrin, folinerin, adynerin, digitoxigenin), *Thevetia peruviana* called yellow

oleander (thevetin A and B, peruvoside, neriifolin, thevotoxin, ruvoside, and theridoside), *Cerbera odollam* called sea mango (cerberin), *Convallaria majalis* called lily of the valley (convallarin, convallamarin, and convallatoxin), and *Strophanthus* sp. (ouabain). Bufadienolides are present in *Urginea maritima* called red squill (scilliroside and proscillaridin A, scillarene A, scilliglaucoiside, and scilliphaeoside) and *Rhinella marina* called cane toad (bufalin, manrinobufagenin, and telocinobufagin). An ouabain-like compound (resibufogenin) is also found in the skin of the bufo toad (*Bufo* spp.). Neriifolin, cerberin, and cerberigenin, contained in the fruit kernel of the red-eye-sea mango tree *Cerbera manghas* L. on which the coconut crab *Birgus latro* L. feeds, are the toxic agents leading to cardenolide poisoning when eating this kind of crab.

Pharmacology and Mechanisms of Toxicity

Digitalis reversibly inhibits the membrane-bound alpha subunits of the Na^+/K^+ -ATPase pump in cardiac, smooth, and skeletal muscles and lungs

and kidneys [1, 7, 8]. By increasing the intracellular sodium concentration in cardiomyocytes, digitalis promotes activity of the $\text{Na}^+/\text{Ca}^{2+}$ -exchanger, thus enhancing the intracellular calcium concentration which is taken up by the sarcoplasmic reticulum. This action directly results in the greater interaction between the myocardial contractile proteins, increasing the force of cell contraction and improving the left ventricular systolic function. Consistently, the intravenous digitalis administration results in the immediate evidence of significant increase in stroke index, cardiac output, left ventricular ejection fraction, exercise tolerance, and decrease in pulmonary capillary wedge pressure [9]. Within the central nervous system, digitalis-mediated Na^+/K^+ -ATPase also reduces the heart rate, by exerting a parasympathomimetic action on the sinoatrial and atrioventricular nodes, slowing their conduction and increasing the refractory period. Additionally, digitalis is responsible for vagal activation shifting the autonomic balance toward parasympathetic dominance. By reducing plasma norepinephrine, digoxin modulates the initially compensatory but finally detrimental neurohormonal activation observed in heart failure patients. This direct anti-sympathetic activity likely reflects the attenuation and sensitization of the augmented baroreflex in heart failure patients with raised filling pressures. Taken together, the pharmacological ability of digitalis to simultaneously increase cardiac inotropy and constrain cardiac chronotropy is unique. Digitalis increases vagal tone and decreases sympathetic activity. The plasma concentration and type of digitalis clearly determine which mechanism predominates. These mechanisms of action are common to all cardiac glycosides, although largely described using digoxin and ouabain; however, differences exist among the glycosides and influence the toxicity and the therapeutic response. Consistently, insulin reverses the effects of digoxin but not ouabain on Na^+/K^+ -ATPase due to their binding to different sites. Similarly, pharmacokinetics highly varies according to the digitalis molecule (Table 1).

In overdose, digitalis-related Na^+/K^+ -ATPase inhibition may result in excessive intracellular

Table 1 Pharmacokinetics of digoxin and digitoxin

Digoxin
<i>Absorption:</i> mainly in the proximal small intestine, bioavailability of 80%
<i>Volume of distribution:</i> 5.6 L/kg; slow but widespread dissemination into the tissues, particularly the myocardium, kidneys, and skeletal muscle; duration of distribution (2–6 h)
<i>Protein binding:</i> 20–30%
<i>Active metabolites:</i> digoxigenin, digoxigenin monodigitoxiside and bis-digitoxiside
<i>Predominant elimination route:</i> kidney
<i>Elimination:</i> as unaltered in urine (93%)
<i>Elimination half-life:</i> mean 40 h, range 20–50 h
Digitoxin
<i>Absorption:</i> in the stomach (15%) and proximal small intestine (85%), bioavailability of >90%
<i>Volume of distribution:</i> 0.56 L/kg; rapid and widespread dissemination into the tissues due to its high lipophilic properties
<i>Protein binding:</i> 95%
<i>Active metabolites:</i> digoxin (minor pathway)
<i>Predominant elimination route:</i> liver (75–90%)
<i>Elimination:</i> as unchanged in the feces and urine
<i>Elimination half-life:</i> 4.9–8.1 days

Ca^{2+} increase resulting in a transient late depolarization (delayed afterdepolarization) accompanied by aftercontraction. Additionally, the increase in sympathetic activity accompanied by nonuniform increase in automaticity and vagal nerve-mediated depression of conduction in His-Purkinje and ventricular myocytes may cause life-threatening dysrhythmias.

Clinical Presentation and Life-Threatening Complications

Poisonings mainly result from pharmaceutical preparations of digitalis and more rarely from self-made preparations of cardiac glycoside-containing plants. Acute digitalis poisoning may result from accidental or suicidal exposure to a single elevated dose. Due to its narrow therapeutic index, chronic toxicity of digitalis has been reported in 6–23% of treated patients, particularly in the elderly [10, 11]. Several factors may alter patient's sensitivity to digitalis including acute

Table 2 Main predisposing and precipitating factors for digitalis toxicity

Advanced age
Underlying cardiac disease
Respiratory disease
Hypoxia, respiratory alkalosis, or acidosis
Renal insufficiency
Hypothyroidism
Electrolytes disturbances
Hypokalemia, hyperkalemia, hypercalcemia, hypomagnesemia
Drug-drug interactions
Diuretics, quinidine, amiodarone, verapamil, β -adrenergic blockers, β -adrenergic agonists, amphotericin B, corticosteroids

renal impairment and drug-drug interactions (Table 2) [10–17]. Macrolides, quinidine, verapamil, diltiazem, amiodarone, and others increase digoxin concentrations, mainly by competitions on their binding sites in tissues with a risk of digitalis toxicity.

Clinical and ECG Features

In the setting of acute poisoning, symptoms generally occur within 6 h of ingestion, but life-threatening symptoms may occur with delay, reflecting the relatively slow tissue distribution of digitalis. The noncardiac manifestations of digitalis toxicity are highly prevalent including gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal pain, and diarrhea), neurological symptoms (fatigue, weakness, hallucinations, delirium, and psychiatric disorders), and visual manifestations (scotoma, blurred vision, color aberration, and blindness). Mesenteric ischemia has been reported rarely. Physician should suspect digitalis toxicity and measure serum digoxin concentration in the onset of unexplained gastrointestinal, neurological, or visual manifestation in a digitalis-treated patient.

Digitalis-related cardiac toxicity results from the combination of conduction and rhythm disturbances [6]. Toxicity should be suspected when there is evidence of increased automaticity and depressed atrioventricular conduction. Flattening

or inversion of the T wave and depression of the ST segment related to long-term digitalis treatment should not be considered as toxicity criteria. The most common cardiac abnormality induced by digitalis is sinus bradycardia. Characteristic electrocardiogram (ECG) changes in the setting of digitalis overdose show dysrhythmias like atrial tachycardia, accelerated junctional rhythms, and fascicular tachycardia, as well as conduction disturbances like premature contractions of junctional or ventricular origin, sinoatrial block, and all degrees of atrioventricular blocks. In the chronic poisoning, the combination of atrial fibrillation and conduction disturbances is commonly observed resulting in irregular bradycardia. Onset of junctional tachycardia is highly suggestive too. Sinus arrest or exit block may occur. Ventricular ectopics and tachycardias are also reported and may be related to the underlying cardiac disease. Life-threatening arrhythmias primarily consist of third-degree atrioventricular block, ventricular tachycardia, and ventricular fibrillation. The contribution of the underlying cardiac disease including cardiomyopathy and coronary artery disease to digitalis toxicity is not clear [12].

When digitalis toxicity is suspected, kalemia and renal function should be urgently measured. Other electrolyte abnormalities should be interpreted in the onset of chronic digitalis poisoning according to concomitant conditions and medications.

Fatality and Prognosticators

Digitalis poisoning-attributed mortality rate ranged from 4.6% to 41% before the availability of anti-digoxin Fab fragments [18, 19] but remained between 6% and 29% after their availability [12, 15, 21]. Poor prognostic factors in acute digitalis poisoning were determined based on series of acute digitoxin poisoning and include age older than 55 years, male sex, hyperkalemia, and any degree of atrioventricular block (Table 3) [20]. Fatality rate significantly increases when serum potassium concentration is >4.5 mmol/L in the absence of adequate treatment. Ventricular dysrhythmias refractory to electrical

Table 3 Prognostic factors of digitalis poisoning^a (The red arrows indicate the conditions of the poorest prognosis and the green arrows the conditions of the best prognosis)

	Age	Atrioventricular block	Plasma K ⁺ >4.5	Death rate (%)
Female	< 55	Yes	Yes	17
		No	No	4
	> 55	Yes	Yes	8
		No	No	2
		Yes	Yes	49
		No	No	18
Male	< 55	Yes	Yes	29
		No	No	9
		Yes	No	38
		No	Yes	11
	> 55	Yes	No	20
		No	Yes	6
		Yes	No	74
		No	Yes	35
		Yes	No	50
		No	No	23

^aData are based on 179 patients who had acutely ingested >2 mg of digitoxin. Adapted from Dally et al. [20]

cardioversion are the leading cause of death (70%), followed by advanced atrioventricular block resulting in asystolic arrest (20%) and cardiac insufficiency causing multi-organ failure (10%). Rarely, death may result from mesenteric infarction.

Diagnosis

Diagnosis depends on whether digitalis poisoning is chronic or acute. Acute poisoning is typically straightforward. QT interval modifications are of diagnostic value only in patients not previously treated with digitalis. Diagnosis is confirmed by the measurement of the serum digitalis concentration. By contrast, in chronic poisoning, diagnosis is more difficult because noncardiac symptoms are nonspecific and some ECG abnormalities look like those related to the underlying cardiac disease. Thus, serum determination of digitalis concentration is the key step to assess the diagnosis and should be largely prescribed in cases of suspected digitalis intoxication, although digoxin toxicity occurs to date less frequently than historically reported.

The range of therapeutic (steady-state) concentrations of digoxin and digitoxin are

0.5–2.0 ng/mL (0.6–2.6 nmol/L) and 10–30 ng/mL (13–39 nmol/L), respectively. According to the various factors that may influence digitalis toxicity, no single serum concentration can definitively establish the presence or absence of toxicity [12]. Of 3434 serum digoxin concentrations assayed in 2009 patients, 320 (9.3%) were higher than the upper limit of the therapeutic range, but only 83 of the 138 patients evaluable for digoxin toxicity had clinical evidence of toxicity for an overall incidence of 4.1% [22]. In another retrospective study reporting 6133 digoxin concentrations measured in 5100 patients, only 13 among the 460 patients with serum digoxin concentration >2 ng/mL (>2.6 nmol/L) were diagnosed as digoxin overdose before obtaining the laboratory results [23]. Hospitalized patients with serum digoxin > 2.1 ng/mL (>2.7 nmol/L) spent a mean of 12.1 ± 17.1 days in hospital. The mean time to death for the patients who died was 5 ± 3.1 days. Two thirds of the patients who died in the hospital had increasing digoxin levels before death. In this study, renal failure was not significantly associated with increased mortality while serum digoxin concentration was. Mortality rate in patients with elevated digoxin concentrations and preexisting ECG abnormalities was 8% compared with 40% in patients with elevated

digoxin concentrations and new ECG abnormalities [23]. A fatality rate of 50% was reported in patients with digoxin concentrations > 6 ng/mL (7.7 mmol/L).

Serum potassium concentration significantly influences the toxicity associated with a given digitalis concentration [24]. In contrast to acute poisoning, most of the more serious arrhythmias found in patients with chronic toxicity are associated with serum potassium concentrations < 3.7 mmol/L [25]. An indication for transient pacemaker placement was present more frequently when digitalis intoxication was accompanied by hypokalemia (72%) than normokalemia (37%). In patients with digitalis intoxication-related dysrhythmias, normokalemic patients had a mean serum digoxin concentration of 6.68 ± 0.17 ng/mL (8.55 ± 0.22 mmol/L), whereas hypokalemic patients had a mean serum digoxin level of 1.13 ± 0.04 ng/mL (1.45 ± 0.05 mmol/L). Repletion of serum potassium sometimes corrected the dysrhythmia without significant changes in serum digoxin concentration. Hypomagnesemia likewise increases digitalis-related toxicity and may be a more frequent contributor to digoxin toxicity than hypokalemia [25]. Finally, prompt termination of the arrhythmias when stopping the drug administration or after infusing anti-digoxin-specific Fab fragments supports the diagnosis of chronic toxicity.

Management

Most cases of chronic toxicity are minor, and the patient may only require temporary withdrawal or reduction in his digitalis dosage on an outpatient or inpatient basis. However, more aggressive hospital treatment is sometimes mandatory to reduce the risk of death.

Gastrointestinal Decontamination

A single dose of activated charcoal (50 g) should be administered to all patients with acute ingestion of a potentially toxic exposure if ingestion occurred less than 2 h before. Although no clinical

trial confirmed its efficacy, this approach is based on the ability of charcoal to reduce digoxin peak in serum as well as on its safety (Grade III recommendation). There are insufficient clinical data to support or exclude the use of repeated doses of activated charcoal to enhance digitalis elimination [26]. Similarly, usefulness of gastrointestinal decontamination in chronically poisoned patients remains to be determined.

Extracorporeal Removal Techniques

The international EXTRIP work group published a systematic review and recommendations on the extracorporeal treatment for digoxin poisoning [27]. Based on data from 84 patients including six fatalities, they concluded that digoxin is slightly dialyzable (level of evidence = B) and that extracorporeal removal techniques are unlikely to improve the outcome of digoxin-toxic patients whether or not anti-digoxin Fab fragments are administered. Despite the lack of robust clinical evidence, they recommended against the use of extracorporeal removal techniques in cases of severe digoxin poisoning when Fab fragments were available (1D) and also suggested against the use of extracorporeal removal techniques when Fab fragments were unavailable (2D).

Indications for ICU Admission

All patients suspected of acute or chronic digitalis poisoning with symptoms, ECG or electrolyte abnormalities, or any other significant underlying morbidity should be admitted to the intensive care unit given the high fatality rate associated with digitalis poisoning. In contrast, clinically stable patients receiving digoxin who meet the following criteria:

- Mildly elevated serum digoxin concentrations
- Without signs and symptoms of digoxin toxicity
- With serum potassium > 3.7 mmol/L and < 4.5 mmol/L
- With no history of severe cardiac disease

are at low risk of developing serious digoxin toxicity and may not require treatment beyond the discontinuation of digoxin therapy.

Electrolyte Disorders

Correction of hypokalemia, hypomagnesemia, and dehydration is important in the presence of chronic toxicity. In chronically treated patients, hyperkalemia may result not only from digitalis toxicity but also from renal insufficiency and other medications (potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and nonselective β -blockers) that should be withdrawn temporarily. In acute poisoning, hyperkalemia (>4.5 mmol/L) is the hallmark of severe toxicity, and the patient may thus require anti-digoxin Fab fragments. Calcium salts should be avoided since one major mechanism of digitalis toxicity is primarily calcium loading of the myocardium. In the presence of severe hyperkalemia (>5.6 mmol/L), glucose/insulin, sodium bicarbonate, and sodium polystyrene sulfonate enema may be started; but severe hypokalemia may result if anti-digoxin Fab fragments are simultaneously administered.

Non-antidotal Therapies

Atropine antagonizes cardiac glycoside vagal activation, increasing heart rate. Atropine is the first-line treatment of digitalis-induced sinus bradycardia or atrioventricular conduction disturbance [6, 28]. The therapeutic success of atropine is unpredictable because the more direct non-vagotonic cardiac effects of digitalis at toxic doses may predominate. Doses of 0.5–1 mg are recommended but higher doses up to 2–3 mg have been used for persistent bradycardia. However, the use of a large cumulative dose of atropine may lead to deleterious anticholinergic encephalopathy.

Antidysrhythmics, including phenytoin, lidocaine, procainamide, propranolol, and amiodarone, have been used to treat digitalis-

induced arrhythmias [29] (Grade II-3 evidence). Propranolol and procainamide must be avoided due to the risk of depression of cardiac conduction and contractility. Quinidine should not be used since it may prolong digoxin toxicity as a result of drug-impaired clearance. Lidocaine and phenytoin should be considered antiarrhythmic drugs of choice in the absence of anti-digoxin Fab fragments to treat digitalis-induced dysrhythmias because they have little effect on the sinus node and on AV conduction [7]. The role of fosphenytoin has not been evaluated in this setting.

Magnesium sulfate was effectively used to treat digoxin-induced arrhythmias, even in patients with normal or slightly elevated serum magnesium concentrations [30–32] (Grade II-3 evidence). Magnesium potentiates the activity of Na^+/K^+ -ATPase without altering digoxin binding. A decrease in serum potassium concentration after magnesium therapy is obtained, but adverse effects from hypermagnesemia, particularly in patients with impaired renal function, may be observed. Hypermagnesemia is unlikely to occur with an initial 10–20 mmol magnesium bolus, but is a real issue with infusion or repeated doses. Anti-digoxin Fab fragments are the most effective and safe antidysrhythmic strategy to prevent and reverse digitalis-induced life-threatening arrhythmias.

Transvenous or transcutaneous cardiac pacing may be used to correct digitalis-induced bradycardia or conduction disturbances and to prevent ventricular dysrhythmias [33]. Retrospective studies have suggested that pacing does not significantly decrease the mortality rate of acute digitalis intoxication [33, 34]. Given the high rate of nonfatal and fatal complications associated with cardiac pacing in acute digitalis toxicity, electrical cardioversion is potentially hazardous, and Fab fragment therapy should be considered first-line treatment.

Anti-digoxin-Specific Fab Fragments

The efficacy and safety of anti-digoxin-specific Fab fragments have been consistently reported in

adults [11–17, 21] and children [35–39] as well as in acute and chronic poisonings (Grade I evidence). A cost-effectiveness analysis supported the use of Fab fragments in the treatment of digoxin toxicity [40]. According to their cross-reactivity, Fab fragments can effectively neutralize digoxin, digitoxin, methyl-digoxin, β -acetyl-digoxin, lanatoside, ouabain, proscillaridin, and scilliroside and cardiac glycosides contained in yellow oleander and in toad and crab venom [41–46]. Anti-digoxin Fab fragments are indicated, based on internationally accepted criteria, to treat patients who present life-threatening tachy-bradyarrhythmias, hyperkalemia (>6 mmol/L), or hemodynamic instability with an elevated digoxin concentration (>2 ng/mL or 2.6 nmol/L) [47].

The theoretical maximum dose of anti-digoxin Fab Fragments is the one required to neutralize the body burden of digitalis. This dose can be calculated using either the supposed ingested dose or the serum digitalis concentration (Table 4). When no data are available regarding the presumed ingested dose or the plasma concentration, empirical dosing recommendations are to administer 400–800 mg of Fab (closely equivalent to 10–20 vials of DigiFab[®]) in acute toxicity and 120–240 mg of Fab (3–6 vials of DigiFab[®]) in chronic toxicity.

However the necessity of administering an equimolar dose of anti-digoxin Fab fragments to obtain an initial beneficial response is not supported by the literature [12, 21, 47]. The calculation of the equimolar dose of Fab fragments based on either the estimated ingested dose or the serum digitalis concentration frequently overestimates the amount of digitalis in the body. The calculation based on the estimate of ingested dose uses only the theoretical bioavailability of cardiac glycosides, whereas during the time interval between ingestion of digitalis and Fab administration, a fraction of the dose of digitalis has been already eliminated [48]. The relationship between the serum digitalis concentration and the corresponding actual amount in the body should also be questioned in patients admitted early during the course of the acute poisoning, since it is only accurate during the drug

Table 4 Calculation of dosage of Fab fragments from body load of digitalis

From the ingested amount, if the amount and type of digitalis are known:
$Q = IA \cdot A$
Q = body load of glycoside (mg)
IA = ingested amount of glycoside (mg)
A = digoxin bioavailability (0.6) or digitoxin bioavailability (1)
From the serum glycoside concentration, if the steady-state serum concentration is known:
$Q = SGC \cdot Vd \cdot Wt \cdot 10^{-3}$
Q = body load of glycoside (mg)
SGC = serum glycoside concentration (ng/mL)
Vd = distribution volume: 5.61 L/kg (digoxin) or 0.56 L/kg (digitoxin)
Wt = patient weight (kg)
Conversion factors: $SGC \text{ (nmol/L)} \times 0.781 = SGC \text{ (ng/mL)}$ for digoxin $SGC \text{ (nmol/L)} \times 0.765 = SGC \text{ (ng/mL)}$ for digitoxin
Determination of the number of 40-mg vials needed ^a : $Q/0.5$
Empirical dosing recommendations with 40-mg vials (according to the authors)
Acute ingestion (adult): 2–4 up to 10–20 vials
Chronic ingestion (adult): 1–2 up to 3–6 vials

Note: For some authors, low dosage at least as starter should be sufficient; calculated full neutralizing doses of digoxin-Fab are expensive and may not be required

^aFab fragment dose (mg) = [molecular weight Fab (50 kd)/molecular weight digoxin (781 d)] \times body load (mg). Using this calculation, 0.5 mg of digoxin is neutralized by each 40-mg vial of Fab fragments

elimination phase and not during its distribution phase, which may last 6 h for digoxin [29]. Thus, since the lowest effective anti-digoxin Fab dose regimen is still not clearly determined, dosing regimens based on much lower initial doses were recently proposed, with 40 mg (one vial) for chronic poisoning and 80 mg (two vials) for acute poisoning, to be repeated after 60 min if inadequate response or recurrence, or earlier if there is a clinical deterioration [47]. Larger initial doses, including that which will achieve full neutralization, were recommended only in peri-arrest patients. Consistently, effectiveness of only 1–2 vials of anti-digoxin Fab fragments to bind all free digoxin in chronic digoxin poisonings was reported in a recent prospective observational study [16]. However, moderate improvement in

heart rate and potassium following the Fab administration was usually observed, suggesting that bradyarrhythmia and hyperkalemia in the chronically poisoned patients could be related to other comorbidities including chronic renal failure, heart diseases, and medications like β -adrenoceptor blockers and calcium antagonists.

On another hand, since equimolar neutralization with Fab fragments is expensive and sometimes not available in small hospitals, antidote administration is often delayed or withheld until serious arrhythmias occur. Under these conditions, ventricular fibrillation and asystole often result in postanoxic brain damage or refractory cardiogenic shock [11–17, 21]. Interestingly, factors associated with the use of anti-digoxin Fab fragments were identified based on a retrospective review of patient records over 2 years in 20 city hospitals in France [17]. Acute overdose (odds ratio, 15.74), antidote availability in the hospital (11.06), serum potassium (1.81), and heart rate (0.96) were significantly linked to the use of anti-digoxin Fab fragments. Mortality was clearly lower in Fab-treated (6%, 4/67) compared to untreated patients (15%, 117/770). Thus, considering their safety, prophylactic administration of anti-digoxin Fab fragments to prevent the occurrence of life-threatening arrhythmias was proposed [48]. In France, this approach was refined, taking into account (1) the prognosticators of acute digitoxin poisoning [20, 49], (2) the lack of evidence for the efficacy of pacing [33, 34], and (3) the frequency and severity of adverse effects of cardiac pacing. Two treatment strategies for two distinct situations of digitalis poisonings were proposed [50]. In patients exhibiting life-threatening disturbances, an equimolar neutralizing dose of anti-digoxin Fab fragments (curative dose) was recommended to be rapidly administered. In patients with mild bradycardia (<50 /min), regardless of the conduction disturbances, especially if associated poor prognostic factors [20], when atropine fails to accelerate the cardiac rhythm to greater than 50/min, a half equimolar neutralizing dose of anti-digoxin Fab fragments (“prophylactic” dose) was recommended. Particular attention was requested to >55 -year-old patients, patients with underlying cardiac disease,

and patients with serum potassium >4.5 mmol/L [51]. This French strategy based on the first-line use of anti-digoxin Fab fragments as curative vs. prophylactic treatment according to the patient’s conditions was associated with a reduced mortality rate (7.6%) [21].

There are no known contraindications, apart from allergy to sheep immunoglobulin. No interactions with other medications have been reported. During and after Fab administration, vital signs, ECG, and serum potassium levels should be recorded frequently to assess the efficacy and safety of treatment. Improvement in cardiac and noncardiac signs and symptoms of digitalis toxicity occurs rapidly after the anti-digoxin Fab fragments administration, with an initial response at a median of 19 min from termination of infusion and complete response at a median time of 88 min. [15] Neither age nor concurrent cardiac disease was associated with any significant delay in the initial response. Partial or no response resulted from (1) a moribund situation with multi-organ failure at the time of infusion, (2) an inadequate dose of Fab, (3) a concomitant toxicity from other drugs, and (4) an underestimated severity of underlying cardiac disease. None of the patients without heart disease who ingested a single acute digitalis dose did not respond to Fab [12]. The administration of additional doses of anti-digoxin Fab fragments should be considered in patients in whom life-threatening toxicity reappears or persists despite initial treatment. Recrudescence toxicity was reported in 20 of the 717 patients (2.8%) within 3 days of the initial Fab treatment in most of the patients, although as late as 4–11 days in a few patients [12]. Inadequacy of the initial dose was the only factor associated with recrudescence digitalis toxicity. In cases of massive digitoxin poisoning, recurrent toxicity has been reported 1–4 days after Fab administration and when the initial dose was less than the estimated adequate dose [35].

Measurement of serum digoxin concentrations after the administration of Fab fragments using the conventional analytical methods is no longer useful since measuring free plus bound digitalis. Detectable free digoxin concentrations may reappear

5–24 h or longer after Fab administration [53]. Measurement of the free digoxin concentration may be of value to determine the need for additional doses of Fab. When free serum digoxin concentration rebounds beyond 0.8 ng/mL (1.02 nmol/L), signs of digoxin intoxication recurred in some patients [53].

Safety is not an actual concern. Mild hypersensitivity reactions, including pruritic rash, facial swelling and flushing, urticaria, thrombocytopenia, shaking, and chills, rarely (~0.8%) occur. Hypokalemia may occur as elevated serum potassium concentrations decline rapidly, starting as soon as 1 h and completely normalizing within 4 h [15, 52]. Worsening of cardiac dysfunction after Fab fragment infusion is rare too (<3%) [15]. Data regarding the safety of Fab fragments in patients treated for more than one episode of digitalis toxicity are limited to draw any conclusion. Therapeutic redigitalization of the patient, if necessary, should be delayed until elimination of anti-digoxin Fab fragments is complete. Digoxin therapy can be administered safely 48–72 h after Fab infusion in patients with normal renal function [53].

Special Populations

Pediatric Patients

Digitalis poisoning has been reported in pediatric patients ranging from 1 day to 17 years old [35–39]. Iatrogenic intoxication is due to errors in the calculation or administration of the digitalizing and maintenance doses in smaller children. Accidental poisonings occur in young children and less commonly, adolescents may ingest digitalis in a suicidal attempt. Digitalis intoxication is most often accompanied by few clinical effects. Neurologic manifestations, life-threatening arrhythmias, conduction defects, and secondary hypotension may be observed like in adults. Hyperkalemia is uncommon. Anti-digoxin Fab fragments were consistently reported to be effective and safe in pediatric patients. Indications of antidote administration are based on the following recommendations: [39]

Known Digoxin Intoxication

- Strong evidence of acute ingestion of ≥ 0.1 mg/kg digoxin
- Elevated (steady-state) serum digoxin concentration ≥ 5 ng/mL (6.4 nmol/L)

Signs and Symptoms of Digitalis Toxicity

- Rapidly progressing features of digoxin toxicity
- Potentially life-threatening arrhythmias, including cardiac conduction disturbances
- Severe hyperkalemia (≥ 6.0 mmol/L)

The prophylactic administration of anti-digoxin Fab fragments was also considered in children, the main objective being, however, to avoid any delay in their administration. Dosage is similar to adults, paying attention to the dilution to avoid fluid overload in small children. The empirical Fab dosing is 400–800 mg in acute poisoning and 40–80 mg in chronic toxicity. Increased serum potassium concentration usually normalizes within 4 h of administration [36]. In the main study, no cases of hypersensitivity have been reported, while hypokalemia occurred in one case and recurrence of cardiac conduction defects after treatment in three children requiring a repeated dose to reverse [39].

Pregnant Patients

During pregnancy, digitalis overdose may result in maternal and fetal digitalis poisoning. Pregnant patients with acute digitalis overdose should be treated similarly to nonpregnant patients. However, there are no definitive data regarding the efficacy or safety of anti-digoxin Fab fragments in pregnant women.

Elderly Patients

Digoxin toxicity in the elderly is common, ranging from minor gastrointestinal symptoms to life-threatening dysrhythmias. Increased risk of toxicity in the

elderly is related to their multiple medications, their decreased renal clearance, and the increased risk of unintentional ingestion of repeated doses due to their cognitive impairments. Mild-to-moderate digoxin toxicity in the elderly may be difficult to recognize from other “signs of old age,” i.e., somnolence, decreased hearing, confusion, agitation, poor appetite, nausea, vomiting, and diarrhea [54]. In the treated elderly patients, chronic toxicity should be suspected in the new onset of dysrhythmias, malaise, gastrointestinal disturbances, or mental status changes. Lethargy, depression, and confusion seem to occur almost exclusively in the elderly [55]. Advanced age seems to be an independent poor prognostic factor.

Renal Dysfunction Patients

Patients with renal dysfunction are at high risk of digoxin poisoning. Fab therapy is effective in patients with renal dysfunction [11–17]. Fab fragments should be given to patients with renal impairment at the same dose as for patients with normal renal function [56]; however, elimination of digoxin-specific Fab complexes is prolonged. Total body clearance of Fab fragments is related linearly to creatinine clearance, whereas their apparent volume of distribution is not affected [56]. Free digoxin concentrations decrease rapidly after Fab therapy but rebound at about 77 ± 46 h postinjection [57]. The magnitude by which free digoxin concentration rebounds is unaffected by the degree of renal dysfunction. There is no evidence to support a dissociation of the Fab/digoxin complexes over extended periods [53]. Because there are rarely complications resulting from circulating Fab/digoxin complexes for a prolonged period, however, there is little evidence to recommend any extrarenal technique to enhance their elimination [27]. Monitoring free serum digoxin concentrations may be of value in selected patients to guide additional Fab dosing, confirm possible rebound toxicity, or guide the re-initiation of digoxin therapy [57].

Key Points in Digitalis Poisoning

1. To date, digoxin poisoning mainly results from chronic toxicity in long-term treated elderly patients with underlying cardiac diseases due to acute renal onset or drug-drug interactions rather than from the suicidal or accidental exposure to a single high digoxin dose.
2. Digitalis poisoning may be life-threatening with the sudden onset of fatal ventricular dysrhythmias.
3. Mild-to-moderate digoxin toxicity in the elderly may be difficult to recognize from other “signs of old age.”
4. The emergency determination of the serum digitalis concentration is mandatory in each patient with suspected digitalis toxicity.
5. Prognosticators including age >55 years, serum potassium >4.5 mmol/L, and atrio-ventricular block of any degree should be recognized on patient management.
6. Antidysrhythmic drugs and cardiac pacing should be not be used anymore if anti-digoxin Fab fragments are available.
7. Anti-digoxin Fab fragments represent the first-line antidote in the presence of hyperkalemia, cardiac conduction disturbances, or life-threatening arrhythmias.
8. The currently recommended dosing regimen of anti-digoxin Fab fragments is to administer 40 mg (one vial) for chronic poisoning and 80 mg (two vials) for acute poisoning and repeat after 60 min if inadequate response or recurrence or earlier if clinical deterioration.
9. Prophylactic semi-molar dosing of anti-digoxin Fab fragments in the presence of bad prognosticators has been proposed with success to reduce digitalis-related fatality.
10. The extracorporeal removal techniques are unlikely to improve the outcome of digoxin-toxic patients whether or not anti-digoxin Fab fragments is administered.

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Antidysrhythmics achieve their therapeutic goals of rhythm control through blockade or antagonism of various cardiac channels or receptors. In the Vaughan Williams convention [1], which endures despite its limitations due to its simplicity and clinical applicability, class I antidysrhythmic agents block the cardiac sodium channel by intent. As highlighted by the Cardiac Arrhythmia Suppression Trials (CAST I and II) of encainide, flecainide, and the subsequently withdrawn moracizine, these agents have the potential to increase mortality even at therapeutic dosing [2]. Cardiac sodium channel blockade may be an “on target” effect of class I agents or antidysrhythmics from other Vaughan Williams classes or an “off target” effect of a host of agents from multiple pharmaceutical classes, including antibiotics, antiepileptic drugs; cyclic, selective serotonin reuptake inhibitor, and serotonin–norepinephrine reuptake inhibitor antidepressants; antihistamines; antipsychotics; amide and ester local anesthetics; mood stabilizers; and opioids (Tables 1 and 2). Of note, this sodium channel blockade may be identified by other terminology, e.g., the “membrane-stabilizing effects” of certain beta-adrenergic antagonists or eponymous “local anesthetic effects.”

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Table 1 Selected agents with sodium channel antagonism

Drug classification	Drug subclassification	Example(s)
Antibiotics	Antimalarials	Chloroquine Hydroxychloroquine Quinine
Antidysrhythmics	Vaughan-Williams Class IA Vaughan-Williams Class IB Vaughan-Williams Class IC	Quinidine Lidocaine Propafenone
	Vaughan-Williams Class II (Beta-adrenergic antagonists)	Acebutolol Betaxolol Carvedilol Labetalol Metoprolol Oxprenolol Pindolol Propranolol
	Vaughan-Williams Class III (Potassium channel blockers)	Amiodarone Dronedarone
	Vaughan-Williams Class IV (Calcium channel antagonists)	Diltiazem Verapamil
Anti-epileptics	Hydantoins	Phenytoin
	Iminostilbenes	Carbamazepine
	Phenyltriazines	Lamotrigine
Antidepressants	Cyclic antidepressants	Amitriptyline Desipramine
	Selective serotonin reuptake inhibitors	Citalopram Escitalopram Fluoxetine Fluvoxamine
	Serotonin–norepinephrine reuptake inhibitors	Venlafaxine
Antihistamines	First-generation H ₁ antagonists	Dimenhydrinate Diphenhydramine Orphenadrine
	Second-generation H ₁ antagonists	Terfenadine
Antipsychotics	Dibenzoxazepines	Loxapine
	Phenothiazines	Chlorpromazine Fluphenazine Mesoridazine Thioridazine
Local anesthetics	Amide local anesthetics	Bupivacaine Lidocaine Ropivacaine
	Ester local anesthetics	Cocaine Procaine
Mood Stabilizers	Minerals	Lithium salts
Opioids	Semisynthetic opioids	Buprenorphine
	Synthetic opioids	Methadone Propoxyphene Tramadol

Table 2 Pharmacokinetics of antidysrhythmic pharmaceuticals with sodium channel antagonism [1, 3, 8–12]

Drug classification	Drug name	Volume of distribution (L/kg)	Elimination half-life (hours)	Relevant active metabolite(s)	Log P	Log D (at pH 7.0)
Vaughan-Williams Class IA (Sodium channel blockers)	Disopyramide ^{a, b}	0.6–1.5	4–10		2.86	0.07
	Procainamide ^{a, c}	3.3–4.8	3–4	Yes	1.23	–1.43
	Quinidine ^{a, b}	1.8–3.0	4–10	Yes	–1.55	1.35
Vaughan-Williams Class IB (Sodium channel blockers)	Lidocaine	1.3	1.5–2	Yes	2.36	0.83
	Mexiletine	6–12	9–15		2.16	0.58
	Tocainide	1.4	12–15		0.76	–0.37
Vaughan-Williams Class IC (Sodium channel blockers)	Encainide	2.7–4.3	2.3–11		4.63	2.39
	Flecainide	9–10	10–18		3.47	0.55
	Propafenone ^d	2.5–4.0	2–32	Yes	4.63	2.39
Vaughan-Williams Class II (Beta-adrenergic antagonists)	Acebutolol	1.0	3–4		2.59	0.52
	Betaxolol	7.7–8.8	15		2.69	0.56
	Carvedilol ^e	1.5	7–10		4.23	3.16
	Labetalol ^e	3.4–10.7	3–4		2.87	0.99
	Metoprolol	5.6	3–4	Yes	1.79	–0.34
	Oxprenolol	1.3	1–2		2.10	–0.10
	Pindolol	1.2–2.0	2–5		1.97	–0.19
	Propranolol	3.3–5.5	3–5		3.10	0.99
Vaughan-Williams Class III (Potassium channel blockers)	Amiodarone ^f	~60	58 days	Yes	8.59	6.29
	Dronedarone ^{e, f}	1200–1400L	24	Yes	7.35	N.A.
Vaughan-Williams Class IV (Calcium channel blockers)	Diltiazem	4.6–5.3	4		4.53	2.64
	Verapamil ^b	3.4	3–7	Yes	4.91	2.91

N.A. not available

^aAdditional antimuscarinic activity

^bAdditional class III activity

^cAdditional class III activity through *N*-acetylprocainamide metabolite (acecainide)

^dAdditional beta-adrenergic antagonism and L-type calcium channel blockade

^eAdditional alpha-adrenergic antagonism

^fAdditional class I, II, and III activity

Clinical Pharmacology

The absorption of antidysrhythmics is nearly complete after oral administration; however, their bioavailability may be reduced by first-pass hepatic metabolism. Protein binding in excess of 80% can occur with amiodarone, dronedarone, encainide, lidocaine, propafenone, propranolol, quinidine, and verapamil [3]. In overdose, toxicokinetics may be modified by drugs or coingestants with opioid or anticholinergic properties that decrease peristalsis or

particularly large ingestions, which independently decrease intestinal motility [4, 5]. Antidysrhythmics' relatively large volumes of distribution (V_D) can be altered in comorbidities. For example, quinidine's V_D can vary from 0.5 L/kg in congestive heart failure (CHF) to 2–3 L/kg in healthy adults to 3–5 L/kg in cirrhosis [6]. Terminal half-lives vary according to the specific agent and comorbid conditions, particularly CHF, and may be further prolonged in overdose [7].

The *SCN5A* gene encodes the tetrodotoxin-resistant, $Na_v1.5$ voltage-gated cardiac sodium

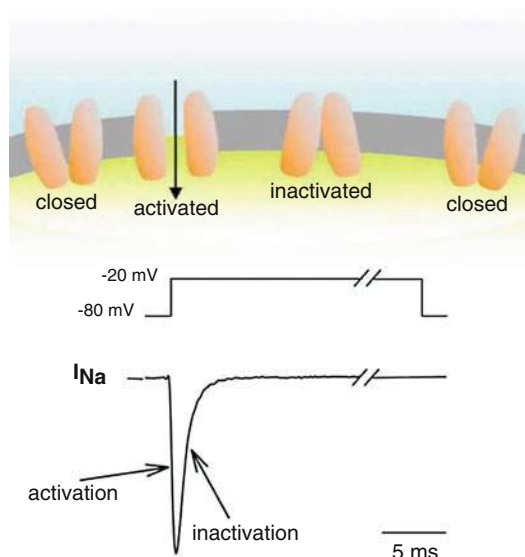


Fig. 1 Activation and inactivation of the Na^+ current linked to the channel conformation. Schematic Na^+ current (bottom) recorded during a voltage pulse (middle). Activation of the current corresponds to an increasing number of Na^+ channels in the open conformation (top) due to the depolarization; inactivation corresponds to an increasing number of channels passed from the open to the inactivated conformation. Repolarization allows the inactivated channels to restore the closed conformation. (From Baró I, Escande D. *Basic Physiology of Ion Channel Function*. In: Gussak I, Antzelevitch C, Wilde AAM, et al., eds. *Electrical Diseases of the Heart: Genetics, Mechanisms, Treatment, Prevention*. London: Springer London, 2008:11–23.)

channel alpha subunit, the desired target of the Vaughan Williams class I agents. $\text{Na}_v1.5$ cycles between resting (closed), activated (open), and inactivated (closed) states (Fig. 1). Closed states are impermeable to sodium. $\text{Na}_v1.5$ contains four homologous transmembrane domains (D1–D4), each consisting of six transmembrane spanning sections (S1–S6) (Fig. 2) [13]. The central pore permitting sodium ion transit is formed by the four S5–S6 sections and their intervening loop domains. A “P-loop,” connecting S5 and S6, folds back into the membrane, and the tips of the four P-loops come together to form the narrow ion selectivity filter determined by a ring of amino acids (asparagine, glutamate, lysine, and alanine) [14]. The receptor site for sodium channel blockers is a collection of amino acid residues that line the

inner surface of the S6 segments of D1, D3, and D4 to create a three-dimensional drug receptor site whose occupancy blocks the pore (Fig. 3) [15].

Beta-subunits and other regulatory partners are important interacting proteins [16]. Congenital $\text{Na}_v1.5$ loss of function mutations is associated with the Brugada syndrome, which places the individual at risk for sudden cardiac death from ventricular dysrhythmia [16]. Class IA and IC sodium channel blockers, such as ajmaline and flecainide, are used to elicit characteristic ST-segment elevations and unmask occult Brugada disease (Fig. 4) [17, 18].

Class I agents may have additional receptor targets. For example, disopyramide, quinidine, and procainamide have antimuscarinic and Class 3 activity, even in therapeutic dosing [19]. Conversely, certain class II–IV agents possess class I effects and other complex properties (Table 2). Some class I agents have active metabolites which exert significant effects. Lidocaine’s metabolite, monoethylglycylxylidide, although less potent, is active and has a longer half-life than lidocaine. Procainamide’s metabolite, *N*-acetylprocainamide (acecainide), is a class III antiarrhythmic agent. Comorbidities or drug-drug interactions may affect metabolite formation [7].

Pathophysiology of Cardiac Action Potentials and Myocardial Toxicity Resulting from Sodium Channel-Blocking Antidysrhythmic Poisoning

In nonpacemaker cells, the action potential consists of five phases (Fig. 5). Phase 4 refers to the resting state, during which voltage-gated sodium channels are closed until activated in response to the spread of electrical membrane depolarization from adjacent tissue or the opening of nearby ligand-gated excitatory ion channels. As the membrane depolarizes and a certain threshold is reached, channels become activated within 1 ms through a simultaneous outward movement of all four S4 segments, resulting in

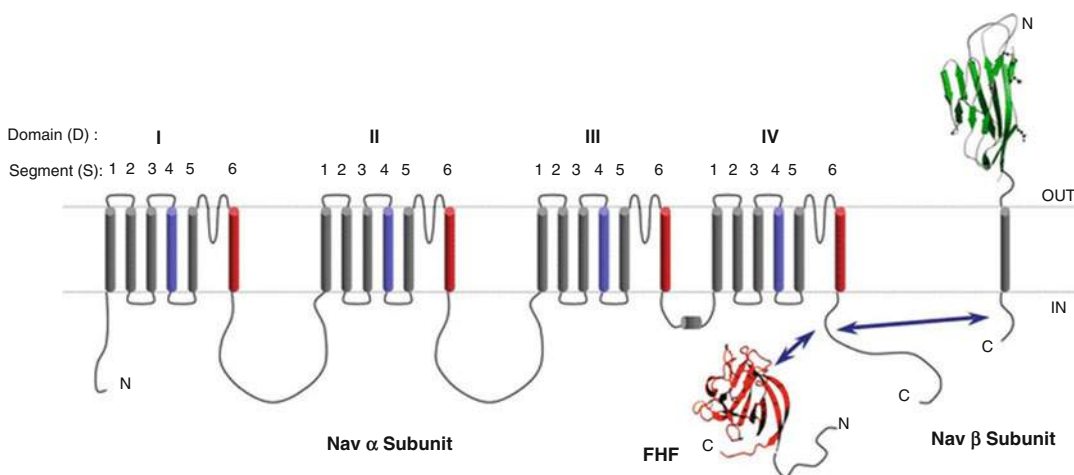


Fig. 2 Structure and interactions of the voltage-gated sodium channel α subunit with β subunit, and the fibroblast growth factor homologous factor (FHF). Nav α represents the α subunit of the sodium channel $\text{Na}_V1.5$. $\text{Na}_V1.5$ consists of four pseudo-homologous domains (DI through DIV), each bearing six transmembrane helical segments (S1 through S6) and partial reentrant loops between S5 and S6 that form the sodium ion selectivity filter (“P loop”). The S4 segments have periodic cationic residues that constitute the voltage sensors. The S6 segments provide the inner walls of the channel beneath the ion selectivity filter. The channel has cytoplasmic amino (N) and carboxyl (C) tails, and the four domains are connected by cytoplasmic loops (not to scale). The small loop between DIII and DIV includes a short α -helical region and the IFM triad required for fast channel inactivation. The C-tail critically modulates fast inactivation and is the site for physical interactions with channel β

subunits and FHFs (arrows). Nav β Beta-subunits (Nav2.1–Nav2.4) are single-pass transmembrane proteins with an extracellular immunoglobulin-like domain and a short cytoplasmic tail that mediates binding to Nav α . Nav β 4 bears a unique motif in its C-tail that serves as a channel-blocking particle responsible for resurgent current. FHFs (FHF1–FHF4, each with multiple isoforms bearing different N-termini) are small cytoplasmic proteins that assume a β -trefoil fold bearing the surface for interaction with the Nav α C-tail. The A-type isoforms of FHFs have N-terminal motifs that serve as long-term inactivation particles. Nav β 4 and A-type FHF particles terminate transient sodium current by competing with the Nav α fast inactivation machinery. (From Goldfarb M. *Voltage-gated sodium channel-associated proteins and alternative mechanisms of inactivation and block*. *Cell Mol Life Sci*. 2012;69(7):1067–76.)

the opening of the channel pore and, due to the electrochemical gradient, inward conductance of sodium ions [16]. This produces the maximum upstroke velocity during phase 0 (V_{max}), which approximates the magnitude of sodium ion influx through opened sodium channels [3, 20]. This conduction results in the normally narrow QRS interval reflected on the surface electrocardiogram. Once depolarized, sodium channels are rapidly closed as the intracellular loop between D3 and D4 acts as a “lid” to close the channel pore [16]. Physiological conditions permit inactivated channels to remain in a closed state until the cell membrane is repolarized, permitting recovery from inactivation to a resting state (Fig. 1). Phase 1 of the nonpacemaker cell action potential begins with this inactivation of

sodium channels at the peak of the action potential and is marked by a brief period of rapid electrical repolarization. Phase 2, the plateau phase, results from a balance between calcium influx through voltage-gated calcium channels and potassium efflux. There is a relatively smaller and more gradual change in the membrane potential during phase 2 because the net ion conductance is minimal. Rapid repolarization (phase 3) results from further activation of transmembrane potassium channels and outward movement of potassium. The cell membrane and its sodium channels then return to the resting state (e.g., phase 4) and again are ready for depolarization and activation. During the action potential, a very small fraction of sodium channels does not inactivate completely and

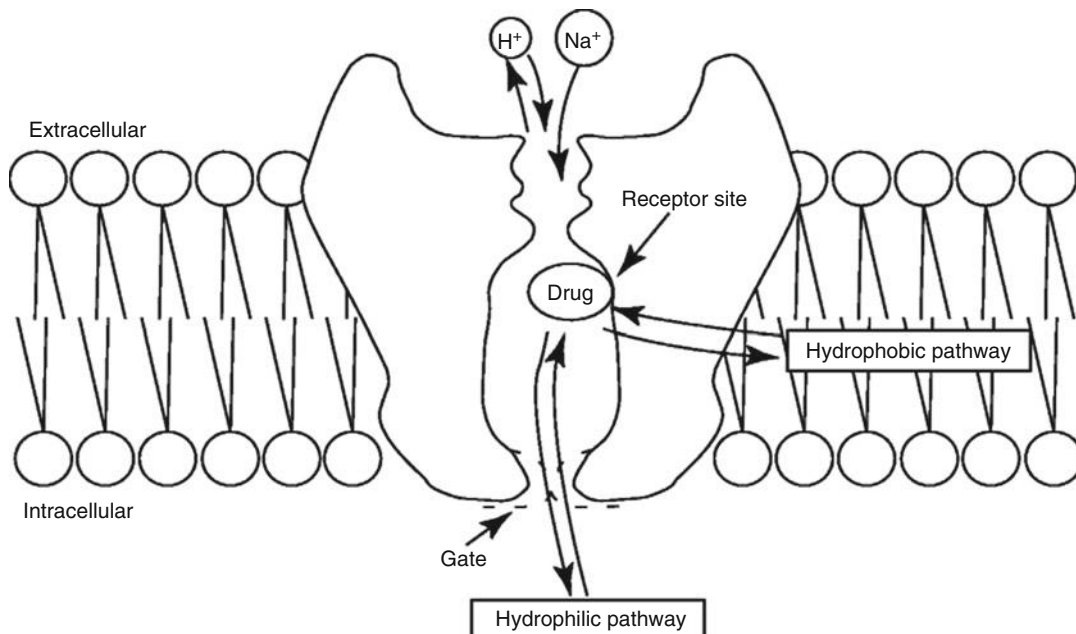
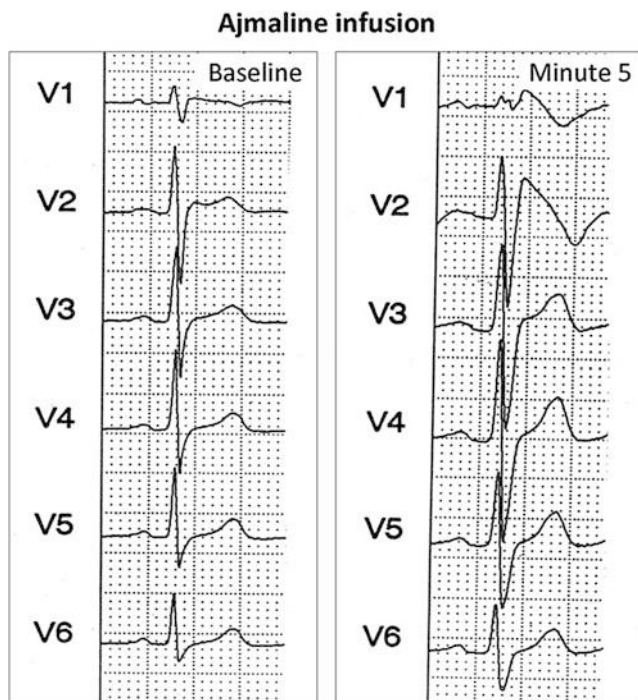


Fig. 3 The binding site of sodium channel blockers via the hydrophobic and hydrophilic pathways. (From Murakami S, Kurachi Y. *Mechanisms of Action of Antiarrhythmic Drugs in Ventricular Arrhythmias*. In: Gussak I,

Antzelevitch C, eds. *Electrical Diseases of the Heart: Volume 1: Basic Foundations and Primary Electrical Diseases*. London: Springer London, 2013:129–40.)

Fig. 4 The ajmaline test unmasks the diagnostic Brugada syndrome pattern (type 1 pattern, coved type). Ajmaline is a class IA agent. (From Arbelo E, Brugada J. *Risk stratification and treatment of Brugada syndrome*. *Curr Cardiol Rep*. 2014;16(7):508.)



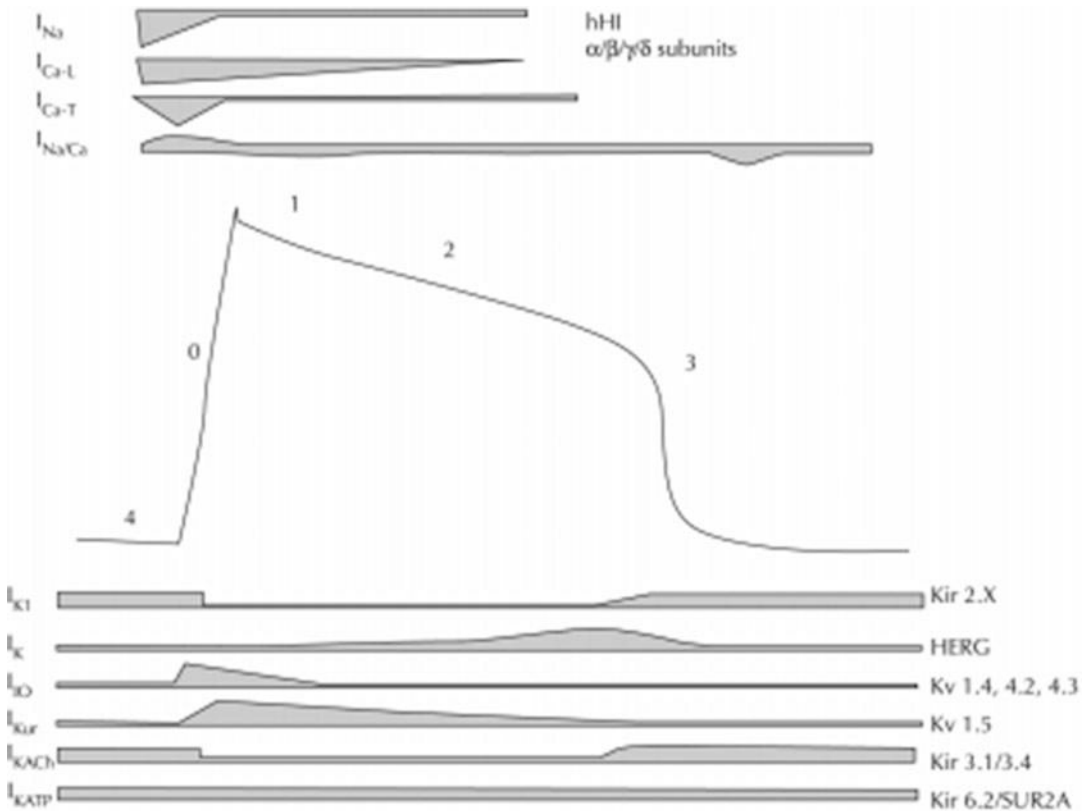


Fig. 5 Currents and channels involved during a typical cardiac action potential. The various phases are indicated by numbers (0–4). The approximate relative time courses of the currents associated with the channels encoding the principal channel subunits are shown symbolically, without representing their magnitudes relative to each other. I_{Na} , inward excitatory current carried by sodium ions; I_{Ca-L} , L-type calcium channels current; I_{Ca-T} , T-type calcium

channels current; $I_{Na/Ca}$, current generated by the Na/Ca countertransport system; I_{K1} , inward rectifier potassium current; I_K , delayed rectifier potassium current; I_{TO} , transient outward potassium current; I_{KACh} , acetylcholine-sensitive potassium current; I_{KATP} , ATP-sensitive potassium current. (From Langan MN. The impact of recent ion channel science on the development and use of antiarrhythmic drugs. *Curr Cardiol Rep*. 1999;1(4):302–7.)

contributes a “sustained current” or “late current” to the action potential duration [3].

The action potential of pacemaker cells is composed of only three phases. In phase 4, which is relatively slow, the hyperpolarization-activated pacemaker current is a mixed Na-K inward current, mediated by cAMP under beta-adrenergic (positive) and muscarinic (negative) control [21]. Additional time- and voltage-dependent ionic pacemaker currents have been identified. A sodium-calcium exchanger current (I_{NCX}) has also been identified. Low voltage-activated T-type calcium current triggers local release of

calcium from the sarcoplasmic reticulum, which in turn stimulates I_{NCX} to depolarize the pacemaker potential to threshold [22]. When the threshold potential is reached, phase 0 is initiated, and influx of calcium occurs to activate the cardiac ryanodine receptor. In contrast to nonpacemaker tissue, little sodium influx occurs during phase 0. Phase 3 repolarization, as in nonpacemaker cells, is due almost entirely to potassium efflux. The summation of pacemaker and other electrical currents across the cardiac cycle and the representation on the surface ECG is shown in Fig. 6.

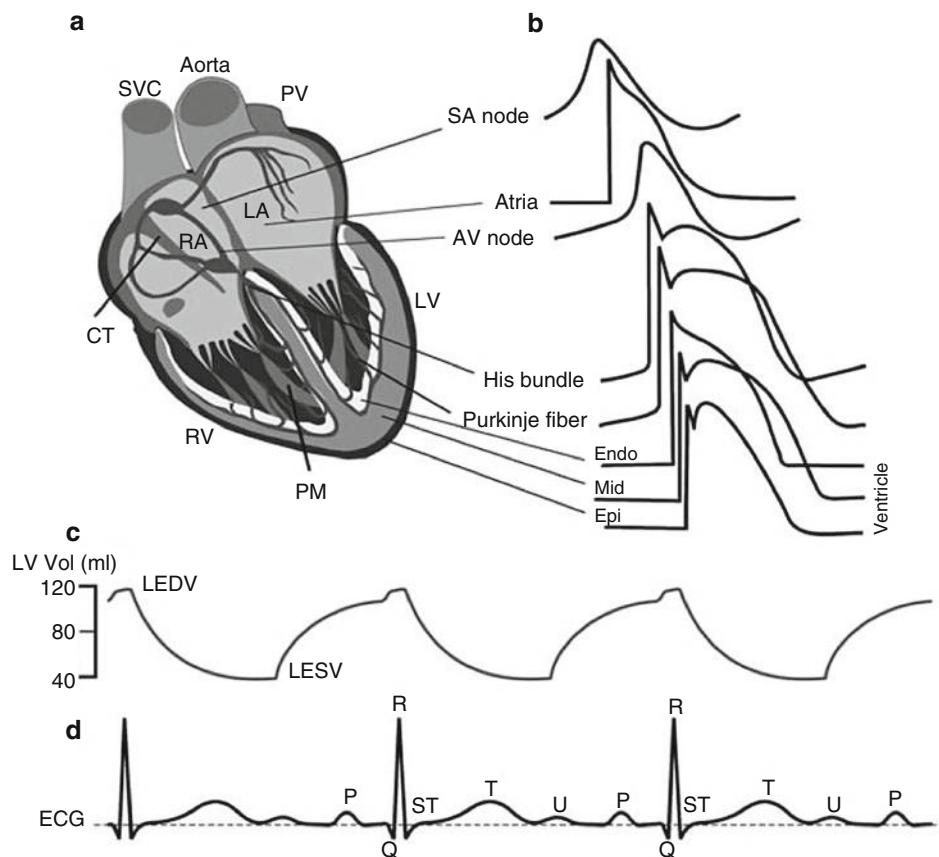


Fig. 6 Currents involved across heart regions during the cardiac cycle. The heart (**a**) depicts the SA node, conducting system, and cardiac tissues. *CT* crista terminalis, *Endo* endocardium, *Epi* epicardium, *Mid* midmyocardium, *LA* left atrium, *LV* left ventricle, *PM* papillary muscle, *PV* pulmonary vein, *RA* right atrium, *RV* right ventricle; and *SVC* superior vena cava. (**b**) The action potentials in the cells of different regions of heart roughly corresponding to different phases of ECG. (**c**) Left ventricular volume (LV) indicating left ventricular

contraction and relaxation; *LEDV* left ventricular end-diastolic volume, *LESV* left ventricular end systolic volume. (**d**) Surface ECG showing the classical P, Q, R, S, T, and U waves; ST indicates end of S and beginning of T waves. (From Tripathi ON. *Cardiac Ion Channels and Heart Rate and Rhythm*. In: Tripathi ON, Ravens U, Sanguinetti MC, eds. *Heart Rate and Rhythm: Molecular Basis, Pharmacological Modulation and Clinical Implications*. Heidelberg: Springer, 2011, p4.)

Sodium channel-blocking antidysrhythmics can produce major adverse cardiotoxic effects including intraventricular conduction defects, hypotension, and supraventricular or ventricular dysrhythmias. Intraventricular conduction defects occur as a result of a sodium channel blockade-related reduction in the slope of phase 0 of the nonpacemaker cell action potential. Class IA, Class IC, and similarly acting drugs such as cyclic antidepressants (CAs) impair V_{max} (Table 3) [3, 20]. Clinical manifestation of this includes widening of the QRS complex and/or the development of bundle-branch block-like

morphology. In a broad molecular assay study of 132 class I antidysrhythmics and other QRS prolonging drugs, QRS prolongation occurred on average at free plasma levels 15-fold below their median blocking potency (IC_{50}) at human cardiac Nav1.5 channels [23].

Toxic exposure to sodium channel-blocking antidysrhythmics may also induce ventricular monomorphic tachycardia or fibrillation. These potentially lethal dysrhythmias are thought to occur by slowing intraventricular conduction to the point that unidirectional block and reentrant

Table 3 Differences among class I antiarrhythmic drugs [2, 19, 26, 27]

Drug classification	Phase 0 depression	Repolarization	Action potential duration
IA	Moderate	Prolonged	Prolonged
IB	Minimal	Shortened	No change or shortening
IC	Significant	Minimal or no effect	Minimal effect

circuits develop [24]. These reentrant circuits can further degenerate into ventricular tachycardia and fibrillation [25].

Access to the sodium channel blocker receptor site by large or hydrophilic drugs (Fig. 3) requires opening (of the usually closed) intracellular activation gate. Sodium channels' "use-dependent block" – also known as "rate dependent block" – thus logically proceeds from more facile binding when the channel is frequently opened (e.g., at faster heart rates). Fenestrations leading from the lipid phase of the membrane sideways into the drug receptor site provide a separate, specific hydrophobic access pathway for binding of small hydrophobic drugs during the channel's resting state [15]. In contrast to IA and IC agents, lidocaine and class IB antidysrhythmics block sodium channels predominantly in their inactivated state at the end of depolarization, during early repolarization, and during periods of myocardial ischemia, and thus have minimal effects on phase 0 depolarization and do not prolong action potential duration [26]. Pharmacogenetic interactions provide further opportunity for different binding and gating effects. For example, SCN5A promoter haplotype variants demonstrate altered flecainide efficacy and toxicity in the form of PR prolongation and QRS widening [28].

As was established from congenital Brugada syndrome loss of function mutants, sodium toxic channelopathy creates the potential for sudden ventricular dysrhythmia in susceptible patients. Class III effects of many of the class IA agents may result in impaired repolarization from potassium channel blockade. Both transmural and epicardial dispersion of repolarization may occur, lengthening the QT interval and predisposing the involved myocardium to the occurrences of polymorphic ventricular tachycardia.

Hypotension after sodium channel-blocking antidysrhythmic poisoning likely results from impaired myocardial contractility, as influx of sodium and calcium is coupled to the release of intracellular calcium stores. Hypotension may also occur secondary to reduced vascular smooth muscle contractility and resultant vasodilation. The peripheral alpha-adrenergic antagonist actions of selected sodium channel-blocking antidysrhythmics (e.g., quinidine, CAs) may also contribute substantially to this clinical effect.

Many sodium channel-blocking antidysrhythmic agents (e.g., type IA agents) possess antimuscarinic properties, resulting in sinus tachycardia after overdose [1, 19]. However, large overdoses of these antidysrhythmics may depress pacemaker cell automaticity, causing sinus bradycardia, junctional escape or other ventricular arrhythmias, and asystole. In sodium channel blocker poisoning by anticholinergic antidysrhythmics, the combination of a wide QRS complex and bradycardia is ominous, as it suggests that the sodium channel blockade is so profound that the myocardium is unable to mount a tachycardic response to muscarinic antagonism.

The mechanism of decreased automaticity in pacemaker cells during severe sodium channel blockade is not entirely clear in class I agents lacking beta-adrenergic antagonism. In the spontaneously beating sinus venosus of the frog, bupivacaine-induced reversible negative chronotropy, a decreased diastolic depolarization rate, and a prolongation of sinus cycle length [29]. While atropine attenuated bupivacaine's effect on spontaneous rate of firing, V_{max} and action potential amplitude worsened. An analogous situation has been studied in Purkinje fibers, in which high doses of imipramine, an anticholinergic sodium channel-blocking CA, depressed the slope of phase four of the pacemaker action potential to asystole [30].

Clinical Presentation and Life-Threatening Complications

Assuming there is no change in gastrointestinal (GI) motility, transit, or absorption, asymptomatic patients ingesting antidysrhythmics are unlikely to

develop further symptoms if the time since ingestion is greater than 6 h for immediate-release products and 24 h for sustained-release formulations [31]. The adverse clinical effects of antidysrhythmics seen in therapeutic use – hypotension, dysrhythmias, conduction disturbances, paradoxical prodysrhythmic response [19, 26, 32] – are magnified in overdose. In a series of 120 class IC antidysrhythmic overdoses, mean mortality was 22.5% [33]. Nausea was the typical, earliest symptom. Heart rate may depend on the associated on- or off-target drug effects. For example, the antimuscarinic properties of disopyramide, procainamide, quinidine, CAs, and diphenhydramine or sympathomimetic properties of cocaine may produce tachycardia, while bradycardia predominates with propafenone and membrane stabilizing beta-adrenergic receptor antagonists. Hypotension, junctional escape, myocardial depression, and asystole have been observed. Conduction defects may include prolonged QRS, high-grade atrioventricular nodal blocks, and bundle-branch blocks, as well as ventricular dysrhythmias (e.g., ventricular tachycardia and ventricular fibrillation). “Quinidine syncope” was identified decades ago as an additional therapeutic complication [34]. Agents or metabolites with class III effects (Table 2) further risk QT interval prolongation and *torsades de pointes*. Class I antiarrhythmic agents may elicit Brugada patterns, amplifying existing sodium ion channel defects with a potency inversely proportional to the rate of dissociation of the drug from the sodium channel [17, 18, 35].

Central nervous system effects, including seizures, may portend subsequent cardiovascular collapse in lidocaine poisoning. The class IA antimuscarinic antidysrhythmics may manifest seizures as well as an anticholinergic syndrome characterized by agitation, coma, respiratory depression, urinary retention, tachycardia, anhidrosis, and depressed GI motility [19]. Seizures may accompany other sodium channel antagonists (e.g., cocaine, CAs, citalopram, diphenhydramine, propoxyphene, etc.).

Hypoglycemia has been reported with quinidine and disopyramide and is also a concern with class II agents [19]. Procainamide is associated

with hypersensitivity reactions including fever, rash, and agranulocytosis [19].

Diagnosis

The differential diagnosis includes a myriad of substances and environmental toxins capable of exerting primary or secondary adverse cardiovascular effects. Pharmaceuticals of note that produce hypotension and/or bradycardia include the class I-IV antidysrhythmics, cardiac glycosides (digoxin), imidazoline derivatives (clonidine, oxymetazoline, tetrahydrozoline, etc.), nitrates, and renin–angiotensin system antagonists. Depending upon the degree of exposure, other agents in the classes listed in Table 1, sedative-hypnotics, mitochondrial toxins, and others may cause cardiovascular compromise. A detailed history and clinical evaluation can support the diagnosis of sodium channel-blocking antidysrhythmic poisoning.

The importance of the ECG in evaluating antidysrhythmics’ toxic effects has been recognized for decades [36]. Disturbances in rate and atrioventricular conduction are readily assessable. Prolongation of the QRS interval beyond 100 milliseconds is a hallmark of impaired myocardial conduction and intraventricular conduction delay seen in sodium channel blocker antidysrhythmic poisoning. QRS widening predicts seizures and ventricular dysrhythmias in CA poisoning [37, 38]. Abnormal right ventricular depolarization, leading to terminal rightward depolarization of the last 40 milliseconds of the QRS complex, gives rise to a terminal R wave in lead AVR and/or an S wave in leads I and AVL [38, 39]. While these additional findings provide reliable ECG criterion for CA toxicity, their predictive value for other sodium channel-blocking antidysrhythmic is less established. The QT interval should be evaluated for delayed repolarization [19]. Tachycardia from antimuscarinic side effects accompanying a wide QRS complex from sodium channel blockade may produce a rhythm that has been mistaken for ventricular tachycardia [40].

While QRS widening is typical of sodium channel blockers, toxicity from sodium channel

openers (e.g., aconitine, amantadine, grayanotoxin, veratridine, etc.) may manifest as QRS widening. QRS widening may be also mimicked by additional pharmaceuticals such as bupropion (though alternative mechanisms such as inhibition of intercellular gap junctional communication) and colchicine (a microtubule inhibitor causing myocyte injury and altered calcium handling) [41, 42]. As might be anticipated from a toxic channelopathy superimposed upon occult mutation, the Brugada pattern has been reported in cases of class I agent therapy and toxicity, as well as in poisonings by noncardiac agents, such as CAs and cocaine [35, 43–45].

A focused emergency ultrasound (FOCUS) may rapidly assess several critical physiological questions in overdose (level III recommendation) [46, 47]. Cardiac imaging provides a gross assessment of the degree to which left (and right) ventricular contractility is preserved or compromised; pulmonary vascular congestion may be evident from pulmonary sonographic B-lines; and inferior vena cava size and collapsibility can provide a noninvasive estimation of right-sided filling pressures.

As significant hypoglycemia may accompany class IA agents, frequent blood glucose monitoring is advisable [19]. Specific antidysrhythmic drug concentrations, even if available, are not typically returned in a timescale to aid clinical management. Class V agents such as digoxin and magnesium are an exception. Coingestants such as acetaminophen, salicylates, ethanol should also be considered for exclusion. Acid–base status should be obtained frequently to detect acidemia and to guide alkalization therapy.

Treatment

A definitive airway, as needed, should ensure adequate oxygenation and ventilation, so as to preclude absolute or relative respiratory acidosis. Continuous cardiopulmonary monitoring and sufficient peripheral or central vascular access to permit resuscitation with intravenous fluids, chronotropes, inotropes, and other therapies to sustain cardiovascular function and end organ perfusion should be ensured.

Decontamination

Given the potential for severe morbidity and mortality with antidysrhythmic poisoning, GI decontamination should be considered in every patient with oral exposure (Grade III recommendation) [33]. The nuances of this decision-making are beyond the scope of this chapter. Approaches to GI decontamination have generally not been shown to alter the outcome or the clinical course in patients. However, a careful risk-benefit assessment – taking into account the exposure, amount, and its timing; the patient's current and anticipated condition; comorbidities and coingestants; and provider skill – should guide the decision to employ adjuncts to alter toxicokinetics. Depending on the agent(s), these may include upper GI tract removal through orogastric lavage, intraluminal binding with activated charcoal, or increasing intestinal transit time and rectal expulsion effected through whole-bowel irrigation. The most recent American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists position paper advised that “gastric lavage should not be performed routinely,” while allowing for “rare” situations of use (Grade III recommendation) [48]. However, several key points are relevant. While GI decontamination measures should be performed early, overdose, in and unto itself, delays gastric emptying (Level II-1 evidence) [5]. Drugs or coingestants with opioid or anticholinergic properties (e.g., CAs) decrease peristalsis (Level II-1 evidence) [5, 49]. These properties render agents more amenable to GI decontamination, such as with activated charcoal (Level II-1 evidence) [4]. New evidence suggests that not infrequently, GI intraluminal pills or pill breakdown products can be found in decedents and even in the stomach of those who survive to the ICU (Level III evidence) [50]. Thus, decontamination may be particularly important in cases of significant gut burden, ongoing absorption, modified- or sustained-release preparations, or drugs or coingestants known to slow GI transit such as those with antimuscarinic or opioid properties [50]. While human studies attempting to

demonstrate a survival benefit of any decontamination modality remain inconclusive, most excluded sick patients or those most likely to benefit, or included patients likely to benefit from supportive care alone [51–53]. Some studies including significantly compromised patients have found benefit to gastric emptying in this subset (Level II-2 evidence) [54]. Particularly deadly toxins with little or absent specific antidotal options have also benefitted from early gastric emptying [55]. In a meta-analysis of healthy volunteers, activated charcoal reduced drug exposure in a sigmoid dose-dependent fashion for up to 4 h after exposure (Level I evidence) [56]. WBI can be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs in situations when activated charcoal is less effective (Grade III recommendation) [57]. Attention to airway protection, contraindications, and the not insignificant complications of the various GI decontamination methodologies is paramount.

Hypertonic Sodium Bicarbonate

The recognition of quinidine-induced ECG alterations in the early 1950s [36] pointed to therapy with molar sodium lactate – which is rapidly hepatically metabolized to sodium bicarbonate – in initial case reports and subsequent human studies of quinidine and procainamide poisoning [58, 59]. Hypertonic sodium bicarbonate is the initial treatment of choice for intraventricular conduction defects, ventricular dysrhythmias, and the negative inotropic effects of a sodium channel-blocking antidysrhythmic overdose. By the 1970s, administration of hypertonic sodium bicarbonate in cases of massive CA ingestion (greater than 2.5 g) decreased mortality from 15% to less than 3% [60]. In CA patients requiring intensive care, sodium bicarbonate therapy improved blood pressure in 96%, narrowed the QRS in 80%, and improved consciousness in patients with altered mental status in 47% [61]. Successful treatment with sodium bicarbonate has been reported in patients poisoned with many other sodium channel-blocking antidysrhythmics, including

encainide, flecainide, and propafenone, as well as other sodium channel blockers [40, 62–64].

Early work that suggested sodium bicarbonate mediated altered CA plasma protein binding to alpha-1-acid glycoprotein (AAG) was not borne out by subsequent experiments with exogenous AAG administration or experiments in isolated Purkinje fibers absent protein [20, 65]. Both sodium concentration and change in blood pH appear to play a role in improving hemodynamic and ECG parameters. The increase in extracellular pH and sodium concentration by sodium bicarbonate administration independently and additively improved Vmax and action potential amplitude in canine models of amitriptyline-induced cardiotoxicity [20]. Similarly, both increased sodium concentration and alkalinization significantly reduced the depressant effects of flecainide and mexiletine on Vmax, although the adverse effects of disopyramide were not mitigated [66]. Increasing the extracellular sodium concentration shifted the flecainide dose–response curve, apparently by decreasing flecainide binding affinity [67]. While amitriptyline-induced ventricular tachydysrhythmias in dogs demonstrated a greater response to the administration of sodium bicarbonate than to hypertonic sodium chloride, the reverse was seen in nortriptyline-poisoned swine [68, 69]. Addition of sodium bicarbonate to achieve a pH of 7.52 mitigated cocaine-induced QRS widening in guinea pig hearts [70].

Respiratory Alkalosis to Induce Serum Alkalization

Both sodium supplementation and serum alkalization are important components in the treatment of sodium channel blockade with ECG manifestations. Theoretically, alkalization can be achieved through repetitive boluses followed by continuous infusion of sodium bicarbonate or by inducing respiratory alkalosis. Hyperventilation can be accomplished when patients succumb to the anticipated or actual need for mechanical ventilation. Canine studies supported equivalent suppression of amitriptyline-induced ventricular

ectopy with hyperventilation to a pH similar to that produced by sodium bicarbonate (7.48); however, sodium bicarbonate outperformed hyperventilation in CA-poisoned rats and swine [68, 69, 71]. Hyperventilation-induced alkalization has narrowed the QRS in human cases (Level III evidence) [72]. While hyperventilation also mitigates severe hypernatremia and fluid overload from sodium bicarbonate, no clinical trial has compared the primary administration of sodium bicarbonate with induced alkalization and saline. If a hyperventilation strategy is chosen, sodium bicarbonate boluses should be administered until adequate serum alkalization to a pH of 7.45–7.55 is achieved and acid–base status closely monitored.

Hypertonic Saline

Hypertonic (3–7.5%) saline has been utilized in cases of CA poisoning-induced ventricular arrhythmias, QRS widening, and hypotension refractory to hypertonic sodium bicarbonate therapy [73, 74]. Optimal human dose of hypertonic saline remains undetermined, and careful attention is necessary to prevent severe hypernatremia. Current data do not conclusively demonstrate the superiority of hypertonic saline over sodium bicarbonate for the treatment of sodium channel-blocking antidysrhythmic toxicity [69, 75]. In addition, the safety and efficacy of the use of hypertonic solution in the treatment of poisoning have not been demonstrated in controlled clinical studies. Pulmonary edema may occur if hypertonic solutions are used and cardiac output is depressed. Hypertonic saline may not reverse sodium channel blockade seen in lidocaine poisoning [76].

Intraventricular Conduction Delays

Based primarily on the experience with CAs, the majority opinion of poison center medical directors was to administer sodium bicarbonate boluses when the duration of the QRS complex reached or exceeded 100 milliseconds, although many used a cut-off of 120 milliseconds (Grade III evidence) [77, 78]. Other patient-specific factors such as

comorbidities, coingestants, hypotension, seizures may inform decision-making. A typical initial dose of hypertonic sodium bicarbonate is 1–2 mEq/kg by rapid intravenous infusion, preferably with continuous ECG monitoring of the QRS complex (Level III recommendation) [77].

As institutions usually stock either an 8.4% solution (1 mEq/mL sodium and bicarbonate ions) or a 7.5% solution (0.892 mEq/mL sodium and bicarbonate ions), a single “standard” 50-mL ampule of 8.4% or 7.5% solution would deliver 50 or 44.6 mEq of NaHCO_3 , respectively. Multiple, frequent boluses may be required, either as initial therapy or as the bolus effect dissipates due to redistribution, with return of QRS widening [79]. Severe toxicity, as manifested by persistent QRS widening or unstable ventricular dysrhythmias, may necessitate massive interval NaHCO_3 bolus dosing [80]. Due to the transient effect of bolus dosing, a continuous infusion of “normal” bicarbonate infused at double the standard rate of intravenous fluid maintenance is typically also provided. This “normal” bicarbonate solution is prepared by adding three ampules of sodium bicarbonate (totaling 132–150 mEq) in 1 L 5% dextrose solution in water (D5W). Typically, the rate and bolus dosing are titrated so as not to exceed a serum pH of 7.55, although some authorities recommend a ceiling pH of 7.60, balancing QRS width and clinical status with the potential side effects of hypernatremia, volume overload, hypokalemia, and hypocalcemia (Level II-2 and Level III recommendation) [61, 77].

Dysrhythmia

Sinus tachycardia accompanying sodium channel antidysrhythmic poisoning usually results from antimuscarinic effects. While this might be a concern from the perspective of rate-dependent block, treatment narrowly focused on this sign can be misguided. Physostigmine, a short-acting anticholinesterase, has been reported to both slow the heart rate and subsequently narrow the QRS complex in patients poisoned with sodium channel blockers (albeit complicated by physostigmine-associated general tonic-clonic seizures) [81]. While slowing

the heart rate might diminish rate-dependent block, physostigmine's indiscriminate use and the failure to adequately address sodium channel blockade and the pathophysiology of CA poisoning were associated with bradydysrhythmias including asystole, seizures, and deaths [82, 83]. In animal models, physostigmine failed to abolish dysrhythmias, decreased blood pressure, and enhanced CA toxicity at high doses [84].

Decreased heart rate may increase the QT interval and predispose to *torsades de pointes*. Because of this, physostigmine is not indicated for the treatment of patients poisoned with sodium channel-blocking antidysrhythmics, CAs, or other agents when sodium channel blockade is clinically and/or electrocardiographically evident. Attempts to decrease heart rate with beta antagonists, including those with mild positive inotropy, were equally futile in canine studies. Despite narrowing the QRS, hypotension and death ensued [79, 85].

Bradydysrhythmias suggest severe sodium channel antidysrhythmic poisoning. In the presence of severe bradycardia, a wide QRS complex, and hypotension, it is recommended – based on anecdotal, theoretical, experimental, and clinical considerations – that intravenous (IV) epinephrine be administered by continuous infusion and titrated to effect if intravenous sodium bicarbonate administration does not elicit an immediate beneficial response (Grade II-1 evidence) [86–89]. While transcutaneous or transvenous pacing may be attempted in the initial management of significant bradydysrhythmia, results are generally unsatisfying due to persistent negative inotropy. There is no compelling theoretical support or clinical evidence for the use of atropine in the treatment of sodium channel blockade-induced bradydysrhythmias.

Initial treatment of sodium channel antidysrhythmic-induced ventricular dysrhythmia is sodium bicarbonate boluses. In the face of ventricular dysrhythmias, further exposure to class IA or IC agents would be anticipated to worsen myocardial toxicity from sodium channel blockade. Based on the on-off receptor kinetics of class IB antidysrhythmics and minimal effects on phase 0 of the action potential in nondiseased hearts, lidocaine has been suggested as the

antidysrhythmic drug for the treatment of ventricular dysrhythmias from class IA or IC agents or CAs (Grade III recommendation) [90]. Canine studies showed transient suppression of ventricular ectopy with lidocaine, complicated by hypotension [68]. Lidocaine reversed QRS widening and slowed ventricular conduction in cocaine-poisoned guinea pig hearts [70]. In a series of CA poisoned patients, lidocaine infusions (2.0 ± 0.5 mg/min) suppressed frequent ventricular ectopy, without adverse events [91]. Lidocaine presents a reasonable option in patients with dysrhythmias that persist after sufficient sodium bicarbonate therapy. It should not be given to patients suffering toxicity from other type IB antidysrhythmics.

Magnesium can be considered as a follow-on agent. In cyclic antidepressant poisoning, one small, controlled study (Grade II-2 evidence) utilizing intravenous magnesium 1 g every 6 h [92] and several case reports [93–95] utilizing various dosing strategies have demonstrated effective treatment of ventricular dysrhythmias, decreased ICU stay, and decreased mortality. Intravenous magnesium has been reported to abolish digitalis-associated dysrhythmias (Grade III evidence) [96, 97]. Magnesium is also reported to reduce the toxicity of drugs with class III properties (Grade II-2 evidence) [98]. It would be reasonable to administer intravenous magnesium in cases of persistent dysrhythmia, in patients unresponsive to standard therapy, or in poisoning with agents with significant class III properties.

Hypotension

Patients with hypotension can be treated with judicious crystalloid boluses, unless they are contraindicated (e.g., pulmonary edema in the failing heart). Adequate treatment with hypertonic sodium bicarbonate is a priority. Murine studies of cyclic antidepressants demonstrated a survival benefit from sodium bicarbonate independently and additively to benefit from inotropic drug treatments, with epinephrine treatment superior to norepinephrine [86, 87]. Norepinephrine effectively resuscitated cyclic antidepressant poisoned canines [99]. In controlled human studies in a

dose-dependent fashion, epinephrine infusion partially or completely reverses quinidine's antiarrhythmic drug effects and prolongation of the ventricular refractory period; epinephrine partially reversed the effects of amiodarone (Grade II-1 evidence) [88, 89]. Epinephrine, with diazepam and mechanical ventilation, demonstrated improved outcomes of previously fatal human chloroquine poisonings (Grade II-2 evidence) [100]. A FOCUS examination may help guide whether positive inotropes or agents with more vasoconstrictive properties are needed.

Given the limitations of existing therapy and the lack of specific antidotes, antidysrhythmic-induced cardiovascular shock remains a leading cause of death [33, 101]. Definitive conclusions regarding the efficiency and indications for "extraordinary measures" are unlikely to emerge from available case reports and case series. However, "extraordinary measures" successfully applied to moribund patients poisoned with cardiotoxins have included prolonged manual chest compressions or "thumper" devices, cardiac pacing, intra-aortic balloon pump, or extracorporeal life support (ECLS) with extracorporeal membrane oxygenation (ECMO) or emergency cardiopulmonary bypass (Grade III recommendation) [31, 101, 102]. Extracorporeal life support in acute cardiogenic shock provides the opportunity to recover cardiac function [103] and permit toxin redistribution away from the cardiac compartment to permit elimination to occur.

High-dose Insulin Euglycemia (HIE) Therapy

For treatment of severe poisoning with class II and class IV agents, high-dose insulin with sufficient supplemental dextrose to ensure euglycemia has emerged as a first-line therapy (Grade III evidence) [104]. HIE would thus be recommended for class II agents which display sodium channel blockade (Table 2) (Grade III evidence) [104]. Insulin dosing consists of a bolus of 0.5–1 units per kg, followed by a 1–10 units per kg per hour continuous insulin infusion [105]. In light of propafenone's beta-adrenergic antagonism,

following successful HIE application in a refractory case of human propafenone poisoning, HIE was found to improve survival, improve central venous oxygen saturation, and delay the hemodynamic and electrocardiographic consequences of propafenone toxicity in murine models [106, 107]. Application of this therapy to poisoning with class I agents with beta-adrenergic antagonism, such as propafenone, would need to take into account the potential side effects of hypoglycemia and electrolyte imbalance (e.g., hypokalemia). Applying the available human (Grade III) evidence for class II agents and animal models, HIE may be considered in propafenone poisoning unresponsive to current treatment methods.

Intravenous Lipid Emulsion

Intravenous lipid emulsion (ILE) (typically 20%), also known as intravenous fat emulsion therapy or "rescue," has been incorporated in guidelines for treatment of cardiovascular collapse associated with Local Anesthetic Systemic Toxicity (LAST) [108]. Many sodium channel blockers possess a distribution constant log D – a better descriptor of the lipophilicity at physiological pH – suggestive of a role for ILE (Table 2). Indeed, case reports document ILE success in resuscitating patients rendered moribund by antidysrhythmic poisoning [109]. However, consensus reviews of ILE and its adverse effects in LAST and non-LAST poisoning highlight the low quality of human data (Grade III) [110–112]. ILE administration too early after oral poisoning has the potential to facilitate GI tract drug absorption or redistribution, exacerbating toxicity and, in theory, compromising the efficacy of lipid-soluble antidotes and concomitant therapies [113]. In swine and lapine models, intravenous lipid emulsion was inferior to sodium bicarbonate and no better than volume resuscitation in CA toxicity, no better than sodium bicarbonate in diphenhydramine toxicity, and no better than sodium bicarbonate in flecainide toxicity [114–117]. Intravenous lipid emulsion could be attempted when conventional therapies have failed. However, current evidence does not support its routine use in sodium channel blocking agent toxicity. Of note, multiple common

analytes can be markedly altered by lipemia after lipid administration [118]. ILE is also reported to cause fat emulsion agglutination, stopcock cracking, clogging and associated malfunction of the membrane oxygenator, and blood clot formation in ECMO circuits [119].

Seizures

Animal data derived from sodium channel blocking cyclic antidepressants and human case reports suggest that seizure treatment with standard antiepileptic drugs other than phenobarbital is not helpful and potentially life-threatening (Grade III recommendation) [85, 120–122]. The cardiac repercussions of seizures associated with sodium channel blockade are severe and include QRS widening, hypotension, acidemia, and cardiovascular collapse [40, 123]. Aggressive, early management with benzodiazepines, barbiturates, or propofol should be a priority.

Hypoglycemia

Given the adverse neurological effects of neuroglycopenia, hypoglycemia should be aggressively managed with age-appropriate concentrated dextrose, 0.5–1.0 g/kg. Octreotide has been successfully applied to suppress quinine-induced hyperinsulinemia and refractory hypoglycemia (Grade III evidence) [124].

Indications for ICU Admission in Sodium Channel-Blocking Antidysrhythmics Poisoning

- Hemodynamic instability and/or shock
- Bradydysrhythmias
- Ventricular dysrhythmias
- Conduction defects (2nd-, 3rd-degree atrioventricular block; intraventricular conduction delay)
- Respiratory failure
- Seizures
- Persistent hypoglycemia

- Moderate to severe anticholinergic toxicity
- Significant coingestants and/or other compromising comorbid medical conditions

Disposition

Although not systematically studied, reviews suggest that patients poisoned with nonsustained-release sodium channel-blocking antidysrhythmics can usually be expected to become symptomatic within 6 h after ingestion, and much sooner after parenteral exposure [31, 78]. The vast majority of patients who manifest no clinical signs of toxicity after 6 h of monitored observation and have consistently normal ECG findings are most likely safe for medical clearance. Ingestion of any of the sustained-release sodium channel-blocking antidysrhythmic formulations, uncertainty regarding the exact formulation ingested, coingestants of concern, or coingestants that alter gut motility may warrant 24 h of cardiac-monitored observation.

Key Points

- Clinical toxicity is usually evident within 6 h of exposure to a nonsustained-release formulation; ingestion of a sustained-release formulation may result in delayed onset and/or prolonged toxicity
- ECG evidence of sodium channel blockade-induced toxicity includes hypotension, bradydysrhythmias, atrioventricular and intraventricular conduction delays, and ventricular tachydysrhythmias
- Other cardiotoxic manifestations associated with sodium channel-blocking antidysrhythmics include prolonged QT/torsades de pointes (potassium efflux blockade) and sinus tachycardia (antimuscarinic effects, e.g., quinidine)
- Noncardiovascular toxicity associated with sodium channel-blocking antidysrhythmic drugs includes central and peripheral

(continued)

anticholinergic syndrome, seizures, and hypoglycemia

- Appropriate treatment of toxicity includes airway/ventilatory support, cautious IV volume expansion, hypertonic sodium bicarbonate (1-mEq/kg IV boluses to an arterial pH of 7.45–7.55), intravenous vasopressors (norepinephrine, epinephrine), intravenous lidocaine for ventricular tachydysrhythmias, and hypertonic (3%) saline for hemodynamic instability or dysrhythmia refractory to other treatments
- Intraaortic balloon pump or ECLS can be considered for severe refractory cardiogenic shock

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Sodium nitroprusside (SNP) entered into clinical practice in 1955 and gained popularity as a vasodilator for hypertensive emergencies because of its rapid onset of action and short duration, which allowed for bedside titration to the desired effect [1]. The introduction of a freeze-dried preparation in 1974 was followed by an additional increase in popularity, and it continued to gain favor for producing controlled hypotension during anesthesia and afterload reduction during low cardiac output states. Availability of alternative agents has more recently limited use of SNP for hypertensive emergencies. However, novel applications, such as for the treatment of schizophrenia, are under investigation [2].

SNP therapy can result in two major distinct toxic syndromes: cyanide toxicity and thiocyanate (SCN^-) toxicity [3]. Each of these two disorders differs in risk factors, pathophysiology, signs and symptoms, diagnostic strategies, methods of prevention, and treatment. Cyanide toxicity is described in greater detail in the chapter on cyanide and is covered more superficially here.

Cyanide Toxicity from Sodium Nitroprusside**Chemistry and Pathophysiology**

The structure of SNP (Fig. 1) explains why desired vasodilation and cyanide toxicity may result from its use. SNP contains about 50%

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cyanide by weight. Early investigators attributed SNP's *in vivo* decomposition to hydrocyanic acid (HCN) to a reaction with oxyhemoglobin. It has been accepted for many years, however, that each SNP molecule decomposes when it reacts with sulfhydryl groups on endothelial cells [4, 5], releasing nitric oxide (producing vasodilation) and five cyanide moieties (Fig. 2).

When solutions of SNP are exposed to intense sunlight, they decompose relatively quickly to release cyanide. Solutions of SNP are relatively

stable, however, when exposed to artificial light. When protected from light, acidic or neutral solutions of SNP remain stable for months to years. It is unnecessary to prepare fresh solutions of SNP every 4 h if the solution has been protected from bright sunlight [3]. The infusion of SNP in the same line as intravenous solutions containing sulfhydryl groups (e.g., amino acid solutions, *N*-acetylcysteine) also would be expected to accelerate its breakdown to cyanide [5, 6].

At physiologic pH, all cyanide exists as HCN, and HCN has two main fates. First, HCN can be detoxified by being transsulfurated to thiocyanate (SCN^-), probably through several mechanisms. SCN^- undergoes renal excretion with an elimination half-life of 2.7 days in patients with normal renal function (see Fig. 2) [7]. Second, HCN can move into tissue and mitochondria to bind to the binuclear copper-iron center of cytochrome oxidase, where it inhibits electron transport, oxygen consumption, and oxidative phosphorylation. Because oxidative phosphorylation is a major buffer of protons, inhibition of cytochrome

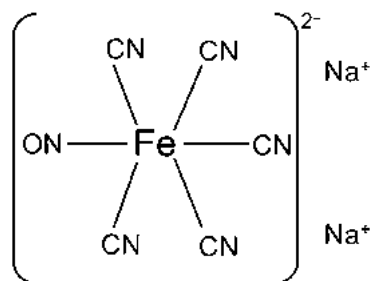


Fig. 1 Chemical structure of sodium nitroprusside

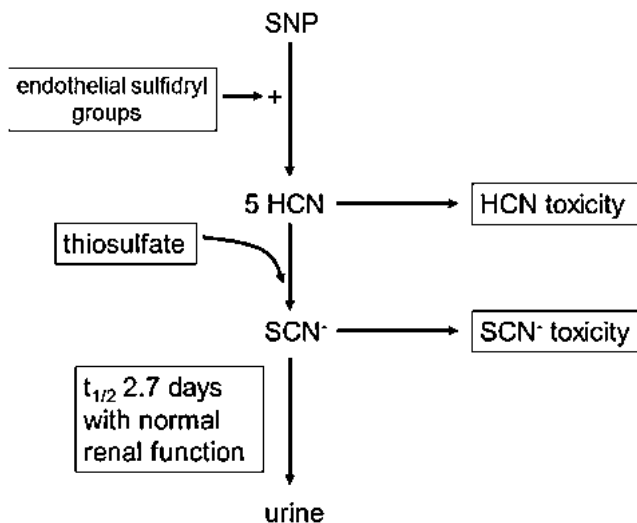


Fig. 2 The fate of sodium nitroprusside (SNP). Nitroprusside reacts with endothelial sulfhydryl groups to release nitric oxide (producing vasodilation) and five cyanide moieties (HCN). In the presence of adequate stores of thiosulfate, HCN is transsulfurated to form thiocyanate (SCN^-), which is excreted in the urine with a half-life of 2.7 days in patients with normal renal function. Inadequate

thiosulfate stores lead to accumulation of HCN, which can move into tissue to produce cyanide toxicity. Large doses of nitroprusside, prolonged infusions, and renal insufficiency can cause the accumulation of SCN^- , which produces a separate toxic syndrome. If SNP routinely is coin fused with sodium thiosulfate, HCN does not accumulate, and cyanide toxicity is prevented

oxidase by cyanide is accompanied by metabolic acidosis. Hyperlactatemia reflects increased glycolytic adenosine triphosphate production and a shift in the redox potential.

An important, and probably the dominant, sulfur donor for detoxification of HCN is thiosulfate ($\text{S}_2\text{O}_3^{2-}$). A healthy adult seems to possess enough thiosulfate to metabolize about 50 mg of SNP over the short term [8]. Patients coming off cardiac bypass or receiving diuretics may have lower plasma thiosulfate concentrations and might be predisposed to cyanide toxicity from a given dose of SNP, although this has never been proved. Short-term starvation, such as after other types of surgery, has been associated with increases in circulating thiosulfate levels [8], probably as a result of mobilization of sulfur-containing amino acids from skeletal muscle catabolism. There are no data supporting the contention that hepatic insufficiency predisposes to SNP-induced cyanide poisoning. Animals with hepatic damage detoxify HCN without difficulty [9]. In dogs, renal insufficiency is associated with lower circulating cyanide levels for a given SNP infusion rate.

Pharmacokinetics

Absorption of SNP is instantaneous and complete with intravenous infusion [5]. In blood, SNP is found almost wholly in plasma, with little to none in blood cells. This fact suggests that the nitroprusside anion distributes mainly to the extracellular space. The rapid breakdown of nitroprusside through interactions with sulfhydryl groups results in an elimination half-life of about 2 min, explaining the requirement of a continuous infusion and the ease with which infusion rates may be titrated to clinical effects.

Clinical Findings and Toxic Doses

Cyanide poisoning has resulted from short-term and long-term infusions of SNP [10–13]. When used as *short-term* infusions, such as those used

during anesthesia, circulating HCN concentrations begin to increase when the total dose (not infusion rate) of SNP exceeds 0.5–1.5 mg/kg [14, 15]. For *long-term* infusions, such as those used in the intensive care unit, circulating HCN concentrations begin to increase when SNP infusion rates exceed approximately 2 $\mu\text{g/kg/min}$ [3, 5]. Vesey and Cole [16] showed that on average, SNP infusion rates less than about 4 $\mu\text{g/kg/min}$ would not be expected to produce toxic plasma cyanide concentrations. Toxic HCN concentrations may be reached within a few hours when infusion rates exceed 5–10 $\mu\text{g/kg/min}$, but this is not always the case. Cyanide toxicity also may not appear until several days after beginning a SNP infusion.

The signs and symptoms of cyanide poisoning are described in detail in the chapter devoted to cyanide. Briefly, cyanide toxicity is characterized by central nervous system and cardiovascular dysfunction and metabolic acidosis. All of these abnormalities are seen commonly in critically ill patients, making it sometimes difficult to discern whether cyanide toxicity accounts for a patient's declining course. Central nervous system dysfunction includes agitation, confusion, convulsions, coma, and cerebral death. Cardiovascular findings comprise tachycardia, bradycardia, hypotension, and, sometimes, early hypertension. SNP and HCN produce vasodilation and a decline in systemic vascular resistance. Serial measurements of cardiovascular parameters with a pulmonary artery catheter reveal a decrease in oxygen consumption and, if cardiac output and hemoglobin concentrations remain unchanged, an increase in mixed venous oxygen content. There are no established values, however, for oxygen consumption or mixed venous oxygen content that provide reliable positive and negative predictive values for the presence of cyanide poisoning. A low systemic vascular resistance, anion gap metabolic acidosis, elevated arterial lactate concentrations, and depressed oxygen consumption are typical of SNP-induced cyanide poisoning, as are sepsis, hepatic failure, toxic shock syndrome, and systemic inflammatory response syndrome.

Diagnosis

The diagnosis of cyanide poisoning from SNP should be considered whenever central nervous system dysfunction, metabolic acidosis, and cardiovascular dysfunction accompany SNP infusion rates greater than about 4 $\mu\text{g/kg/min}$. Theoretically, however, infusion rates greater than 2.5 $\mu\text{g/kg/min}$ over many hours might be capable of producing HCN toxicity in an exceptional patient. Serious cyanide poisoning always results in metabolic acidosis, unless the patient is receiving alkaline infusions (e.g., sodium bicarbonate) or has a significant baseline metabolic alkalosis. Arterial lactate concentrations are elevated. Most patients with cyanide toxicity do not have unusually pink or bright red skin or blood; many are cyanotic. The presence of bright red skin or unusually bright red venous blood or retinal veins suggests the possibility of cyanide poisoning, however. Hypothermia commonly is noted in comatose victims of cyanide toxicity. An abnormal odor, including that of bitter almonds, would not result from SNP-induced cyanide poisoning.

It has been noted anecdotally that the onset of cyanide poisoning is accompanied by an increase in blood pressure and what seems to be resistance to SNP-induced vasodilation. Whether this is true and serves as a useful clinical clue or whether simply the higher doses of SNP result in cyanide toxicity has not been clarified in controlled trials with serial measurements of red blood cell or plasma cyanide concentrations. Resistance to SNP certainly can occur in the absence of cyanide poisoning.

Whole-blood cyanide concentrations, as performed at most reference laboratories, commonly are elevated falsely in patients receiving long-term SNP infusions because of elevated plasma SCN^- concentrations (see ► Chap. 97, “Cyanide: Hydrogen Cyanide, Inorganic Cyanide Salts, and Nitriles”) [17], and this has led to the misdiagnosis of cyanide poisoning from SNP in patients without evidence of cyanide toxicity [18, 19].

Plasma cyanide concentrations would be more helpful but are difficult to measure accurately. *Red blood cell* cyanide concentrations are easier to

measure and correlate well with severity of cyanide poisoning. In general, metabolic disturbances from cyanide poisoning appear with red blood cell cyanide concentrations of about 1 mg/L (approximately 40 mmol/L). Obvious cyanide poisoning is evident with red blood cell HCN concentrations of 5 mg/L (approximately 200 mmol/L) [18].

Many laboratories do not offer measurement of red cell cyanide concentrations, and results from any of these tests usually do not return for hours to days after the specimen is obtained and sent. The delay in obtaining results, false elevation in whole-blood cyanide concentrations in many patients receiving SNP, and difficulty in obtaining red blood cell cyanide concentrations or accurately measured plasma cyanide concentrations limit the practical value of cyanide bioassay in establishing a timely diagnosis of cyanide toxicity.

Most patients with SNP-induced cyanide poisoning have nontoxic serum SCN^- concentrations, although they may be elevated above the reference range. Serum SCN^- levels are not helpful in establishing or excluding the diagnosis of cyanide toxicity.

Prevention

Numerous studies have shown that the coinfusion of sodium thiosulfate with SNP prevents increases in circulating HCN concentrations, even with SNP infusion rates approaching 20 $\mu\text{g/kg/min}$ [5, 20]. Each 100 mg of SNP should be mixed with 1 g of sodium thiosulfate [3]. These mixtures are stable for at least 7 days when protected from light [20]. Each 1 g of sodium thiosulfate contains 12.6 mmol of sodium.

Cyanide poisoning from SNP becomes virtually impossible if the correct dose of sodium thiosulfate has been coinfused. Patients receiving mixtures of thiosulfate and nitroprusside experience more rapid detoxification of HCN to SCN^- , however, and higher plasma SCN^- levels. SCN^- toxicity is rarely a problem and

can be monitored easily with measurement of serum or plasma SCN^- concentrations.

Treatment

SNP should be discontinued in patients suspected of having cyanide toxicity. The SNP infusion can be restarted if SNP is mixed or coin fused with sodium thiosulfate as described earlier. Patients with serious cyanide poisoning (e.g., coma, hypotension, moderate-to-severe metabolic acidosis) should receive either sodium nitrite and sodium thiosulfate or hydroxocobalamin or dicobalt EDTA as described in the chapter on cyanide or whichever cyanide antidote is locally available. One should begin treating promptly on the basis of clinical suspicion, rather than waiting for results of blood cyanide concentrations. In a nonanemic adult, 300 mg of sodium nitrite intravenously should be infused, followed by 12.5 g intravenously of sodium thiosulfate if using the Nithiodote[®] kit. If using the Cyanokit[®], 5 g hydroxocobalamin should be infused over 15 min. Patients who are only mildly symptomatic from cyanide toxicity and in whom induction of methemoglobinemia with sodium nitrite may be dangerous (e.g., those with severe anemia) are likely to improve with discontinuance of SNP and infusion of sodium thiosulfate alone.

Vesey and Cole [16] showed that accurately measured red blood cell and plasma HCN concentrations decrease with a half-life of about 30 min after SNP is halted and decrease with a half-life of about 10 min if thiosulfate (without nitrite) is also given. These HCN concentrations were not in the highly toxic range, however, and it is not known if this half-life can be extrapolated to much higher HCN levels.

Thiocyanate Toxicity from Sodium Nitroprusside

Most of the HCN released from SNP undergoes transsulfuration to form SCN^- , which is excreted in the urine with an elimination half-life of 2.7

days in patients with normal renal function and 9 days in patients with severe renal insufficiency [7, 16]. Because of its long elimination half-life, SCN^- can accumulate in patients receiving SNP infusions over several days.

Clinical Findings and Toxic Doses

Most knowledge concerning SCN^- toxicity and the definition of toxic plasma concentrations has resulted from past extensive use of oral SCN^- salts in the treatment of hypertension. This older literature describes SCN^- toxicity as comprising abdominal colic, vomiting, weakness, rash, tinnitus, and hypothyroidism. More severe toxicity results in delusions, agitation, disorientation, tremor, convulsions, coma, and death.

The mechanism by which SCN^- produces toxicity is unknown. The older literature described the enzymatic conversion of SCN^- to HCN, but this now is known to have been an *in vitro* artifactual phenomenon. In contrast to cyanide poisoning, SCN^- toxicity is not accompanied by a metabolic acidosis in the absence of other causes, such as convulsions or shock.

Diagnosis

Although serum or plasma SCN^- concentrations do not assist in establishing or excluding the diagnosis of cyanide poisoning, they are of diagnostic utility with regard to SCN^- toxicity. Normal plasma SCN^- concentrations in non-smokers are approximately less than 4 mg/L (<0.4 mg/dL [<0.07 mmol/L]), whereas smokers, who inhale HCN in cigarette smoke, have plasma SCN^- levels of less than 8 mg/L (<0.8 mg/dL [<0.14 mmol/L]). Even serum or plasma SCN^- concentrations of 100 mg/L (10 mg/dL [1.7 mmol/L]) are not accompanied by significant toxicity. Serious SCN^- toxicity occurs when plasma SCN^- concentrations are greater than 150–200 mg/L (>15–20 mg/dL [>2.6 –3.4 mmol/L]) [16].

Prevention of and Monitoring for Toxicity

Patients receiving long-term infusions of SNP commonly have plasma SCN^- concentrations above normal reference values [16]. Plasma concentrations only rarely reach a level associated with systemic toxicity, however. SCN^- toxicity is not expected until the total SNP dose infused (not infusion rate) exceeds about 70 mg/kg [16]. In patients with normal renal function, SCN^- toxicity could occur in 7–14 days, whereas in patients with renal insufficiency, SCN^- toxicity can occur as early as 3–6 days [5].

Patients receiving coinfusions of sodium thiosulfate with SNP form SCN^- more readily and develop higher plasma SCN^- concentrations for a given SNP infusion rate. SCN^- toxicity remains uncommon, however, when SNP infusions are limited to 1–2 days in patients with renal failure or to 6–7 days in patients with normal renal function.

Treatment

Several authors have described effective removal of SCN^- with hemodialysis [21, 22]. Hemodialysis is considered the treatment of choice (level III evidence) for patients with severe SCN^- toxicity, especially in the presence of renal insufficiency.

Common Errors in the Management of Sodium Nitroprusside Toxicity

Using sodium nitroprusside without coinfusion of sodium thiosulfate

Failing to recognize falsely elevated whole-blood cyanide concentrations in many patients receiving sodium nitroprusside

Using serum or plasma thiocyanate levels to diagnose or exclude cyanide toxicity

Believing that most patients with cyanide poisoning have bright red skin or blood or exude a bitter almond odor

Believing it is necessary to mix a new bag of sodium nitroprusside every 4 h when the solution is covered and protected from bright sunlight

Special Populations

Pregnant Patients

Case reports and series document successful use of SNP for short infusions (e.g., during aneurysm clipping), with low total doses (e.g., ≤ 60 mg) and with low infusion rates (e.g., $< 3 \mu\text{g/kg/min}$) in pregnant women and gravid ewes [23–26]. Concern has been raised appropriately, however, with regard to the induction of fetal cyanide toxicity during maternal use of SNP. SNP infusions in gravid ewes can produce increases in maternal and fetal red blood cell cyanide concentrations [27]. Nitroprusside crosses the ovine placenta to produce equal concentrations in fetal and maternal blood [28]. Hydrogen cyanide, a small, lipophilic molecule, also crosses the placenta easily.

In gravid near-term ewes, the coinfusion of sodium thiosulfate with SNP prevents increases in maternal and fetal cyanide concentrations [28]. In this model, thiosulfate does not cross the placenta to enter the fetal circulation [29]. Maternally administered thiosulfate prevents ovine fetal cyanide toxicity by keeping maternal HCN concentrations low, allowing HCN to diffuse from the fetal circulation back into the maternal circulation for detoxification [29]. Fetal SCN^- concentrations do not increase during short-term infusions of maternal SCN^- in the ewe model [28].

No studies examining fetal and maternal HCN concentrations in pregnant women receiving SNP compared with pregnant women receiving SNP mixed with thiosulfate have been conducted. Given the safety and lack of adverse effects associated with sodium thiosulfate combined with data from ewe studies, it is recommended that the use of SNP in pregnant women always be

accompanied by coinfusion of sodium thiosulfate as described previously for nonpregnant patients.

Key Points in Sodium Nitroprusside Toxicity

1. SNP therapy produces two toxic syndromes: cyanide poisoning and thiocyanate toxicity.
2. Doses of SNP for short-term administration (e.g., 1–2 h) should not exceed 0.5–1.5 mg/kg to prevent cyanide toxicity.
3. Circulating cyanide concentrations begin to increase when long-term SNP infusions (>2 or 3 h) exceed about 2 µg/kg/min. Cyanide toxicity may occur when infusion rates exceed about 4 µg/kg/min.
4. Cyanide toxicity may occur within minutes to hours with large doses or fast infusion rates or may be delayed for hours to days with lower infusion rates.
5. The clinical picture of SNP-induced cyanide poisoning is similar to that of septic shock, liver failure, and other disorders (e.g., low systemic vascular resistance, hypothermia, lactic acidosis, lethargy/coma, tachycardia and hypotension, decreased oxygen consumption).
6. SNP-induced cyanide poisoning is prevented completely with coinfusion of sodium thiosulfate; 1 g of sodium thiosulfate should be mixed with each 100 mg of SNP.
7. SNP-induced cyanide toxicity is treated in an adult by stopping the SNP infusion and administering 300 mg of sodium nitrite and 12.5 g of sodium thiosulfate intravenously or by giving 5 g hydroxocobalamin intravenously.
8. Whole-blood cyanide concentrations rarely return quickly enough to be helpful and commonly are falsely elevated in patients receiving SNP infusions.

9. Serum or plasma thiocyanate concentrations are nontoxic in most patients with cyanide toxicity and are not helpful in establishing or excluding the diagnosis of cyanide poisoning.
10. Thiocyanate accumulates over days to weeks to produce thiocyanate toxicity. Thiocyanate toxicity is prevented by limiting total SNP doses to <70 mg/kg and by monitoring serum or plasma thiocyanate concentrations.
11. Moderate-to-severe thiocyanate toxicity (e.g., confusion, coma, rash, abdominal pain, seizures) does not appear until serum or plasma thiocyanate concentrations exceed about 150–200 mg/L (15–20 mg/dL).
12. Severe thiocyanate toxicity is treated with hemodialysis, especially in patients with renal insufficiency.

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Sympathomimetics constitute a large group of drugs with a spectrum of uses that range from over-the-counter cough and cold preparations to critical care medications. Their clinical effects are similar and theoretically should be predictable based on an understanding of the specific pharmacology of the drugs. However, because of the complexity of the autonomic nervous system and its responses to physiologic changes within the body, the actual clinical effects of these drugs vary and may be unpredictable.

Chemistry and Biochemistry of Sympathomimetic Agents

β -Phenylethylamine, the parent compound of the sympathomimetic amines, consists of a benzene ring and ethylamide side chain (Fig. 1). Substitutions are possible on the aliphatic ring, the α and β carbon, or the terminal amino group to yield a variety of compounds with sympathomimetic activity. Less polar molecules are more lipophilic and possess a greater tendency to cross the blood–brain barrier, resulting in central effects. Examples of such sympathomimetic amines are ephedrine and amphetamines. The more polar compounds (e.g., epinephrine, norepinephrine, and isoproterenol) cross the blood–brain barrier poorly, and their effects are peripheral (see Fig. 1).

Pathophysiology

The sympathomimetic toxidrome, addressed in detail in ► [Chap. 25, “Sympathomimetic Syndrome,”](#) is technically a misnomer. Excess autonomic stimulation and agents that mimic this process produce the clinical syndrome typically described as “sympathomimetic.” Prediction of the clinical effects of particular adrenergic agonists is possible based on their preferred adrenergic binding activity; their ability to cross the blood–brain barrier; and their direct, indirect, or mixed activity. Following an overdose, the receptor specificity may be diminished and the clinical effects of the various agents may become less predictable. The sequelae of sympathomimetic overdose are most significantly related to the cardiovascular and neurological systems and include, respectively: cardiac dysrhythmia, hypertension or hypotension; end-organ injury such as myocardial ischemia and infarction; and psychomotor agitation, stroke, and seizure.

The endogenous catecholamines include epinephrine, norepinephrine, and dopamine. These neurotransmitters, released from adrenergic and dopaminergic nerve endings, from the adrenal medulla, and locally within the sympathetic nervous system, are involved in numerous physiologic functions, including homeostasis and response to stressors. The actions of catecholamines are terminated rapidly by reuptake into

nerve terminals with metabolic degradation by monoamine oxidase (MAO) or by repackaging in vesicles (Fig. 2). Alternatively, termination of catecholamine activity may result after diffusion from the synaptic cleft with subsequent degradation at extraneuronal sites by catechol *O*-methyltransferase (COMT).

Synthetic sympathomimetic amines are structural analogues of the endogenous catecholamines. They lack several crucial hydroxyl groups, a property that increases their oral bioavailability by reducing their hepatic metabolism by COMT. In some cases, substitutions on the phenyl group (see Fig. 1) confer MAO resistance to these agents.

Adrenergic Receptors

Adrenergic receptors are broadly classed as α and β , but numerous subtypes exist. The clinically relevant types addressed here are α_1 , α_2 , β_1 , β_2 , and β_3 (Table 1). α_1 -Adrenergic receptors are postsynaptic and cause contraction of smooth muscle with various clinical effects. α_2 -Receptors are primarily presynaptic and function in an autoregulatory capacity. Synaptic norepinephrine inhibits further release of presynaptic norepinephrine by feedback inhibition. Postsynaptic α_2 -receptors share many of the properties of α_1 -receptors but also mediate a few unique effects (see Table 1).

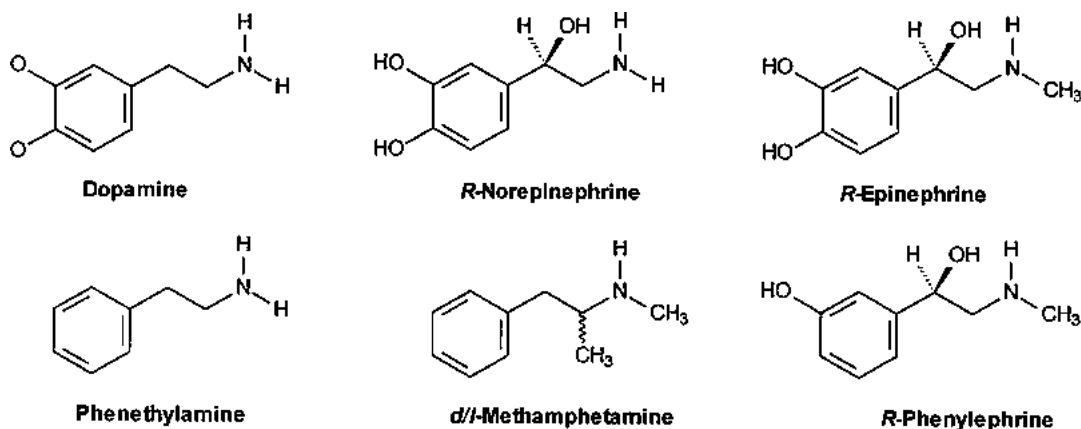


Fig. 1 Chemical structure of phenylethylamine and related sympathomimetics

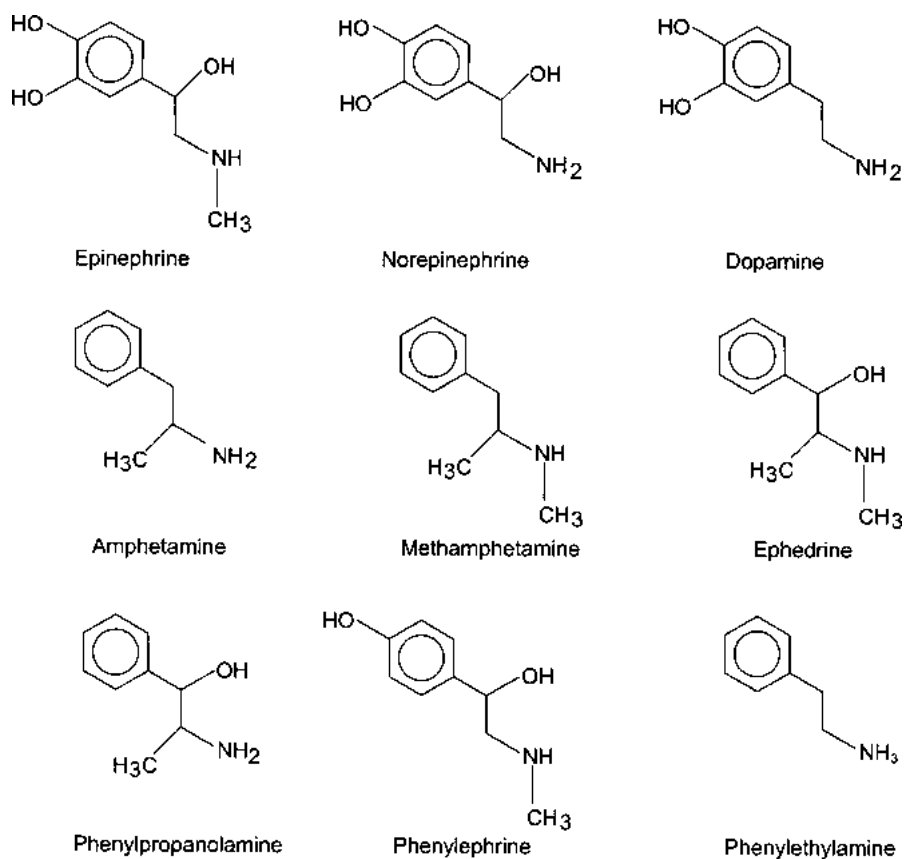


Fig. 2 Prejunctional and postjunctional sites of action of drugs that modify noradrenergic transmission at a sympathetic neuroeffector junction. L-Tyrosine is actively transported into the axoplasm of the neuron, where it is converted first to L-dopa by tyrosine hydroxylase (TH) and then to dopamine by aromatic L-amino acid decarboxylase (ALAAD). Dopamine is actively transported into synaptic vesicles, where it is converted by dopamine β -hydroxylase (DBH) to norepinephrine (NE). The arrival of a nerve action potential at the varicosity causes the influx of calcium ions, which promotes the exocytotic release of NE into the neuroeffector junction, where NE can activate receptors on postjunctional smooth muscle or glandular cells (α_1 or α_2) or cardiac cells (β_1) or on the prejunctional neuronal membrane (α_2). Activation of the α_2 -receptor inhibits the further release of NE. The action of NE is terminated by transport back into the varicosity, uptake 1.

In the synapses, NE can be stored in the synaptic vesicle or metabolized by monoamine oxidase (MAO) to inactive deaminated products. NE also is lost from the neuroeffector junction by diffusion and by transport into the postjunctional cell, where it is metabolized to normetanephrine by COMT. Drugs that enhance or mimic noradrenergic transmission (1) facilitate release (e.g., amphetamine), (2) block reuptake (e.g., cocaine), and (3) are receptor agonists (e.g., phenylephrine). Drugs that reduce noradrenergic transmission (1) inhibit synthesis (e.g., 1a, α -methyltyrosine; 1b, carbidopa; 1c, disulfiram), (2) disrupt vesicular storage (e.g., reserpine), (3) inhibit release (e.g., guanethidine), and (4) are receptor antagonists (e.g., phentolamine) (From Brody TM, Larner J, Minneman KP [eds]: Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, with permission)

β_1 -Receptors are located primarily on the myocardium and are involved in cardiovascular stimulation. β_2 -Receptors mediate numerous clinical effects, but the most important are related to smooth muscle relaxation in the vasculature and bronchioles. β_3 -Receptors are located in adipose tissue, the

gallbladder and urinary bladder. The main effects are relaxation of the urinary bladder, and lipolysis and thermogenesis in adipose tissue (see Table 1).

The endogenous catecholamines dopamine, epinephrine, and norepinephrine are nonspecific adrenergic agonists; they stimulate α -adrenergic

Table 1 Adrenoreceptor subtypes

Adrenoreceptor type	Tissue	Response
α_1	Most smooth muscle	Contraction
	Hepatic	Glycogenolysis, gluconeogenesis
	Intestinal smooth muscle	Relaxation
	Pupillary dilator muscle	Contraction (dilates pupil)
α_2	Vascular smooth muscle	Contraction
	CNS adrenoreceptors	Multiple effects, including lowering blood pressure
	Nerve terminals	Inhibits norepinephrine release
	Fat cells	Inhibits lipolysis
	Pancreatic β cells	Decreases insulin secretion
β_1	Cardiac	Increases inotropy and chronotropy
β_2	Smooth muscle	Relaxation
	Skeletal muscle	Glycogenolysis
β_3	Hepatic	Glycogenolysis, gluconeogenesis
	Bladder smooth muscle	Relaxation
	Adipose	Lipolysis, thermogenesis

CNS central nervous system

and β -adrenergic receptors. When administered exogenously all are predominantly peripherally acting and do not exert significant central nervous system (CNS) effects. Epinephrine and norepinephrine are direct-acting sympathomimetics, meaning they bind to and stimulate adrenergic receptors. They differ slightly, however, in their receptor selectivity. Most significantly, epinephrine is a potent β -adrenergic agonist, whereas norepinephrine is in all practicality a pure α -adrenergic agonist. Clinically, epinephrine has potent chronotropic and inotropic activity and norepinephrine has less effect on cardiac contractility or rate. In doses >0.1 mcg/kg/min, both epinephrine and norepinephrine cause an increase in peripheral vascular resistance. Epinephrine also exerts many metabolic effects and hormone-like effects on secretory glands

that norepinephrine does not (Table 2). Dopamine acts indirectly by affecting increased release of norepinephrine from the presynaptic neuron. At increased serum concentrations, dopamine may exert mixed, direct, and indirect activity. Several distinct types of dopamine receptors mediate the peripheral effects of dopamine. At low doses, <3 mcg/kg/min, dopamine's primary effect is vasodilatory rather than vasoconstrictive. Stimulation of D_1 receptors results in vasodilation, particularly in the renal, mesenteric, and coronary vasculature. At increasing doses >3 mcg/kg/min, dopamine stimulates β_1 -adrenergic receptors, with resulting increase in cardiac chronotropy and inotropy, and at doses >5 mcg/kg/min, stimulates α_1 -receptors, resulting in vasoconstriction.

The synthetic sympathetic amines are a large group of agents each with a unique combination of pharmacologic effects. Their mechanism of action is similar to the endogenous catecholamines, but because of unique structural and chemical qualities, they have unique pharmacologic and clinical properties. As a group, these agents have much greater CNS penetration than the catecholamines, although there are tremendous variations within the group. For example, methamphetamine is a more potent CNS stimulant than other amphetamine congeners, such as ephedrine, owing to its enhanced CNS penetration and to receptor binding potency.

Specific agents can be classified by their activities at α -receptors and β -receptors and their subtypes or alternatively classified according to their direct, indirect, or mixed action as adrenergic agents. Because the clinical effects of these agents vary based on their receptor selectivity, this is the framework used for discussion. These effects from amphetamines and their derivatives are discussed in ► [Chap. 72, "Amphetamines and Their Derivatives."](#)

Agents with Combined α -Adrenergic and β -Adrenergic Activity

Epinephrine, Norepinephrine, and Dopamine

Poisoning from epinephrine, norepinephrine, and dopamine may result from inhalational,

Table 2 Method of action and adrenoceptor effects of sympathomimetics

Drug	Direct, indirect, or mixed activity	Predominant adrenoceptor effect	Comments
Dopamine	Mixed	β_1	Dopaminergic activity as well
Dobutamine	Direct	β_1	
Epinephrine	Direct	$\alpha_1, \alpha_2, \beta_1, \beta_2$	
Norepinephrine	Direct	α_1, α_2	
Ephedrine	Mixed	$\alpha_1, \alpha_2, \beta_1, \beta_2$	
Pseudoephedrine	Mixed	$\alpha_1, \alpha_2, \beta_1, \beta_2$	
Mitodrine	Direct	α_1	
Synephrine	Direct	α_1	
Phenylephrine	Direct	α_1	
Methoxamine	Direct	$\alpha_1, \alpha_2, \beta_1, \beta_2$	
Metaraminol	Mixed	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Only α_1 effects at low dose
Mephentermine	Mixed	$\alpha_1, \alpha_2, \beta_1, \beta_2$	
Isoproterenol	Direct	β_1, β_2	
Metaproterenol	Direct	$\beta_2 > \beta_1$	β_1, β_2 equivalent when used intravenously
Aformoterol Albuterol Clenbuterol Formoterol Indacaterol Levalbuterol Oldoterol Pirbuterol Ractopamine Ritodrine Salmeterol Terbutaline Vilanterol	Direct	β_2	
Mirabergon	Direct	β_3	

intravenous, or subcutaneous administration. Iatrogenic injury or death from administration of parenteral catecholamines is a relatively common occurrence. This may occur with appropriate therapeutic dosing [1], but most typically occurs with inappropriate dosing or use. This includes improper preparation of an infusion, inappropriate infusion rate, or infusion pump malfunction. Dosing errors associated with miscalculated dose due to varying epinephrine concentrations and mg/kg dosing in pediatrics are a well-described issue [2–4]. Administration into inappropriate locations may occur as a result of injection of local anesthetic containing epinephrine into end organs, particularly digits, or similarly by release of an epinephrine autoinjector into the digit [5, 6].

Epinephrine and norepinephrine have direct α -adrenergic and β -adrenergic activity. Both are

metabolized by COMT and MAO and are not bioavailable when taken orally. Similarly, because of this efficient metabolism, they have brief durations of action.

Dopamine, a mixed acting agent, produces principally α -adrenergic and β -adrenergic effects at low parenteral doses. As the dose escalates, the α -adrenergic effects predominate. Although the clinical effects of epinephrine, norepinephrine, and dopamine are qualitatively similar, there are important differences (Table 2).

Ephedrine and Pseudoephedrine

Ephedrine was once commonly available in its herbal form, *Ephedra* or Ma Huang. In the USA, the Food and Drug Administration banned use of this dietary supplement in 2004 after numerous

reports of severe adverse events and fatalities. This led to a near resolution of these poisonings [7]. Though its commercial availability is less widespread than previously, Ephedra is still available in other countries, such as Canada, and is legal in the USA if contained in dietary supplements sold for purposes other than weight loss, such as in dietary supplements marketed for respiratory health.

The optical isomers ephedrine and pseudoephedrine are extremely similar to each other in pharmacologic properties and clinical use. Poisonings due to ephedrine or pseudoephedrine cause identical syndromes and require similar treatments. Ephedrine and pseudoephedrine are mixed-acting sympathomimetics, meaning that they have direct-and indirect-acting properties at adrenergic receptors. Similar to dopamine, they cause the release of norepinephrine. α -Adrenergic and β -adrenergic stimulation occur with ephedrine or pseudoephedrine poisoning. The half-life of ephedrine and pseudoephedrine is approximately 5 h [8, 9].

Metaraminol, Mephentermine, Methoxamine, and Midodrine

These medications are both α - and β -adrenergic agonists, but their α_1 effects are most prominent [9] and this agonism is their therapeutic purpose. Methoxamine is a relatively selective direct-acting α_1 -adrenergic receptor agonist. Metaraminol and mephentermine are mixed-acting and have direct vasoconstrictive effects but also cause release of endogenous norepinephrine. All of these agents may result in typical complications of α -adrenergic agonist poisoning, including hypertension, tachydysrhythmias or bradydysrhythmias, and CNS stimulation. Reflex bradycardia may result in response to hypertension associated with α_1 -adrenergic receptor toxicity. Metaraminol half-life is minutes long, methoxamine half-life is 3–6 h, mephentermine elimination half-life is 18 h, and midodrine half-life is 3–4 h. The extremely long half-lives relative to endogenous catecholamines have been associated with adverse outcomes when these medications have been used for cardiopulmonary resuscitation [9].

β -Adrenergic Agonists

Nonselective β -Adrenergic Agonists

Nonselective adrenergic agonists, such as isoproterenol, are typically used in the intensive care setting. Isoproterenol is a potent β_1 -receptor and β_2 -receptor agonist; causes decreased peripheral vascular resistance in skeletal muscle, renal vasculature, and mesenteric vasculature; and has a positive chronotropic and inotropic effect on the heart. As a result, isoproterenol typically causes an increase in systolic blood pressure and a decrease in diastolic blood pressure. Isoproterenol is metabolized by COMT and has a half-life of 2–5 min [9].

Selective β_2 -Agonists

The selective β_2 -agonists stimulate receptors located in bronchial, uterine, and vascular smooth muscle and are used to treat bronchoconstriction and preterm labor. Although these agents primarily stimulate β_2 -receptors, they may produce some β_1 -agonist effects, particularly at high doses.

The β_2 -agonists have nearly identical clinical effects, and the principal differences among the various agents derive from their pharmacokinetics. As such, this chapter does not examine each β_2 -agonist individually; rather, they are discussed as a class. The β_2 -agonists include albuterol, clenbuterol, formoterol, indacaterol, levalbuterol, oldoterol, pirbuterol, ritodrine, salmeterol, terbutaline, and vilanterol. The half-lives of these agents varies tremendously, with albuterol having a half-life of 4 h, but long-acting beta agonists such as albuterol, clenbuterol, formoterol, indacaterol, oldoterol, salmeterol, and vilanterol have half-lives of 20–50 h [9].

Use of β_2 -agonists is widespread, which presents several problems to the clinician treating potential toxicity. Excessive use of β_2 -agonists such as those contained in metered-dose asthma inhalers or oral preparations can result in tachyphylaxis, a phenomenon in which downregulation of receptors occurs, and the effects from this drug diminish as a result of excessive use [10]. Consequently, patients may require higher doses to achieve the same clinical effect they previously experienced at lower doses, resulting in more profound systemic side effects.

Some aspects of clenbuterol toxicity are unique and differ from other β_2 -agonists. Although clenbuterol is a selective β_2 -agonist used in human and veterinary medications as a bronchodilator, it is commonly abused by people seeking its β_3 -agonist activity, which includes anabolic and lipolytic effects.

Selective β_3 -Agonists

Mirabegron is a selective β_3 -agonist that is the only drug of its kind in this class [11]. It is a relatively new drug used to achieve relaxation of urinary bladder smooth muscle to treat symptoms of overactive bladder. The half-life is approximately 50 h.

α -Adrenergic Agonists

α -Adrenergic agents can be classified according to their relative affinity for α_1 -adrenergic or α_2 -adrenergic receptors. The primary effect of α_1 -adrenergic agonists is vasoconstriction resulting in increased peripheral vascular resistance, increased blood pressure, and often reflex bradycardia. Examples of α_1 -agonists include phenylephrine and synephrine. These medications undergo complex metabolism resulting in a duration of effect for IV doses of approximately 15 min, and by oral dosing 2–4 h.

Phenylephrine is a direct-acting α_1 -adrenergic agonist used topically as a nasal decongestant and mydriatic and intravenously as a pressor. Toxicity from topical application is described, particularly in infants and geriatric patients. Phenylephrine undergoes extensive metabolism by MAO in the intestinal wall, resulting in poor oral bioavailability. Synephrine is a plant-derived product similar in structure to phenylephrine, differing by the presence of a hydroxyl group in the para-position (synephrine) rather than the meta-position (phenylephrine or neosynephrine) on the benzene ring. Synephrine is typically present in dietary supplements derived from the herbal called bitter orange. These are often advertised with emphasis that the stimulant is “ephedra-free,” and bitter orange is now a leading sympathomimetic stimulant included in ergogenic dietary supplements since the ban on ephedra [12].

α_2 -Receptors are found in the peripheral nervous system and CNS. Peripherally, α_2 -receptors function similarly to the α_1 subtype and mediate smooth muscle contraction, causing vasoconstriction. At central adrenergic sites α_2 -adrenergic agonism result in feedback inhibition and a decreased release of catecholamines. The most prominent clinical effects include a centrally mediated reduction in blood pressure and heart rate. Common α_2 -agonists are guanabenz, guanfacine, and methyldopa; and the imidazoline agents apraclonidine, clonidine, naphazoline, oxymetazoline, tetrahydrolazine, and xylo-metazoline. Dexmedetomidine is an α_2 -adrenergic agonist with a primary effect of CNS sedation and is used specifically as a sedative or anesthetic agent. α_2 -Adrenergic agonists are discussed in detail in the ► [Chap. 35, “Alpha-2 Adrenergic and Imidazoline Receptor Agonists: Clonidine, Dexmedetomidine, and Related Antihypertensives, Decongestants, and Sedatives.”](#)

Clinical Presentation

Epinephrine, Norepinephrine, and Dopamine

The predominant clinical effects of epinephrine, norepinephrine, and dopamine are cardiovascular and include vasoconstriction and cardiac stimulation. The sequelae of poisoning with these agents include hypertension, tachycardia, dysrhythmia, acute coronary syndromes, pulmonary edema, and cerebrovascular injury [13–18]. With toxicity, patients often complain of chest pain, palpitation, headache, as well as the neuropsychiatric symptoms of anxiety, apprehension, and a sense of impending doom. Catecholamines, which generally do not cross the blood–brain barrier, produce minimal direct CNS effects [19]. The psychological and cerebrovascular effects likely are secondary to cardiovascular stimulation.

Tissue necrosis secondary to localized vasoconstriction is the potential result of end-organ administration; this most typically occurs as a result of α -adrenergic vasoconstriction, usually due to locally applied epinephrine. The

performance of “bloodless field” surgery, particularly hand and cosmetic surgery, demonstrates that epinephrine administration to digits or end organs is not an indication for mandatory antidotal therapy.

Ephedrine and Pseudoephedrine

The adverse effects of ephedrine and pseudoephedrine are the result of excessive cardiovascular stimulation by the autonomic nervous system. The expected complications of their use are qualitatively similar to the complications that occur with catecholamine use. Relative to amphetamine or methamphetamine, ephedrine and pseudoephedrine have poor CNS penetration and cause much more profound peripheral sympathomimetic effects. Patients attempting to achieve the degree of CNS stimulation produced by methamphetamine may take massive doses of ephedrine or pseudoephedrine, resulting in profound cardiovascular stimulation and its sequelae.

β -Adrenergic Agonists

Nonselective β -Adrenergic Agonists

Nonselective adrenergic agonists, such as isoproterenol, a potent β_1 -receptor and β_2 -receptor agonist, typically are used in the intensive care setting.

Selective β_2 -Agonists

The selective β_2 -agonists stimulate receptors located in bronchial, uterine, and vascular smooth muscle and are used to treat bronchoconstriction, and preterm labor. They are also used for the treatment of hyperkalemia because of their β -receptor-mediated ability to cause an intracellular influx of potassium. Although these agents primarily stimulate β_2 -receptors, they may produce some β_1 -agonist effects, particularly at high doses [20].

The β_2 -agonists have nearly identical clinical effects, and the principal differences among the various agents derive from their pharmacokinetics. As such, this chapter does not examine each β_2 -agonist individually; rather, they are discussed as a class. The β_2 -agonists include albuterol,

clenbuterol, formoterol, indacaterol, levalbuterol, oldoterol, pirbuterol, ritodrine, salmeterol, terbutaline, and vilanterol.

Use of β_2 -agonists is widespread, which presents several problems to the clinician treating potential toxicity. Excessive use of β_2 -agonists such as those contained in metered-dose asthma inhalers or oral preparations can result in tachyphylaxis, a phenomenon in which downregulation of receptors occurs, and the effects from this drug diminish as a result of excessive use [21]. Consequently, patients may require higher doses to achieve the same clinical effect they previously experienced at lower doses, resulting in more profound systemic side effects.

In the USA, clenbuterol is not approved for use in humans, and exposure to clenbuterol occurs by various manners including indicated use of clenbuterol as a bronchodilator prescribed in another country; exposure to illicitly obtained clenbuterol as an anabolic and lipolytic drug used to increase lean weight and decrease body fat; [22] use of heroin tainted with clenbuterol [23]; and consumption of beef or liver from cattle that were being clandestinely fed clenbuterol [24].

Though an illegal practice, clenbuterol is sometimes added to livestock feed to grow cattle that are more muscular and also more lean, and it is illicitly used by humans seeking the same effects of increasing muscle mass and decreasing body fat.

Adverse Effects of β -Adrenergic Agonists

The toxic effects of isoproterenol poisoning are related to its cardiostimulatory and vasodilatory properties and include tachycardia, hypotension, tachydysrhythmias, myocardial ischemia, and flushing. Commonly, CNS effects of anxiety, fear, and headache occur. Excess selective β_2 -adrenergic agonism is associated with fewer clinically significant effects than combined β_1 and β_2 agonism; this probably relates to the vasodilatory properties of the β_2 -agonists and the lack of vasoconstrictive (i.e., hypertensive) effects after their overdose.

Adverse Effects of β_2 -Adrenergic Agonists

The primary toxic effects of β_2 -agonists are cardiovascular, including hypotension, tachycardia,

and tachydysrhythmias. Elevations of creatine phosphokinase muscle (CPK-MM) and cardiac (CPK-MB) fractions as well as troponin may result after large doses of β_2 -agonists, particularly terbutaline infusions and continuous albuterol nebulization [25–27]. The clinical significance of increased CPK-MB is unclear, and it has not been shown to correlate with clinically adverse effects. Cardiac troponins may also be elevated as a result of terbutaline infusion, but the clinical significance of elevations of CPK-MB and troponin, particularly in children who most commonly receive IV β_2 -agonists, is also unclear [28, 29]. Cardiac dysrhythmia, although described with β_2 -agonist poisoning, is most frequently supraventricular in origin and clinically inconsequential. Dysrhythmias other than sinus tachycardia should not be attributed routinely to β_2 -agonist toxicity until other causes have been excluded.

Metabolic effects result from β_2 agonist toxicity but are usually of minimal consequence. Severe hypokalemia can result from β_2 -adrenergic stimulation [30]. This condition results from influx of extracellular potassium into the intracellular compartment despite normal total-body potassium content. Electrocardiographic and neuromuscular complications of hypokalemia rarely, if ever, develop. Although β_2 -agonists cause hyperglycemia, prolonged poisoning can result in hypoglycemia from depleted glucose and glycogen stores. Other effects of β_2 -adrenergic poisoning include tremor, agitation, vomiting, and hypophosphatemia [31–33].

Pediatric toxicity from β_2 -agonists, which occurs predominantly in young children treated with oral albuterol preparations, can cause significant gastrointestinal symptoms and tachycardia [27]. Nevertheless, these unintentional pediatric poisonings are extremely well tolerated in children and rarely require more than supportive treatment. For oral albuterol poisoning, 1 mg/kg seems to be the dose threshold for developing significant toxicity [34].

Clenbuterol toxicity includes cardiovascular elements expected of β_2 -agonists, most prominently palpitations and tachycardia, with β_2 -mediated hypotension. Myocardial ischemia [35] and

infarction, atypical of other β_2 -agonist poisonings, has been reported [36]. Metabolic effects of significant hypokalemia and hyperglycemia are also expected, but lactic acidemia and venous hyperoxia have been reported with clenbuterol toxicity mimicking cyanide poisoning [37]. The mechanism for this lactic acidemia is unclear. These severe effects, combined with a half-life of 24 h or greater, result in greater morbidity from clenbuterol relative to other drugs in this class.

Ritodrine, used in pregnant women for tocolysis, is associated with numerous unique toxic effects. It is unclear if these are specific to ritodrine, or if they are the result of using β_2 agonists for tocolysis, but these include agranulocytosis [38], cardiomyopathy [39], myocardial infarction [40], pulmonary edema [41], rhabdomyolysis [42], and pulmonary edema [43]. In most reported cases, these effects resolve rapidly after discontinuation of ritodrine, but standard therapies for these conditions is needed until the patient returns to baseline health.

Adverse Effects of β_3 -Adrenergic Agonists

As there is only one β_3 -agonist medication, mirabegron, that has been in use for only a few years, reports of adverse events and toxicity are very limited. The specific adverse effects are not well reported, but would be expected to be similar to β_2 -agonist toxicity. Although in theory stimulation of β_3 -receptors causes negative chronotropy, in practice medications with β_3 -agonist effects cause tachycardia as a result of its activity as β_1 and β_2 -receptors. Animal toxicity data suggests that the cardiovascular effects of mirabegron, including hypotension, tachycardia, including tachydysrhythmia and cardiac arrest may result [44]. In animal models, significant lacrimation and salivation, which are not typical of β agonist toxicity, result from high doses [45].

Adverse Effects of α_1 -Adrenergic Agonists

Direct-acting α_1 -selective agonists include phenylephrine and methoxamine, and mixed-acting α_1 -selective agonists include mephentermine,

metaraminol, and mitodrine. All of these agents are used clinically for their vasoconstrictive effects. After overdose, hypertension and reflex bradycardia typically occur. The reflex bradycardia is a homeostatic response that maintains cerebral blood flow in a physiologically acceptable range, even in the presence of a severely elevated blood pressure

Phenylephrine and Sympheprine

Though described independently, it is likely that complications resulting from either of these agents are possible with both drugs. Complications described with phenylephrine include psychosis, seizure, hypertension, myocardial infarction [46], and intracerebral hemorrhage [47, 48].

The most significant adverse effects of syneprine are cardiovascular, and include palpitations, tachycardia, tachydysrhythmia, myocardial infarction [49, 50], cardiac arrest, and stroke. Ischemic colitis [51] and rhabdomyolysis [52] have also been described in association with syneprine use.

Methoxamine, Metaraminol, and Mitodrine

All of these agents may result in typical complications of α -adrenergic agonist poisoning, including hypertension, tachydysrhythmias or bradydysrhythmias, and CNS stimulation. Reflex bradycardia may result in response to hypertension associated with α_1 -adrenergic receptor toxicity.

Diagnosis

Sympathomimetic overdose is a clinical diagnosis. Some laboratory findings, such as hypokalemia and hyperglycemia, may be present, but they play little role in diagnosis. Although sympathomimetic drugs and the endogenous catecholamines can be selectively assayed, the results typically are not available in a clinically relevant period of time. Urine drug screens, which can detect the structurally similar amphetamine derivatives by immunoassay, are neither

Table 3 Differential diagnosis of sympathomimetic syndrome

Anticholinergic syndrome
Dietary supplements (e.g., <i>Citrus aurantium</i>)
Hyperthyroidism
Mania
Neuroleptic malignant syndrome
Other situations of increased endogenous catecholamine release
Pheochromocytoma
Poisoning by illicit agents with adrenergic activity (e.g., cocaine or amphetamine derivatives)
Serotonin syndrome
Subarachnoid hemorrhage
Thyroid storm
Withdrawal syndromes

sufficiently sensitive nor sufficiently specific to be clinically useful during the acute management of sympathomimetic drug toxicity. The differential diagnosis of sympathomimetic poisoning is listed in Table 3.

Treatment

The mainstay of therapy for adrenoceptor overstimulation is correction and maintenance of vital signs to within acceptable limits. For agents that produce predominantly psychomotor agitation and increased autonomic activity, sedation and control of symptoms such as vomiting are generally sufficient.

Patients poisoned by peripherally acting agents occasionally require the judicious use of specific α or β antagonists but most commonly need nonspecific medications such as antiemetics, benzodiazepines, or nonadrenergic antihypertensives such as hydralazine or calcium channel blockers (Evidence: Level I) (Table 4).

These therapies should not be initiated prematurely or indiscriminately because inappropriate use of these antagonists can result in unpredictable adverse effects. In a patient with a nonspecific adrenergic agonist overdose, such as ephedrine poisoning, the unopposed α -adrenergic stimulation that remains after β -adrenergic blockade may

Table 4 Drugs used in treatment of sympathomimetic toxicity

Drug	Indication	Action	Dose
Hydralazine	Hypertension	Vasodilation	0.1–0.5 mg/kg/dose (up to 20 mg)
Nicardipine	Hypertension	Vasodilation	0.5–1 mcg/kg/min IV titrated up to 5 mcg/kg/min
Nitroprusside	Hypertension	Vasodilation	0.3–10 µg/kg/min IV, titrated to effect
Phentolamine	Hypertension	α antagonism	Child: 0.1 mg/kg/dose (up to 5 mg/dose) IV repeated every 10 min PRN Adult: 5 mg IV repeated every 5 min PRN
	Extravasation of catecholamine	α antagonism	5–10 mg in 10 mL of normal saline infiltrated SC in appropriate quantity
Terbutaline	Extravasation of catecholamine	β ₂ agonism	Child: 0.01 mg/kg/dose SC every 15 min to maximum of 0.4 mg/2 h ^a Adult: 0.1 mg SC every 15 min to maximum of 0.4 mg/2 h ^a
Esmolol	Hypertension	β antagonism	500 µg/kg/min IV bolus followed by infusion 50 µg/kg/min titrated to effect up to 500 µg/kg/min
Metoprolol	Hypertension	β antagonism	Child: Pediatric dose not established Adult: 2.5–5 mg IV every 5 min to a maximum of 15 mg
Propranolol	Hypertension	β antagonism	Child: 0.05–0.1 mg/kg slow IV (up to 1 mg/dose), repeated every 15 min to maximum of 5 mg total dose Adult: 0.5–1 mg slow IV, repeated every 15 min to maximum of 5 mg total dose
Labetalol	Hypertension	β antagonism, some α antagonism	Child: 0.2–0.5 mg/kg/dose IV, maximal dose 20 mg, followed by infusion of 0.25–1 mg/kg/h Adult: 20 mg slow IV, may repeated every 10 min PRN or 2 mg/kg/min infusion titrated to effect

IV intravenously, PRN as needed, SC subcutaneously

^aThese doses are based on 1 mg/mL solution

be associated with acute deterioration of the patient's vital signs [53].

Indications for ICU Admission in Sympathomimetic Agent Poisoning

- Manifestations of vital end-organ injury (e.g., myocardial ischemia or infarction, cerebrovascular accident, cerebral hemorrhage, liver function abnormality)
- Cardiac dysrhythmias other than sinus tachycardia
- Hypokalemia requiring cardiac monitoring or potassium supplementation
- Cardiovascular effects requiring ongoing therapy with cardiovascular agents (e.g., nitroprusside infusion)
- Ongoing morbidity requiring monitoring and treatment (e.g., hyperthermia, rhabdomyolysis, or renal insufficiency)

Treatment of Toxicity from Combined α-Adrenergic and β-Adrenergic Agents

Because of the short duration of action of epinephrine, norepinephrine, and dopamine, the treatment of systemic toxicity, beyond supportive care, is typically unnecessary, unless complications arise (Evidence: Level III). Discontinuation of the infused or administered drug is followed by fairly prompt cessation of signs and symptoms.

Treatment of systemic toxicity resulting from longer acting sympathomimetic agents should focus on correcting the vital sign abnormalities to within acceptable limits, including aggressive management of hyperthermia and control of neurobehavioral effects. Vasoconstrictive effects may be managed safely with phentolamine, hydralazine, a dihydropyridine calcium channel blocker, or sodium nitroprusside, but the

chronotropic and inotropic effects are abated only by the administration of diltiazem, verapamil, or a β -adrenergic antagonist. β -Adrenergic antagonists are not advised routinely, however, unless a vasorelaxant agent is coadministered (Evidence: Level III). The concern over the use of a β -blocker in such a situation is that it may result in unopposed α -adrenergic activity and hypertension. The danger of administering a β -blocker in the presence of an agent with combined α -adrenergic and β -adrenergic activity may be overstated, and β -blockers have been administered successfully in these situations [54]. At this time, if patients are manifesting sympathomimetic signs, we do not recommend routine use of a β -blocker to treat patients exposed to adrenergic agonists, such as cocaine, amphetamines, or ephedrine unless a second antihypertensive with vasodilatory effects, such as an alpha blocker or calcium channel blocker, is coadministered (Evidence: Level III).

Psychomotor agitation can be treated with benzodiazepines, such as lorazepam or diazepam (Evidence: Level III). Attempts at gastrointestinal decontamination of these patients with activated charcoal has not been shown to affect their outcome. If the patient is capable of drinking the AC without the need for a nasogastric tube, has not vomited, and is at risk for an adverse outcome due to the poisoning, then a single dose of AC is indicated for most patients.

Although there are not sufficient published data to make broad-based recommendations about treatment for digital administration of epinephrine, it is generally accepted that in the absence of comorbidities, such as diabetic vasculopathy, pallor in a digit or end organ lasting only a few hours is usually safe (Evidence: Level II-2). If deemed necessary, such as for severe ischemic pain, treatment for end-organ epinephrine administration is directed at increasing blood flow to the affected area; this can be accomplished by warming the area or by vasodilation achieved by application of topical nitroglycerin paste. Alternatively phentolamine may be injected into the affected area, directly into the initial puncture wound if possible, to antagonize epinephrine's α_1 -adrenergic vasoconstrictive

effect [55]. Many clinicians have limited experience with phentolamine, and because this agent is not used frequently it may be difficult to obtain. Injection of terbutaline into the affected tissues may also produce local vasodilation. In cases of inadvertent digital administration of epinephrine, terbutaline can be injected into the site of pallor in a manner similar to that described above [56]. Terbutaline offers the advantage of being much more readily available and better known to clinicians, though use for this indication has limited evidence supporting it [57, 58]. Terbutaline typically is available in a concentration of 1 mg/mL. In our experience in adults, an intravenous injection of 0.1 mg is an appropriate initial dose; this dose can be repeated in 15 min if necessary. If the epinephrine injection occurred in an area of loose flesh such as the thenar eminence or pad of the distal phalanx, the dose of terbutaline can be diluted in 0.3–0.5 mL of normal saline to allow greater tissue distribution. Terbutaline may cause tachycardia is not recommended for patients at risk for myocardial ischemia.

Treatment of β -Adrenergic Agonist Poisoning

Supportive care is the mainstay of treatment. Most patients with β -adrenergic agonist-mediated hypotension and tachycardia respond to intravascular volume expansion with intravenous saline. In our experience, administration of vasopressors generally is unnecessary but may be required in patients with refractory, symptomatic, and vasodilatory hypotension.

Conceptually the use of a β -blocker is an ideal therapy for hypotensive patients following β -adrenergic agonist poisoning. Although use of a β -blocker to treat hypotension may seem counterintuitive, reversal of the β_2 -mediated vasodilation is expected to raise the blood pressure (Evidence: Level II-2). This use should be approached cautiously however, and generally only after other therapies have failed, particularly because there are currently no short-acting selective β_2 -blockers. Patients with hemodynamically

consequential tachydysrhythmias may be treated with β -blockers. In this situation, it is prudent to use a short-acting agent, such as esmolol. Although they are typically contraindicated in asthmatic patients, there is evidence that the judicious use of short-acting β -blockers such as esmolol may be acceptable [59].

Treatment of clinically significant hypokalemia consists of cautious small boluses of potassium (Evidence: Level III). This use must be distinguished from the higher doses used in total-body potassium repletion however, because efflux of potassium from the extracellular compartment follows resolution of the β_2 -agonist effect. Aggressive administration of potassium during the period of symptomatic hypokalemia potentially can result in hyperkalemia.

Treatment of α -Adrenergic Agonist Toxicity

General principles of normalization of vital signs within acceptable limits should be employed. The considerations regarding attempts at gastrointestinal decontamination are the same as those described above for β agonist poisoning. Further, many agents are concentrated liquid preparations used parenterally, topically on mucous membranes, or as inhalational agents, so the ability to perform gastrointestinal decontamination may be limited.

Treatment of hypertension should be administered based solely on measured, not anticipative, elevations in blood pressure. This recommendation is particularly important in healthy patients whose normal blood pressures are far lower than the blood pressures used to define hypertensive urgency or emergency (Evidence: Level II-2).

Hypertension resulting from α_1 -adrenergic stimulation can be treated most specifically with phentolamine, an α_1 -adrenergic antagonist. Less specific but still effective therapy more familiar to most clinicians includes direct-acting vasodilators, such as hydralazine, nitroprusside, nitroglycerin, or the dihydropyridine class of calcium channel blockers such as nicardipine or fenoldopam. In our experience, the treatment of

reflex bradycardia is rarely necessary and should resolve with improvement in the patient's blood pressure.

Special Situations

Several unique issues relevant to sympathomimetic toxicity warrant mention. Monoamine oxidase inhibitor use can result in exaggerated pressor response to indirect-acting sympathomimetics because of increased presynaptic stores of catecholamines. The concomitant use of inhalational or halogenated anesthetics can sensitize the myocardium to β -adrenergic agonism, resulting in dysrhythmia on release of endogenous or exposure to exogenous catecholamines. Patients requiring pressors after poisoning by catecholamine reuptake inhibitors, such as tricyclic antidepressants, may not respond to the administration of dopamine or other indirect-acting pressors. These patients may respond, however, to a direct-acting adrenergic agonist. Similarly, patients with catecholamine depletion, such as patients who have been using large amounts of a sympathomimetic agent, may not respond to indirect-acting agents but do respond to direct-acting agents.

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Part V

Medications: Decongestant/ Antihistaminergic/Bronchodilatory

Jerry W. Snow and R. Brent Furbee

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By the turn of the twentieth century, interest in allergic response and particularly the phenomenon of anaphylaxis had become intense. In 1902, Portier and Richet provided further focus for the study by developing the concept of altered animal reactivity, which they termed *allergy* [1]. Of the biologic amines released in the inflammatory process, histamine was the first described, originally termed β -aminoethylimidazole. Histamine's actions on the gut, bronchioles, and heart were reported in 1910 [2, 3]. The work on the receptor theory of drug action was well under way when the first articles on anaphylaxis were published. It was not until 1933, however, when Clark published *The Mode of Action of Drugs on Cells* [4], that acceptance of that theory became sufficient to stimulate a search for compounds that might block histamine's effects. Many compounds with antihistaminic activity were produced, but their toxicity precluded use in humans. In 1941, a French patent was obtained for N₁N-dimethyl-N₁-benzyl-N-phenylethylenediamine, the first antihistamine in human clinical use. Diphenhydramine followed in 1945. The designation *H₁ receptors* was proposed in 1966 [5], and by 1972, the existence of H₂ receptors had been confirmed [6]. Subsequently, use of H₁ and H₂ antagonists became widespread. Nonsedating second-generation antihistamines were developed in the 1980s when their inability to penetrate the central nervous system (CNS) was exploited. Adverse effects, particularly the occasional occurrence of torsades de pointes, were noted in the late 1980s. Emanuel [7] provides a

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detailed history of the understanding and development of antihistamines.

Biochemistry and Clinical Pharmacology

Kinetics for Oral Exposure in Healthy Adults

See Table 1.

Antihistamines are classified based on their affinities for either H_1 or H_2 receptors. Antihistamines classified as H_1 -receptor antagonists are divided further into first-generation agents (less H_1 receptor specificity and high blood–brain barrier penetration) and second-generation agents (more H_1 receptor specificity and low blood–brain barrier penetration) (Figs. 1 and 2) [8].

Pathophysiology of Toxic Effects

The therapeutic effects of antihistamines are related to their ability to bind to and block histaminic receptors throughout the body (Fig. 3). The therapeutic effects of H_1 -receptor antagonists result from the blockade of receptors in the vasculature, bronchioles, cardiac tissues, and sensory nerves as well as prevention of release of further histamine from mast cells and basophils [9]. Clinically, this activity results in decreasing the systemic effects of allergic reactions. H_2 -receptor antagonists derive their benefit from inhibiting gastric acid secretion and subsequently treating and preventing gastric and duodenal ulcers. The toxic effects of antihistamines occur when either histaminic receptors in the CNS or non-histaminic receptors in the CNS and peripheral nervous system are antagonized.

In the CNS, there are four classes of histamine receptors: H_1 , H_2 , H_3 , and H_4 receptors [10, 11]. H_1 receptors are thought to have a modulatory role in the CNS, affecting numerous functions, including sleep–wake cycles, thirst, thermoregulation, and prevention of seizures [12, 13]. Antagonism of central H_1 receptors can result in somnolence [14] and seizures [15].

Table 1 Pharmacokinetics of oral exposures to commonly used antihistamines in healthy adults

Compound	Peak effect (h)	Half-life (h)
H_1 blockers		
Brompheniramine	3–9	12–34
Cetirizine	1–2	6.5–10
Chlorpheniramine	2	12–43
Cyproheptadine pharmacokinetics: cyproheptadine	6–9	8–9
Dexchlorpheniramine	3	3–6 (duration)
Dimenhydrinate	0.25–0.5 (onset)	3–9.3
Diphenhydramine	1–3	2–8
Doxylamine	1–4	7–13
Hydroxyzine	0.25–0.5 (onset)	3–6 (duration)
Loratadine	8–12	12–15
Meclizine	1 (onset)	8–24 (duration)
Promethazine	0.3 (onset)	2–6 (duration)
Tripeleennamine	0.25–0.5 (onset)	2–8 (duration)
H_2 blockers		
Cimetidine	1–2	2–4
Famotidine	1 (onset)	10–12 (duration)
Nizatidine	0.5–3	1.3
Ranitidine hydrochloride	1–3	2.5

The mechanism of sedation is believed to be the inhibition of central H_1 receptors [16]. In cultured human cortical neurons, histamine blocks the background leakage of potassium, resulting in neuronal membrane depolarization and consequent generation of action potentials. This blockade, along with histamine's distribution in the CNS, is the basis of histamine's presumed role in arousal. The blockade of background potassium currents can be inhibited by selective H_1 -receptor

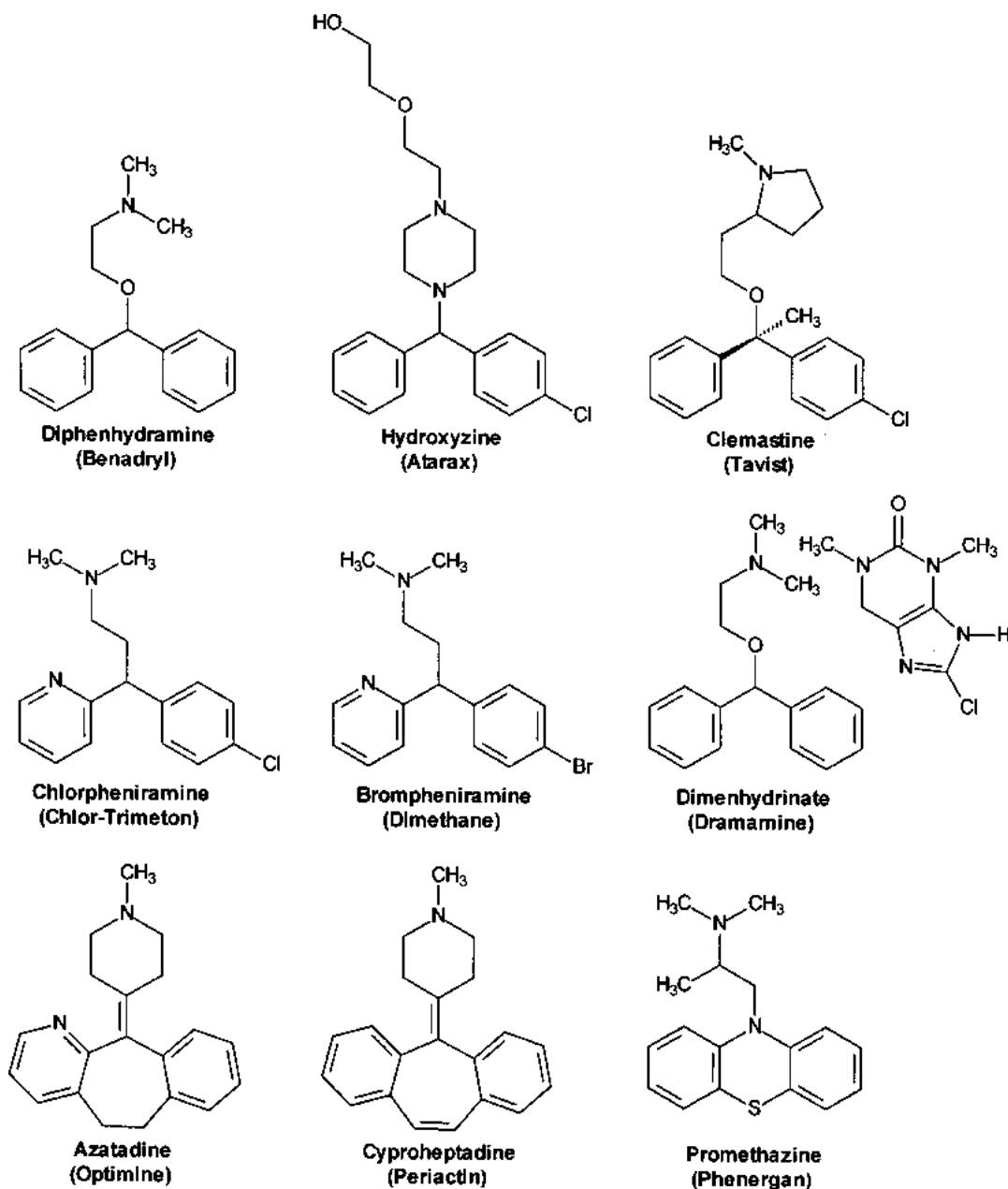


Fig. 1 Chemical structures of first-generation antihistamines (sedating)

(but not H_2) antagonists, resulting in decreased neuronal firing and CNS depression [14]. Traditionally, antihistamine-induced seizures were thought to be due to either their local anesthetic effects or their anticholinergic effects. Antihistamines' ability to cause seizures does not correlate, however, with their affinity for muscarinic

receptors and is not reversed by physostigmine [15, 17]. Laboratory studies in mice and rats using histidine, a histamine precursor, and blockers of histamine metabolism have shown significant decreases in the incidence of experimentally induced seizures, suggesting that histamine may play a role in the CNS in seizure

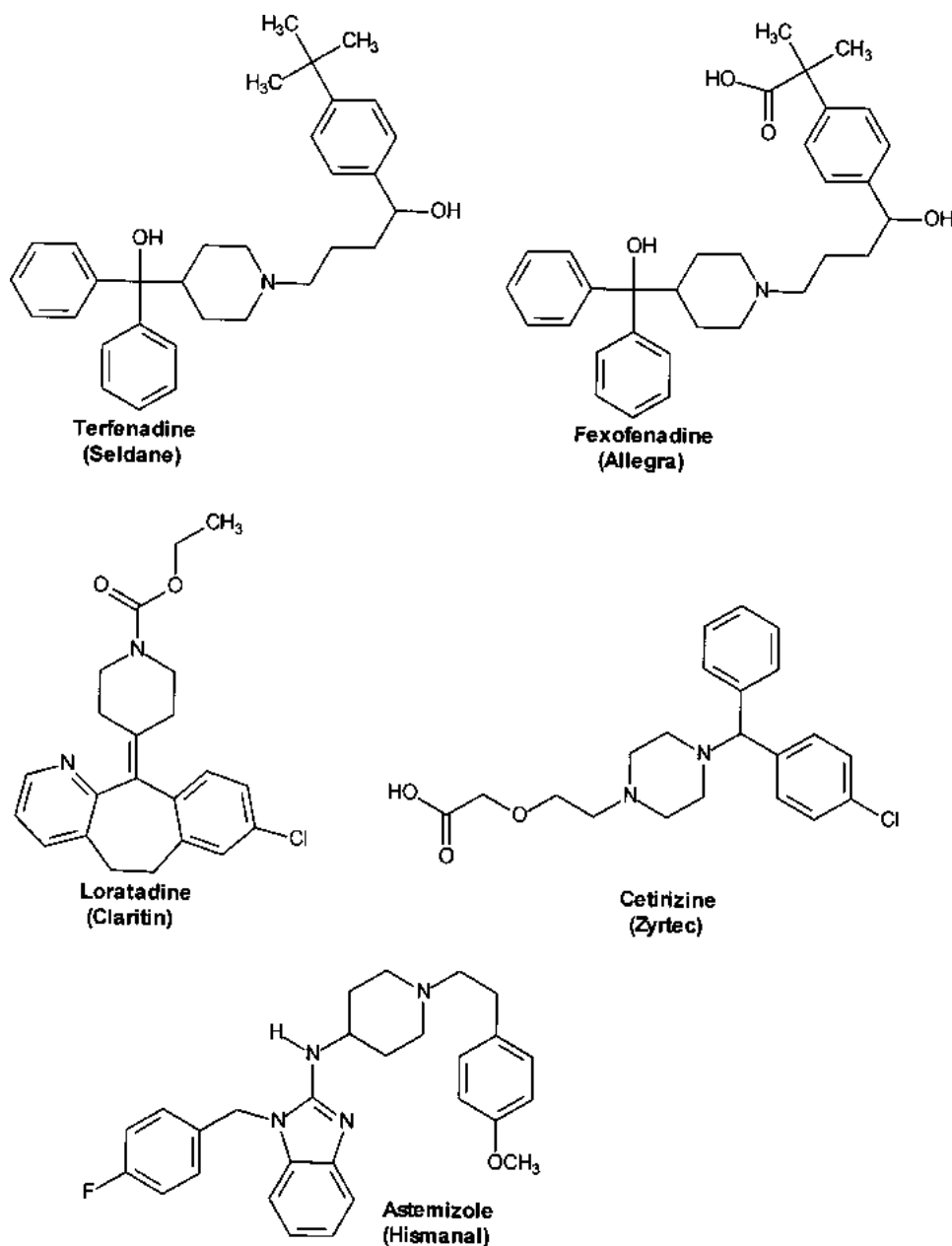


Fig. 2 Chemical structures of second-generation antihistamines (nonsedating)

prevention. Administration of H_1 antagonists lowers the seizure threshold, resulting in epileptic activity [12, 18–21]. The role of central H_2 receptors is not well known, but when animals are given large doses of H_2 blockers, seizures may occur [22]. The presynaptic H_3 receptor works as an autoreceptor regulating the release and

synthesis of histamine. Although experimental H_3 -receptor antagonists are being investigated as possible anticonvulsants [23], no clinically relevant agents currently are available.

In part as a result of the similarity in amino acid sequences between H_1 and muscarinic receptors [24], first-generation H_1 antagonists cause CNS

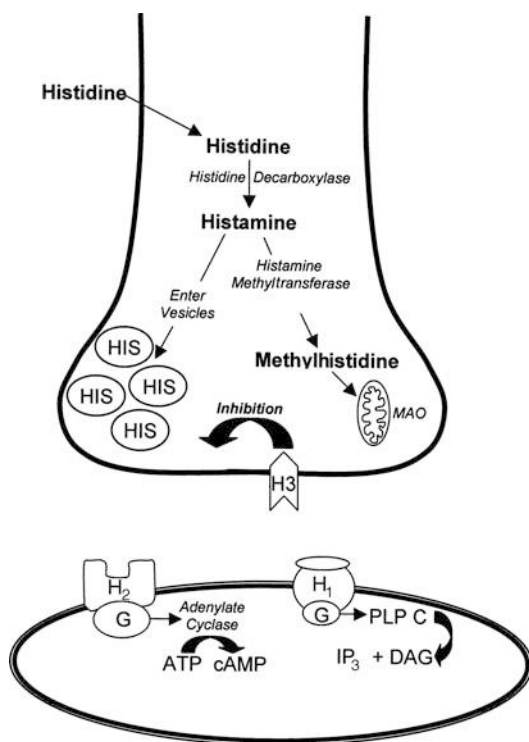


Fig. 3 Schematic model of a central histaminergic neuron. Histidine crosses the blood–brain barrier and, when inside neurons, is converted to histamine (*H*) via the enzyme histidine decarboxylase. *H* is transported into vesicles, where it is stored before release. Free *H* can be metabolized by histamine methyltransferase with methylhistamine and then metabolized further through the monoamine oxidase (*MAO*) system. *H* binding to *H*₁ receptors stimulates phospholipase C (*PLP C*) with the liberation of inositol triphosphate (*IP*₃) and diacylglycerol (*DAG*) as second messengers. *H* binding to *H*₂ receptors stimulates adenylate cyclase with the generation of cyclic adenosine monophosphate (*cAMP*) as a second messenger. *H* binding to *H*₃ autoreceptors results in feedback inhibition and decreases release of *H* and numerous other neurotransmitters. *ATP* adenosine triphosphate, *G* G protein

and peripheral nervous system anticholinergic effects. Some adverse effects of antihistamines are related to complications of overdosage (aspiration pneumonia, anoxia, and rhabdomyolysis) or are idiosyncratic (dystonia, thrombocytopenia, and leukopenia).

The cardiac effects of antihistamines include effects resulting from sodium channel blockade (e.g., ventricular dysrhythmias) and potassium efflux blockade (e.g., torsades de pointes). Serious cardiac effects of first-generation (sedating)

antihistamines generally are thought to be secondary to sodium channel blockade. Numerous reports of diphenhydramine toxicity have shown QRS widening and hypotension. Some of these patients showed resolution of these effects after receiving doses of physostigmine and sodium bicarbonate [25, 26], whereas others responded to sodium bicarbonate alone, supporting the theory that sodium channel blockade was a major factor. Wang and colleagues [27] studied the effects of “conventional” antihistamines on cardiac conduction and found that cardiac repolarization was slowed in the following order: clemastine, hydroxyzine > brompheniramine, chlorpheniramine, diphenhydramine > cyproheptadine, chlorcyclizine, promethazine. They also showed the dose-dependent ability of these drugs to prolong the QT interval. The authors suggested that large doses of these medications might have adverse effects on cardiac conduction. Zareba and associates [28] reviewed 12-lead electrocardiograms of 126 consecutive patients with diphenhydramine overdoses reported to regional poison centers. Of patients, 25% had heart rates greater than 120 beats/min, probably owing to the anticholinergic effects of diphenhydramine. QT_c prolongation was common, with 50% of the patients having a QT_c interval of greater than 450 ms and 11% greater than 500 ms. Only one patient presented with monomorphic ventricular tachycardia, and no patients had torsades de pointes.

Second-generation antihistamines, such as astemizole, terfenadine, and ebastine, seem to cause torsades de pointes by inhibiting potassium efflux from cells in the cardiac conduction system. The blockade of the “delayed rectifier” potassium current in late phase 2 and early phase 3 of the action potential seems to be responsible for prolongation of the QT interval and a contributor to the development of torsades de pointes (Fig. 4) [29].

Blockade of potassium channels leads to an increase in membrane potential (i.e., toward zero) and allows Purkinje fibers to “refire.” This event is termed an *afterdepolarization* because it must follow a normal cellular depolarization and cannot arise de novo. When an afterdepolarization occurs

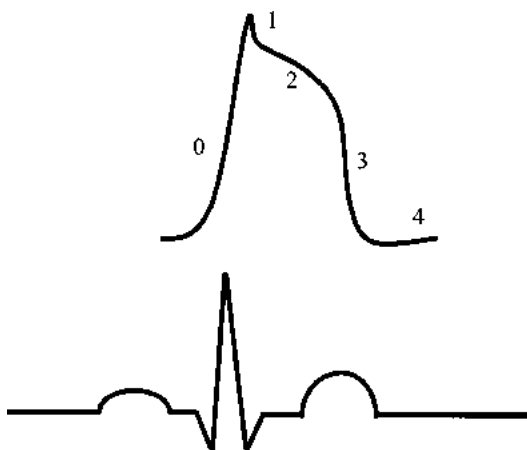


Fig. 4 The relationship between the action potential and the QRS. Although changes in sodium influx during phase 0 leads to QRS prolongation, blockade of potassium channels in phase 2 and phase 3 lengthens the QT interval

in late phase 2 or early phase 3, it is termed an *early afterdepolarization* (EAD). These early afterdepolarizations initiate “triggered” activity, such as torsades de pointes (Fig. 5) [30]. Terfenadine and astemizole have been removed from the market in most countries due to this effect. Fexofenadine, a metabolite of terfenadine without significant potassium channel-blocking properties, has largely replaced them.

Clinical Presentation and Life-Threatening Effects

Neurologic Effects

Diphenhydramine and the older first-generation H_1 -receptor antagonists commonly are used in over-the-counter sleep preparations, and one of the most common manifestations of H_1 -receptor antagonist overdose is sedation. At therapeutic doses, H_1 -receptor antagonists have been shown to decrease time to sleep, psychomotor function, and cognitive function [16, 31]. In a well-designed simulated driving performance test, drivers who ingested 50 mg of diphenhydramine performed similarly to, and in some scenarios worse than, drivers ingesting ethanol (blood ethanol concentration 0.1%) [32]. As a result of

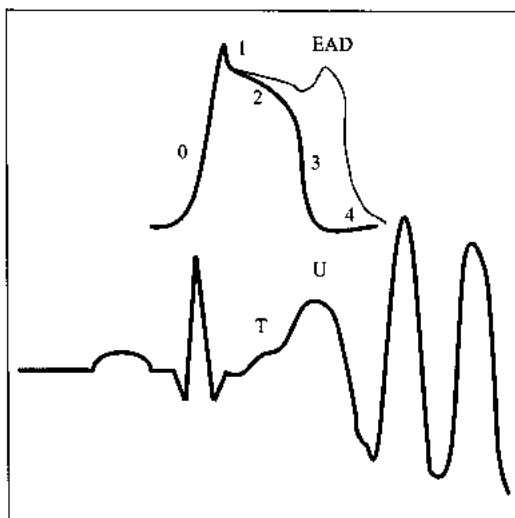


Fig. 5 The production of early afterdepolarization (EAD) and torsades de pointes. The retention of potassium ions within Purkinje cells leads to a refring of the cell and the production of an EAD. This can lead to the onset of torsades de pointes, which is heralded by a slowing of the rate and a prominent U wave. T T wave

diminished CNS penetration, second-generation H_1 antagonists have a lower incidence of sedation [31]. In overdose, patients can present with a spectrum of CNS depression ranging from mild sedation to coma.

Antihistamines’ association with seizures has been known since shortly after their initial clinical usage [33]. Focal and generalized seizures in overdoses, supratherapeutic doses, and therapeutic doses were reported [33–35]. In a 2-year retrospective poison center review of 191 cases of poisoning associated with seizure, Olson and colleagues [36] showed diphenhydramine to be the third leading cause. In fatal overdoses involving antihistamines, seizures often are premonitory to cardiac arrhythmias and death [37–39]. According to a study from the ToxIC database in 2013, over-the-counter anticholinergics/antihistamines were the second leading cause of drug-induced pediatric seizures [40]. All first-generation H_1 -receptor antagonists have the potential to cause anticholinergic syndrome. There are many examples in the literature of anticholinergic poisoning with peripheral nervous system signs (dry mouth, dry skin, decreased bowel sounds, urinary retention,

mydriasis, and tachycardia) and CNS anticholinergic signs (altered mental status, confusion, psychosis) in antihistamine overdoses. For further discussion on the presentation and treatment of anticholinergic poisonings, see ► Chap. 23, “Anticholinergic Syndrome.”

Diphenhydramine often is used as a first-line treatment for extrapyramidal effects secondary to dopamine antagonists. Its mechanism of reversal may occur through either its central antimuscarinic effects [41] or its ability to inhibit dopamine uptake in neuronal cells [42–44]. Despite this, antihistamines also have been reported to be a cause of extrapyramidal symptoms. Cases of orofacial dyskinesias, acute dystonia, torticollis, trismus, tremors, and incoordination have been reported in patients with acute and long-term usage of antihistamines in therapeutic doses and overdoses [45–54]. Patients who develop antihistamine-associated extrapyramidal effects should be treated with either benzodiazepines or benztropine, a relatively potent inhibitor of central dopamine uptake (see ► Chap. 44, “Antipsychotics”).

Cardiac Effects

Tachycardia due to anticholinergic effects is the most common cardiac presentation [55] and seldom requires treatment. Wide QRS and ventricular tachycardia have been reported and may be treated with sodium bicarbonate in a fashion similar to that caused by tricyclic antidepressants (LOE III) [56]. Prolonged QT_c and torsades de pointes also have been reported, especially with nonsedating agents, such as terfenadine and astemizole. Hypertension and hypotension have been documented [57].

Nonsedating second-generation H₁ antagonists were introduced in the 1980s. In 1986, Craft [58] reported torsades de pointes in a 16-year-old who ingested an overdose of astemizole. By 1990, reports of an association between second-generation antihistamines (terfenadine, ebastine, and astemizole and its metabolite desmethylassemizole) [59] and torsades de pointes began to appear in the medical literature [60, 61]. In 1988,

Snook and colleagues [62] reported torsades de pointes associated with astemizole use. Monahan and coworkers [63] reported 25 cases of terfenadine toxicity resulting in torsades de pointes. The cardiac effects of these drugs seem to be independent of their antihistaminic properties and better associated with substitutions at the nitrogen atom (see Fig. 2) [64].

Other Effects

Rhabdomyolysis in uncomplicated antihistamine overdose is a rare event without complicating factors. Diphenhydramine and doxylamine exposures have been the most commonly reported [65–70]. As with other serious intoxications, however, antihistamine overdose can result in rhabdomyolysis. Severe cases of rhabdomyolysis typically are associated with seizures and hyperthermia [71–73]. Other features of antihistamine overdose that may contribute to the development of rhabdomyolysis include prolonged periods of inactivity with the development of compartment syndromes and agitation in patients fighting against restraints. A thorough discussion of drug-induced rhabdomyolysis is provided in the chapter devoted to that topic.

Therapeutic use of H₂ antagonists has been associated idiosyncratically (i.e., in a non-dose-related fashion) with thrombocytopenia and granulocytopenia. Numerous case reports have been published of thrombocytopenia isolated [74–86] or in combination with anemia or leukopenia or both [87–94]. The data behind most of these case reports are confounded by complicating factors and other medications not taken into account. In a systematic review of published case reports of drug-induced thrombocytopenia, only cimetidine had data considered level I evidence (definite), and ranitidine had level II evidence (probable) [95]. The cause of thrombocytopenia with H₂ antagonists generally is thought to be immune mediated with the development of IgE [75, 95, 96] or IgG and IgM antibodies [75, 76, 84] against an H₂ antagonist–platelet complex. Although some authors have suggested cross-reactivity between different H₂ antagonists [76,

96], others have shown no recurrence of thrombocytopenia when a different H₂ antagonist was used [83, 97]. Similarly, numerous case reports of granulocytopenia have been associated with therapeutic administration of cimetidine [87–91, 94, 98–101] and famotidine [92]. In most of these cases, patients either were critically ill or were using other medications with suspected bone marrow toxicity. The causes of leukopenia have been thought to be either H₂ blockade on bone marrow cells [102] or peripheral destruction of leukocytes secondary to antibodies to cimetidine [91].

Diagnosis

There are no specific laboratory or physical examination findings that indicate a diagnosis of antihistamine poisoning. Rather, a combination of CNS depression, anticholinergic findings, and electrocardiogram findings would put antihistamines on the list of differential diagnoses. Anticholinergic findings typically predominate. More important is the ability of the critical care physician or medical toxicologist to recognize and treat the features of antihistamine overdoses that are potentially life-threatening, including a loss of airway protection, widened QRS, ventricular tachycardia, prolonged QT_c, torsades de pointes, rhabdomyolysis, or seizures. Interestingly, urine drug screen testing using immunoassay kits has been reported to give false-positive methadone and phencyclidine (PCP) tests with doxylamine toxicity [103]. In addition, diphenhydramine has been reported to cause false-positive results for PCP, methadone, and tricyclic antidepressants [104–107]. Brompheniramine and ranitidine have been shown to result in false-positives for amphetamines [104].

Treatment

Treatment of antihistamine poisoning focuses on the prevention and treatment of life-threatening complications. Although antihistamines are effectively bound to charcoal, there are no specific decontamination recommendations for

antihistamines because none have been validated empirically. A further discussion of the issue of activated charcoal can be found ► [Chap. 10, “The Critically Poisoned Worker.”](#)

Secondary to the relatively high volume of distribution and protein binding of most antihistamines, extracorporeal removal is not effective in antihistamine poisoning. However, the use of hemodialysis has been reported for diphenhydramine toxicity in a child with wide complex tachycardia and persistent seizures who ultimately survived without sequelae [108]. Given that hemodialysis is unlikely to remove pharmacologically significant quantities of diphenhydramine, it is unlikely that this intervention contributed to the child’s recovery.

The management of CNS sedation with H₁-receptor antagonists rests largely on supportive care, including airway management if indicated clinically. The anticholinergic effects of antihistamines can be reversed with physostigmine (LOE II-3) [109, 110]. Because of the remote risk of seizures and arrhythmias, the empirical use of physostigmine should be reserved for patients with major anticholinergic manifestations (see ► [Chaps. 23, “Anticholinergic Syndrome,”](#) and ► [161, “Physostigmine”](#)) [111–113]. It should be recognized that physostigmine is contraindicated in the presence of seizures and/or ventricular tachycardia. It should be used with caution in patients with significant QRS prolongation. Use of dexmedetomidine as an adjunctive therapy for anticholinergic toxidrome from diphenhydramine has been recently described. The authors suggest that adding this agent may help relieve symptoms of agitation, psychosis, and tachycardia, while decreasing the risk of respiratory depression that can develop with high-dose benzodiazepines (LOE III) [114].

Benzodiazepines (e.g., diazepam and lorazepam) should be considered the first-line treatment for seizures associated with antihistamine overdosage (LOE III), followed by barbiturates (e.g., phenobarbital and pentobarbital) (LOE III) or propofol (LOE III) (see ► [Chap. 20, “Toxicant-Induced Seizures”](#) for a more detailed account of seizure management. Phenytoin is not recommended in most cases of toxin-induced

Table 2 Level of evidence regarding indications for ICU admission in antihistamine poisoning

	Evidence level
Central nervous system depression or coma	III
Seizures	III
Anticholinergic delirium	III
New-onset QRS widening beyond 110 ms	III
New-onset QT _c interval prolongation	III
Ventricular tachycardia	III
Hypotension	III
Airway compromise, hypoventilation	III

seizures because numerous animal studies have suggested that it is inferior to benzodiazepines or barbiturates and, in some overdoses, may lower the seizure threshold [115].

Indications for ICU Admission in Antihistamine Toxicity

See Table 2.

Tachycardia associated with anticholinergic effects seldom requires treatment. Prolonged QRS or ventricular tachycardia may respond to boluses of sodium bicarbonate (LOE III) [56]. Bicarbonate dosing is variable, typically with a starting point of 1–2 mEq/kg. Sodium bicarbonate infusions of 100–150 mL in 1000 mL of 5% dextrose in water (with potassium chloride added) often have been used after conversion of ventricular tachycardia, although the scientific basis for this practice is marginal (see ► Chap. 39, “Sodium Channel-Blocking Antidysrhythmics”). Lidocaine is a second-line drug for ventricular tachycardia (LOE III), and magnesium sulfate has also been used successfully (LOE I) [15, 116, 117]. The role of amiodarone is less clear, and concerns of the development of torsades de pointes have been raised [118] because of its tendency to prolong the QT_c. However, amiodarone-induced torsade is rare. Recently, intravenous lipid emulsion (ILE) therapy has also been reported as a possible

treatment option in cases of diphenhydramine-induced ventricular tachycardia not responding to treatment with sodium bicarbonate (LOE III) [119–121]. However, certain potential complications must be kept in mind concerning ILE therapy including laboratory interference, pancreatitis, and possibly acute respiratory distress syndrome [122]. The clinical pharmacology of intravenous lipid emulsion therapy is discussed in the chapter devoted to it in the “Antidotes” section. Intravenous magnesium sulfate may be effective in the treatment of torsades de pointes (LOE III). Although there are no clear guidelines for magnesium sulfate dosage, adults may be treated with 2 g (16 mEq) mixed in 50–100 mL of 5% dextrose in water intravenously over 5 min (faster if the patient is unstable) and repeated if no improvement is noted; infusion of 3–50 mg/min also may be administered. Other treatment modalities for torsades de pointes include intravenous administration of isoproterenol and use of electrical cardiac pacing (LOE III). Both modalities have had some success in torsades de pointes treatment. Isoproterenol (LOE III) may be used in patients who are bradycardic [123, 124] but should be avoided in patients with poor left ventricular function or severe coronary artery disease. Other drugs that have been used include verapamil [125, 126] and drugs that facilitate potassium channel opening, such as pinacidil [127, 128]; however, their roles in treatment remain to be determined. Further detail can be found in ► Chap. 21, “Cardiac Conduction and Rate Disturbances.” Finally, if readily available therapeutic interventions fail to terminate life-threatening dysrhythmias, extracorporeal membrane oxygenation should be considered [129, 130] (LOE II-3).

Special Populations

Pediatric Patients

In one reported case series of antihistamine poisonings, it was suggested that children are more prone to seizures than adults [34]. This association has not been validated prospectively. Antihistamines are used widely in children and carry risks

similar to those in adults. Patients with long QT syndrome due to congenital alteration in cardiac ion channels (Jervell and Lange-Nielsen and Romano-Ward syndromes) may be at increased risk for drug-induced torsades de pointes.

Female Patients

Women seem to be at a greater risk of developing torsades de pointes because of genetic differences in the number of potassium channels [131]. In a review of 332 cases of torsades de pointes, Makkar and associates [132] found a female predominance among all of the drug-induced cases except procainamide.

Elderly Patients

Elderly patients may be more prone to develop altered mental status in association with H₁- and H₂-receptor antagonists. A prospective cohort study showed that patients older than 70 years of age who received a dose of antihistamines during hospitalization had a relative risk of 1.7 for delirium [133]. Other articles have suggested a similar trend with H₂ antagonists in the elderly, particularly if concomitant renal impairment is present [134].

Patients Taking Other Medications

As a result of its ability to inhibit cytochromes 1A2, 2C18, 2D6, and 3A4, cimetidine can increase serum concentrations of numerous drugs, including theophylline, opioids, antihypertensives, antibiotics, and antidepressants. H₂ antagonists can reduce the bioavailability and effectiveness of the antifungal medications ketoconazole and itraconazole because these medications require an acidic medium in the gut for absorption.

Coingestion of cytochrome 3A4 inhibitors, such as ketoconazole, itraconazole, cyclosporine, erythromycin, nifedipine, verapamil, and grapefruit juice, may lead to a buildup of the cardiotoxic

second-generation antihistamine (i.e., terfenadine and astemizole) parent compounds, which can induce torsades de pointes. Terfenadine and astemizole have been removed from the market in many countries.

Pregnant Patients

US Food and Drug Administration safety ratings for use in pregnancy vary with specific agents, but antihistamines often are rated category C (risks in animal but not in human studies; benefits may outweigh risks). In a meta-analysis of 24 articles involving 200,000 enrolled participants, Seto and colleagues [135] concluded: "H₁ blockers used mainly for morning sickness during the first trimester do not increase the teratogenic risk in humans and may, in fact, be associated with a protective effect."

Key Points

1. Must recognize and treat the potentially life-threatening complications of antihistamine overdoses, including loss of airway protection, widened QRS, ventricular tachycardia, prolonged QT_c, torsades de pointes, rhabdomyolysis, and seizures.
2. Common cause of drug-induced pediatric seizures, second only to antidepressants.
3. Although a common presentation, sinus tachycardia seldom requires treatment.
4. Benzodiazepines should be considered the first-line treatment for seizures.

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Ann-Jeannette Geib

This chapter is dedicated to the memory of Michael W. Shannon.

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Key Points in the Evaluation and Management of Methylxanthine Poisoning

1. In acute intoxication, serum concentration is the most important prognostic indicator of life-threatening events.
2. In chronic intoxication, age is the most important prognostic indicator of life-threatening events.
3. Extracorporeal drug removal should be considered in any patient who is at high risk for a life-threatening event. When a life-threatening event occurs, there may be significant morbidity and mortality despite extracorporeal drug removal.

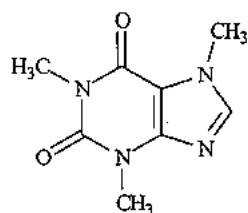
The methylxanthines are a group of pharmaceuticals that antagonize adenosine receptors in the central nervous system and peripheral tissues. Pharmaceutically active methylxanthines include caffeine, theophylline, and pentoxifylline. A fourth methylxanthine, theobromine, is present in cocoa products, but is not used as a pharmaceutical, and has toxicological importance in nonhuman animal species. Severe intoxication with methylxanthines may result in life-threatening arrhythmias and seizures and has a historic mortality of up to 10% [1–4].

Differential substitution on the core xanthine structure confers varying properties and organ effects on the methylxanthines (Fig. 1). For example, the presence of a methyl group at the three

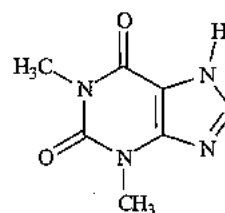
Holly Perry and Michael W. Shannon contributed to the previous edition of this chapter.

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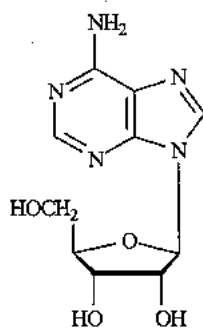
Fig. 1 Chemical structures of selected xanthines



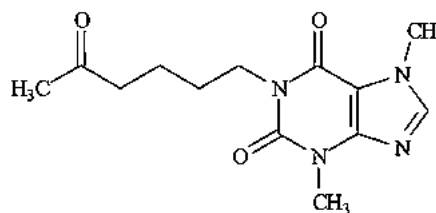
Caffeine



Theophylline



Adenosine



Pentoxifylline

position of theophylline confers its bronchodilatory properties and is preferentially used in bronchospastic diseases.

Theophylline is used for its bronchodilator properties in chronic obstructive pulmonary disease and asthma and in neonates for apnea and bradycardia of prematurity. It is used less frequently today because new pharmacologic agents have been introduced to treat these diseases and because of concerns about its narrow therapeutic index. Oral forms of theophylline are available as either immediate-release or sustained-release preparations. Sustained-release preparations have been prescribed more frequently. Theophylline is absorbed completely after oral therapeutic doses. Theophylline intoxications have been classified as acute intentional, chronic unintentional intoxication, and acute on chronic intentional. Aminophylline is an ethylenediamine salt of theophylline that has greater water solubility and is used intravenously for the same indications. It may be used off-label as a reversal agent for pharmacologic cardiac stress testing.

Caffeine is the most commonly used psychoactive substance worldwide [5] and is contained

in beverages such as coffee, tea, cola drinks, and energy drinks. As a pharmaceutical, caffeine is used in combination with headache remedies (e.g., acetaminophen/aspirin/caffeine/+/–diphenhydramine, butalbital/acetaminophen/caffeine, butalbital/aspirin/caffeine) and for apnea of prematurity and post-lumbar puncture headache treatment. Caffeine is also found in dietary supplements, where its “thermogenic” properties are marketed for weight loss purposes. Natural sources of caffeine include coffee beans, *Camilla sinensis* leaves (tea leaves), kola nut, and guarana seeds. Patients have presented with caffeine toxicity and atrial fibrillation after consumption of guarana extract [6]. Excessive caffeine consumption may contribute to, trigger, or exacerbate psychiatric disorders such as psychosis or mania [7]. Caffeine toxicity has been reported after mesotherapy subcutaneous injections [8]. Acute caffeine intoxication has pathophysiology, symptoms, and management similar to those of theophylline intoxication.

Recently, major clinical effects and fatalities have been reported from the use of caffeine-containing energy drinks when taken by small

children or in large quantities. In a study of approximately 3200 energy drink-related exposures reported to US poison centers over 1 year, approximately half involved children under the age of 6. Energy drinks containing ethanol were associated with a higher rate of major adverse effects, such as seizures, dysrhythmias, and tachypnea [9]. Combining ethanol with caffeine-containing energy drinks appears to be associated with decreased performance on some psychometric testing parameters, and subjects reported feeling less clear-headed and clumsier on subjective symptom assessment [10]. Caffeine was deemed an “unsafe food additive” to ethanol containing malt beverages, and in 2010 the US Food and Drug Administration issued warning letters to manufacturers of these beverages to cease marketing and distribution of such beverages. Ethanol has been banned from commercially available energy drinks marketed in the USA [11].

Severe toxicity and even fatalities have also been reported from the use of anhydrous caffeine powders that are commonly purchased on the Internet [12–14]. Caffeine may also be found as an undeclared ingredient in packages of novel psychoactive compounds and “club drugs” and may confound or contribute to the toxicity of these compounds [15–17]. Restrictions in the quantities of caffeine sold over the counter may reduce some morbidity and mortality [18]. Coffee enemas are sometimes touted as alternative cancer treatments and for relief of constipation. While caffeine toxicity has not been reported from rectal coffee instillation, thermal and chemical injury to the rectal and colonic mucosa has been [19–23].

Pentoxifylline is a xanthine derivative with hemorrheologic properties. By decreasing blood viscosity and erythrocyte deformability, it increases blood flow and tissue oxygenation. Its exact mechanism remains unknown [9]. It is used in the treatment of peripheral vascular and cerebrovascular disease to improve blood flow to ischemic areas [24]. Studies have found decreased blood viscosity due to decreased plasma fibrinogen and increased flexibility of erythrocytes, not due to vasoactive or cardioactive properties [25, 26].

Biochemistry and Pharmacology

Theophylline, caffeine, and pentoxifylline are all xanthine derivatives. Their structures closely resemble that of purines, such as adenosine (Fig. 1).

Theophylline is absorbed completely after oral therapeutic doses. For each 1 mg/kg ingested, a peak serum concentration of 2 µg/mL is expected to result. In therapeutic use, peak serum concentrations occur 1–2 h after ingestion of an immediate-release formulation and 6–8 h after ingestion of a sustained-release preparation. In overdose, sustained-release tablets may have prolonged and erratic absorption, possibly because of bezoar formation [27, 28]. Peak levels may be delayed for 24 h [29] and may continue to rise despite repeated doses of activated charcoal [30]. One case of fatal intoxication has been associated with rectal instillation of theophylline-containing tablets [31].

Theophylline has a relatively small volume of distribution (0.4 L/kg), although it tends to be larger at extremes of age (0.64 L/kg) in premature neonates [32]. It is distributed rapidly to all tissues [33]. It is metabolized by cytochrome P-450 isoenzymes 1A2, 2E1, and 3A4. Demethylation products include 1-methylxanthine and 3-methylxanthine; these metabolites are converted to 1-methyluric acid (1-MU) and 3-methyluric acid (3-MU) via xanthine dehydrogenase (Fig. 2) [34, 35].

Across the therapeutic range, theophylline elimination follows Michaelis-Menten kinetics; first-order kinetics changes to zero-order elimination as higher serum theophylline concentrations are attained. In an acute overdose, elimination can be expected to initially follow zero-order kinetics [29].

Patients taking theophylline therapeutically are at risk for developing theophylline toxicity for two reasons. First, because theophylline elimination follows Michaelis-Menten (i.e., saturable) kinetics, a small increase in dose (e.g., when a patient takes doses additional to those prescribed) may result in a disproportionately large increase in serum concentrations. Second, the rate of

[42]. Theophylline metabolism may be impaired by chronic use of St John's wort [43]. Theophylline concentrations may increase after influenza vaccination, an interaction thought to be mediated by interferon-gamma effects on CYP 2E1 activity [44]. Theophylline clearance is increased in the third trimester of pregnancy and up to 13 weeks postpartum [45]. Theophylline may increase concentrations of some drugs, such as tacrolimus [46].

Caffeine is demethylated at any of its three positions by CYP 1A2 to either theobromine, paraxanthine, or theophylline. There are minor contributions to caffeine metabolism by CYP 2A6, 2C9, 2E1, 2C8, and 3A4; xanthine dehydrogenase; and *n*-acetyltransferase (Fig. 3) [47]. Animal studies indicate increased hyperthermia, tachycardia, and seizures when MDMA or MDA are co-administered with caffeine [48]. Animal pharmacokinetic models demonstrate decreased conversion of MDMA to MDA, a CYP 1A2-mediated process, in the presence of caffeine [48]. However, one human volunteer study of MDMA users shows increased CYP 1A2 activity in the presence of caffeine [49]. Due to these conflicting results, it is thought that the increased toxicity of MDMA when combined with caffeine is likely due to a complex pharmacodynamic interaction [48].

Pentoxifylline is nearly completely absorbed after oral ingestion. It undergoes extensive first-pass metabolism to 1-[5-hydroxyhexyl]-3,7-dimethylxanthine and 1-[3-carboxypropyl]-3,7-dimethylxanthine. The half-life of pentoxifylline is 0.4–0.8 h and that of its metabolites is 1–1.6 h. Urinary excretion of pentoxifylline metabolites consists almost exclusively of 1-[3-carboxypropyl]-3,7-dimethylxanthine [24]. Increased bleeding has been reported in some patients taking pentoxifylline with and without anticoagulants such as warfarin and antiplatelet medications [24]. Drug-induced hepatitis has been reported in association with pentoxifylline. In one case biopsy demonstrated centrilobular cholestasis [50, 51].

Table 1 compares the structures, pharmacokinetics, and pharmacodynamics properties of methylxanthines. Caffeine is metabolized predominantly by CYP 1A2 and 2E1. Theophylline

is metabolized by CYP 1A2, 2E1, and 3A3. In adults, theophylline has a longer half-life than caffeine.

Pathophysiology of Toxic Effects

Therapeutic effects are mediated primarily through activity at adenosine and adrenergic receptors. Theophylline is a potent adenosine antagonist. Its beneficial effect is due primarily to antagonism of adenosine A₁ receptors in the lungs, which produce bronchodilation. Adenosine antagonism is also a major factor in producing toxicity. In the central nervous system, antagonism of A₁ receptors can result in sustained, unmodulated discharge of neurotransmitters – including glutamate, a major excitatory neurotransmitter – resulting in seizure activity. In the heart, A₁ receptor antagonism leads to an increase in the rate of discharge of cardiac pacemaker cells and increased arrhythmogenesis. Antagonism of A₂ receptors, present throughout the vascular system, results in vasoconstriction [52]. Vasoconstrictive effects have been shown to be important in the central nervous system [53] and are presumed to be important in the myocardium as well [54].

Methylxanthines exert their effects as antagonists of adenosine at adenosine receptors. Adenosine (Fig. 4) is a product of purine biosynthesis that is omnipresent in the human body and acts on any of four G protein-linked receptors: A₁, A_{2A}, A_{2B}, and A₃ (Table 2). In the central nervous system, adenosine serves as a neuromodulator [55] and has anticonvulsant properties [56]. In the heart, adenosine lowers the heart rate and atrioventricular nodal conduction and promotes microcirculatory vasodilatation. Adenosine agonists are used for pharmacologic cardiac stress testing. In the renal circulation, adenosine causes vasoconstriction. Effects of stimulating the adenosine receptor subtypes are listed in Table 2 [57, 58]. Therefore, expected clinical effects of methylxanthines are opposite those of adenosine.

Adenosine receptors A₁ and A₃ are coupled to Gi proteins and A₂ to Gs proteins. Therefore, A₁ and A₃ stimulations lead to inhibition of adenylate cyclase (AC), whose end product is

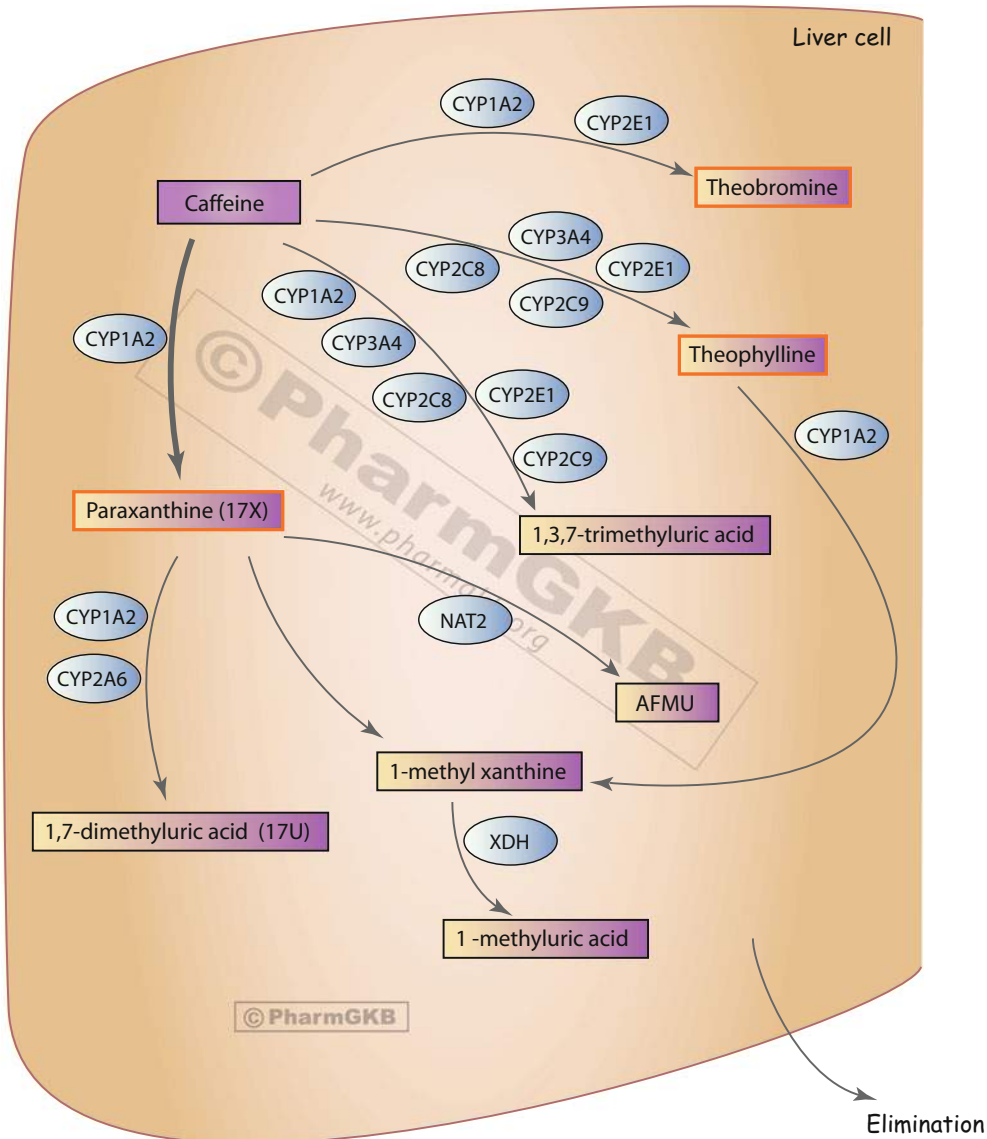


Fig. 3 Stylized liver cell showing pathways involved in the metabolism of caffeine (From: Thorn Caroline F, Aklilu Eleni, McDonagh Ellen M, Klein Teri E, Altman Russ B. “PharmGKB summary: caffeine pathway”

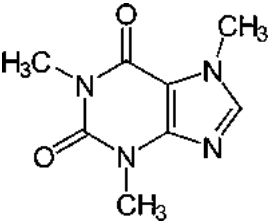
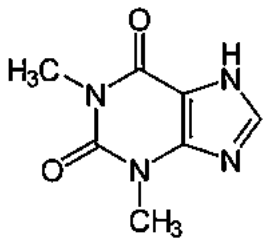
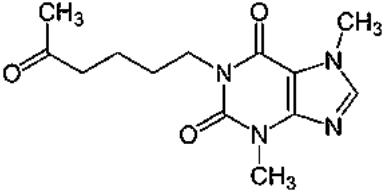
Pharmacogenetics and genomics (2012). In <https://www.pharmgkb.org/pathway/PA165884757>. Copyright PharmGKB and Stanford University, 2012. Used with permission)

cyclic AMP. When A1 and A3 receptors are antagonized, then adenylate cyclase activity would be expected to increase. A2 receptors, when stimulated, increase AC activity, so antagonism would be expected to decrease this activity. Downstream targets of cyclic AMP signaling include protein kinase A, inositol triphosphate, and protein kinase C. These enzymes are the

same as those downstream from beta-adrenergic receptors (Fig. 3) [59]. Therefore, the net result of antagonism by methylxanthines resembles beta-adrenergic stimulation.

In addition to being a potent adenosine antagonist, methylxanthines have powerful indirect adrenergic activity. Theophylline intoxication has been shown to produce increased

Table 1 Structures and pharmacokinetic data of the methylxanthines

Substance	Half-life (T 1/2)	Volume of distribution (Vd)	Metabolism	Protein binding	Clearance
 Caffeine (1,3,7-trimethylxanthine) [http://commons.wikimedia.org/wiki/File:Koffein_-_Caffeine.svg]	4.1 +/- 1.3 h (Lelo et al.) Preterm 52 h Neonates 20 h Adults 5 h	0.5–0.8 L/kg (Magkos & Kavouras) 0.61 L/kg (0.4–0.8 L/kg)	CYP 1A2 CYP 2E1 (M & K)	35% (Blanchard)	2.07 +/- 0.96 ml/ min/kg (Lelo et al.)
 Theophylline (1,3-dimethylxanthine) [http://eternawiki.org/wiki/index.php5/Theophylline]	6.2 +/- 1.4 h (Lelo et al.) Neonates 25 h Adults 8 h Adult >60 10 h [173]	0.44 +/- 0.8 L/kg (Lelo)	CYP 1A1 CYP 2E1 CYP 3A3 13.7–16.8% excreted unchanged [172] Children: Hepatic 50% Renal 50% Adults: Hepatic 90% Renal 10% (Hendeles 1995)	53–65% [171] ?40–65%	0.93 +/- 0.22 ml/ min/kg (Lelo et al.)
 Pentoxifylline [http://commons.wikimedia.org/wiki/File:%3APentoxifylline_Structure_V.1.svg]	0.4–0.8 h (Trental PI)	2.4 L/kg (Eden)	Hepatic (Trental PI)	Not protein bound (Eden)	0.15 +/- 0.06 L/ min/kg [174]

plasma catecholamines (epinephrine and norepinephrine) in animal models [60, 61] and in case series of human victims of theophylline intoxication [62, 63]. The magnitude of catecholamine elevation and the specific catecholamine released seem to vary depending on the type of intoxication. Acute intoxication has been shown to be associated with epinephrine concentrations elevated fourfold to eightfold greater than controls and norepinephrine levels fourfold to tenfold normal [62, 63]. In a few patients with chronic overdose who have been

studied, norepinephrine and dopamine levels were elevated compared with normal controls and patients with an acute theophylline overdose [62].

Theophylline and caffeine are phosphodiesterase inhibitors at toxic concentrations. Inhibition of phosphodiesterase results in increased levels of cyclic adenosine monophosphate and augmentation of adrenergic effects. Alterations in intracellular calcium transport have also been postulated to be important in theophylline and caffeine toxicity, although this has not been well studied [64].

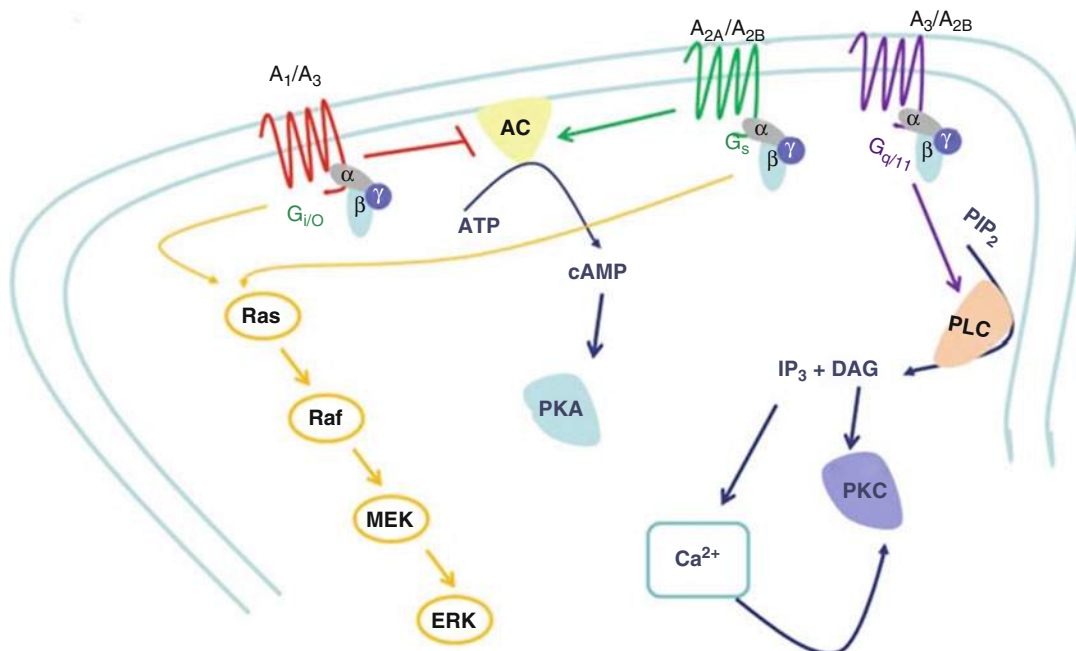


Fig. 4 Schematic representation of the different signaling pathways associated with adenosine receptors. Adenosine receptors are GPCRs. A1R and A3R couple to Gi/o, inhibiting AC, which will reduce cAMP levels and consequently decrease PKA activity. A2AR and A2BR are coupled to Gs, promoting AC activity and consequently PKA activity. A3R and A2BR can also couple to Gq/11, enhancing PLC activity. PLC catalyzes PIP2 into DAG and

IP3. DAG will directly activate PKC, while IP3 will increase intracellular Ca^{2+} levels. Furthermore, all adenosine receptors can activate the MAPK pathway (From Sebastiao A, Cristovao-Ferreira S, and Ribiero J. Downstream Pathways of Adenosine. In: Adenosine: A Key Link Between Metabolism and Brain Activity. Masino S and Boison D, Eds; Springer Science & Business Media, 2012 used with permission)

Clinical Presentation and Life-Threatening Complications

Organ System Effects

Methylxanthine toxicity primarily affects the gastrointestinal, cardiovascular, and central nervous systems. Characteristic metabolic disturbances, including hypokalemia and hyperglycemia, are noted frequently. Severe lactic acidosis and rhabdomyolysis have been reported. Here, theophylline is discussed as the prototypical methylxanthine.

Gastrointestinal Manifestations

Nausea and vomiting are the predominant gastrointestinal system manifestations. Vomiting is an almost universal feature of severe, acute

intoxication; it is less common after chronic intoxication [1–3, 65]. Vomiting results from gastric acid hyperstimulation [66] and central stimulation of the chemoreceptor trigger zone. Vomiting may be difficult to control and may make it impossible for the patient to tolerate activated charcoal, a potentially important therapeutic intervention [65, 67]. Hematemesis may occur as a consequence of a Mallory-Weiss tear [2, 67]. One case of pancreatitis related to a critically ill patient with theophylline toxicity has been reported [68].

Cardiovascular Manifestations

Theophylline predisposes to arrhythmias by reducing the ventricular fibrillation threshold and by nonuniformly increasing cardiac conduction, favoring reentrant arrhythmias [69]. It predisposes the heart to develop arrhythmias even at

Table 2 Functions and targets of adenosine receptors

Receptor	Second messenger	Target organs	Agonism	Antagonism
A1	Gi	Kidney	Increased proximal tubular Na transport	Diuresis
		Adipocytes	Antilipolysis	Lipolysis
		Neurons	Limit excitatory neurotransmission	Excitation; seizures
		Cardiac	Atrioventricular blockade; decreased chronotropy and dromotropy	Increased inotropy/chronotropy
A2A	Gs	Neurons	Increased pain	Alertness
		Cardiac	Coronary vasodilation	Coronary vasoconstriction
		Vascular	Splanchnic vasoconstriction	Splanchnic vasodilation
A2B	Gs	Vascular endothelium; mast cells	Increased permeability; degranulation; bronchoconstriction	Bronchodilation
A3	Gi	Widespread	Inhibits action of pro-inflammatory cytokines; modulates NF- κ B and Wnt pathways; inhibits expression of PKB, IKK, NF- κ B, and TNF α Anti-ischemic effect on cardiac and skeletal muscle Antinociception	

therapeutic serum concentrations [70]. At toxic serum concentrations, tachyarrhythmias and hypotension are common findings [1, 3, 30]. Any type of atrial (e.g., multifocal atrial tachycardia) or ventricular tachyarrhythmias may be seen after theophylline intoxication. Death frequently results from an intractable ventricular arrhythmia [1, 3, 30]. Other factors potentially contributing to arrhythmias include coronary ischemia due to A₂ receptor antagonism, increases in circulating catecholamines, hypokalemia, and acidosis [54, 70].

The hypotension associated with theophylline intoxication is multifactorial. Vasodilatation [71, 72] is likely to be in part due to theophylline-stimulated catecholamine release and beta₂-adrenoceptor stimulation [60, 73–75]. In addition, tachyarrhythmias result in reduced filling time and decrease cardiac output; hypovolemia secondary to gastrointestinal losses and theophylline-induced diuresis also contribute to hypotension.

Central Nervous System Manifestations

Central nervous system manifestations of theophylline toxicity include agitation, tremor, and

seizures. Seizures may occur without warning, particularly in those with chronic theophylline intoxication [1]; these may be either focal or generalized. Some [76, 77], but not all [1], studies have found seizures to occur more frequently in patients with underlying neurologic disorders, such as cerebrovascular accident or seizure disorder. When seizures begin, they are frequently difficult to control [78]. Nonconvulsive status epilepticus has been reported [79].

Theophylline-induced seizures have a high morbidity and mortality. In most studies, mortality has been reported to be 10%, although 50% mortality has been reported [2]. Higher mortality and morbidity are associated with prolonged seizures [80]. In a study of children with status epilepticus from diverse causes, there was a 50% morbidity and mortality in children with status epilepticus associated with supratherapeutic theophylline concentrations compared with a 23% rate in children with status epilepticus from other causes [81]. Theophylline-induced seizures may be associated with poor neurologic outcome ranging from profound memory deficit to persistent vegetative state. Selective bilateral hippocampal lesions have been

reported after theophylline-related status epilepticus [82]. Morbidity, such as arrhythmia, has been reported even when status epilepticus has not occurred [80, 83, 84].

Metabolic Manifestations

Theophylline toxicity also is associated with hypokalemia, hyperglycemia, mild hypomagnesemia [85], and metabolic acidosis. Hypokalemia and hyperglycemia are more common in acute than in chronic intoxication [1, 2, 62, 86] and may be helpful in determining the type of intoxication if not clear by history. While not demonstrated in formal studies, it seems to reason that electrolyte abnormalities may contribute in some part to the arrhythmias and cardiac irritability seen in methylxanthine toxicity. Generally, hypokalemia is thought to be from intracellular shifting of potassium [87]. Significant alterations in pH are uncommon, although severe lactic acidosis has been reported with pH as low as 6.63 [88]. Hyperlactemia has been reported with therapeutic use of theophylline with salbutamol in an asthma exacerbation [89]. Similarly, caffeine intoxication has been associated with hyperlactemia [90]. Rhabdomyolysis and compartment syndrome have been reported after acute theophylline and caffeine intoxication [1, 2, 38, 91–93]. Caffeine poisoning has also been associated with hyponatremia [92] and acute renal failure [92, 93].

Drug Concentrations: Therapeutic and Toxic Drug Monitoring

In acute intoxication, serum theophylline concentrations correlate with the risk for major complications, although no serum concentration has been shown to have an acceptable degree of predictive sensitivity and specificity. In a series of 98 patients who were reported to a regional poison center, a serum theophylline concentration of 60 µg/mL (333 µmol/L) had a sensitivity of 90% and a specificity of 75% for identifying patients who developed major toxicity. In contrast, a serum theophylline concentration of 80 µg/mL (444 µmol/L) had a specificity of 97% but a sensitivity of only 67% [94]. Similarly, Paloucek and Rodvold [1], in a review of cases of theophylline intoxication published between 1975 and 1985,

found that seizures occurred only when the serum concentration was greater than 50–60 µg/mL (278–333 µmol/L) [1]. In a series of 14 patients who presented to an emergency department after acute ingestion, life-threatening effects (LTEs) were seen only in patients with serum concentrations greater than 80 µg/mL (444 µmol/L) [2]. A serum theophylline concentration of 43 µg/mL (239 µmol/L) has been reported with seizures after acute overdose, however [30].

For patients with chronic intoxication, age rather than serum theophylline concentration is the most important prognostic factor. In a prospective poison center-based study of 92 patients with chronic intoxication, patients older than age 60 had a 50% probability (confidence interval 38–63%) of developing LTE. Using the criterion of age greater than 60 for predicting major toxicity had a sensitivity of 80% and specificity of 62% [94]. Other case series support the correlation of advanced age with occurrence of LTE [1, 2, 80, 81]. In the only study of children, LTEs were associated with younger age, with infants younger than 1 year being at greatest risk [86]. Serum theophylline concentrations have poor predictive value in chronic intoxication. In the only study designed to study risk factors systematically, there was no correlation between serum concentration and occurrence of LTE [94]. There are reports of LTE occurring with serum concentrations in the therapeutic range of 10–20 µg/mL (56–111 µmol/L) [1, 95]. Most case series have not reported LTE, however, unless the serum theophylline concentration is greater than 30 µg/mL (167 µmol/L) [2, 3, 86, 96].

In summary, while serum concentrations generally are predictive of LTEs, they may not correlate exactly, and a patient with a severe clinical presentation must be considered to have a serious poisoning, even with a therapeutic or moderately elevated serum concentration.

Treatment

There are four components of treatment for xanthine poisoning: (1) supportive care, (2) gastrointestinal decontamination, (3) pharmacologic

treatment of manifestations, and (4) enhancement of elimination.

Indications for ICU Admission in Theophylline and Other Methylxanthine Poisoning

Seizure

Ventricular arrhythmia

Hypotension

Rising theophylline concentration despite decontamination

Supportive Care

This text presumes that appropriate supportive measures have occurred. Patients with abnormal vital signs typical of methylxanthine intoxication should be cared for in a clinical setting with cardiac, pulse oximetry, and blood pressure monitoring and qualified personnel.

It is axiomatic that crystalloid should be given to replace losses from diuresis and emesis and that continuous electrocardiographic monitoring to assess for myocardial irritability should be instituted. Isolated premature ventricular contractions that are not associated with hemodynamic compromise require no treatment. More significant signs of myocardial irritability should be treated with appropriate doses of lidocaine (Grade III recommendation). Although the proconvulsant actions of lidocaine pose a theoretical risk, there is no evidence suggesting that lidocaine is detrimental in methylxanthine toxicity when used in appropriate doses [97–99].

Gastrointestinal Decontamination

Methylxanthines are adsorbed by activated charcoal, and in one volunteer study, charcoal reduced the dose of ingested theophylline by 64% [100]. Compared with gastric lavage, activated charcoal has been shown to be superior for reducing absorption of theophylline in a simulated overdose scenario volunteer study [101]. For a patient who has ingested a large dose of methylxanthine, or who is showing signs of toxicity, administration of single-dose activated charcoal

is indicated as long as there is an intact or protected airway [102]. No clinically significant benefit has been established from the addition of cathartic to the activated charcoal [103]. Methylxanthine toxicity is often associated with nausea and vomiting which may limit activated charcoal use [65, 67]; antiemetics may facilitate administration of activated charcoal; however, the clinician should assess whether the patient's mental and airway protection status will allow for its safe administration. Ondansetron (8 mg) has been reported to be successful in terminating vomiting in a single case report of theophylline poisoning after failure of other antiemetics [104].

The American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists have recommended that whole-bowel irrigation (WBI) should be considered in an acute overdose with a sustained-release preparation [105], although an animal model of acute theophylline overdose did not show that whole-bowel irrigation significantly reduces absorption of theophylline [106]. One small human trial demonstrated decreased absorption of a 200 mg dose of sustained-release theophylline with charcoal, but no statistically significant effect of adding whole-bowel irrigation to activated charcoal [107]. Therefore, the current state of evidence does not support the routine use of whole-bowel irrigation for the treatment of methylxanthine toxicity. A bezoar should be suspected in patients who continue to have rising serum concentrations despite tolerating activated charcoal. Rarely, endoscopy has been used to remove a bezoar [28] and whole tablets [108].

Pharmacologic Management

Recommendations for pharmacologic treatment of theophylline overdose (Table 3) are based on an understanding of pathophysiology and anecdotal experience. No large series or randomized clinical trials have studied the efficacy of specific pharmacologic interventions for theophylline intoxication.

Table 3 Pharmacologic treatment in theophylline overdose^a

Effect	Agent	Dose	Comment
Emesis	Ondansetron	8 mg IV (0.15 mg/kg IV)	Cimetidine should not be used, as it inhibits metabolism of theophylline
	Ranitidine	50 mg IV (2 mg/kg)	
Seizure	Lorazepam	4 mg IV (0.1 mg/kg IV)	Other benzodiazepines may be used
	Phenobarbital	300–800 mg (20 mg/kg IV)	May augment respiratory depression
Hypotension	Propranolol	1–3 mg slow IV push (0.02 mg/kg IV)	May precipitate bronchospasm in asthmatic patients; if effective, consider infusion 5–10 mg/hr
	Esmolol	500 µg/kg over 1 min, then 50 µg/kg/min	May increase left ventricular stroke work index
			May be effective if hypotension is due to tachycardia

IV intravenous

^aNumbers in parentheses indicate pediatric dose

Vasopressors

Hemodynamic monitoring is indicated for all patients with methylxanthine poisoning. Intravenous crystalloid fluid boluses are the first-line treatment for hypotension and any volume losses from diuresis. There are no randomized controlled trials of the ideal treatment of hypotension in methylxanthine poisoning; however, one case report describes the use of esmolol, a selective beta-1 antagonist, to slow the heart rate and allow for greater ventricular filling time and stroke volume, improving cardiac output [109]. Pharmacologically, esmolol would be expected to reduce heart rate and thus possibly improve hypotension (Grade III recommendation).

Electrolytes

Hypokalemia should be treated cautiously with potassium supplementation because total body potassium is not depleted. Rather, hypokalemia results from intracellular sequestration secondary to sympathomimetic effect [110]. Cardiac dysrhythmias may occur during the treatment of acute asthma for a number of reasons, including electrolyte abnormalities due to pharmacotherapy. A comparison of two treatment regimens by a double-blind protocol found that aminophylline was not any more arrhythmogenic than standard epinephrine treatment [99].

Hyperkalemia may occur as the serum theophylline concentration decreases in a patient who is receiving potassium supplementation [111, 112] or if a patient is being treated with propranolol [113]. Administration of magnesium and sodium bicarbonate is indicated for clinically significant hypomagnesemia and acidosis (Grade III recommendation).

Arrhythmias

The initial approach to methylxanthine-induced, clinically significant cardiac arrhythmias is standard advanced cardiac life support algorithms (Grade III recommendation). Atrial tachyarrhythmias have been shown to be reversed by beta-blockers [109]. Nonspecific β -blockers, such as propranolol, should be administered cautiously to patients with asthma because they may precipitate bronchospasm. Additionally, the use of nonspecific β -receptor antagonists may lead to unopposed α -adrenergic activity, resulting in coronary vasoconstriction and left ventricular dysfunction. One animal study of caffeine toxicity described increased survival time in rats receiving either propranolol or verapamil [114]. One case report describes unsuccessful use of propranolol to control pressor-refractory hypotension, and the patient died despite this and charcoal hemoperfusion. In this case, propranolol had been given in an effort to reverse peripheral

vasodilation and reduced cardiac output ensued. Propranolol's side chain is demethylated by CYP 1A2, and though there is a possibility of pharmacokinetic drug interaction with theophylline, none has been described [115]. Esmolol, a selective β_1 -adrenoreceptor antagonist, seems to be safe to use in patients with asthma; however, their respiratory status should be monitored closely. It has been used successfully in a theophylline overdose patient with supraventricular tachycardia and hypotension [109], a finding that has been supported in an animal model [116]. Thus, esmolol is reasonable choice for the treatment of xanthine-induced tachyarrhythmias (Grade III recommendation). Esmolol may increase left ventricular stroke work index by increasing filling time; thus, hemodynamics in patients so treated should be carefully monitored [117].

Adenosine has been reported to reverse theophylline-induced paroxysmal supraventricular tachycardia at typical adult doses of 6 mg [118], although higher doses may be required [119, 120]. Adenosine is likely to be of minimal clinical usefulness, however, because of its ultra-short half-life, and continuous infusions of adenosine can lead to bronchoconstriction and atrioventricular block [120–122]. Verapamil has been used to treat multifocal atrial tachycardia [123] but has failed in the treatment of supraventricular tachycardia [30].

Hypotension

Hypotension that persists despite fluid resuscitation and treatment of clinically significant arrhythmias has been reported to be effectively treated with the α -receptor agonist, phenylephrine [124] (Grade III recommendation). Hypotension also has been treated successfully with propranolol, a nonselective beta antagonist that antagonizes β_2 -mediated vasodilation [63, 113]. Invasive cardiovascular monitoring is indicated for patients who are persistently hypotensive. One case report describes the use of an intravenous lipid emulsion [ILE] infusion (but not a bolus) combined with continuous venovenous hemodiafiltration (CVVHD) to treat refractory vasodilatation and

arrhythmias after caffeine overdose [125]. Caffeine does not inherently possess properties amenable to treatment with ILE. There is insufficient evidence to recommend the use of ILE for methylxanthine intoxication. Vasopressin has been reported to increase blood pressure to facilitate hemodialysis in near-fatal caffeine poisoning; the mechanism is purported to be vasopressin receptor subtype 1 (V1) receptor stimulation activating phospholipase C and releasing intracellular calcium stores from vascular smooth muscle [126].

Seizures

Seizures are notoriously difficult to control in patients with theophylline intoxication [78]. Although not specifically studied with methylxanthines, in most seizures of toxic origin, benzodiazepines, of which large doses may be required, are generally considered to be first-line therapy (see ► Chap. 20, “Toxicant-Induced Seizures”). Phenobarbital or other barbiturates or propofol may be used as adjunctive anticonvulsants. Barbiturates have the disadvantage of delayed onset and have a synergistic action with benzodiazepines, potentiating respiratory depression. Administration of propofol may require higher than typical dosing [127]. Phenytoin should be considered to be contraindicated based on the empirical observation that it is ineffective in the termination of theophylline-induced seizures and based on animal data suggesting increased mortality [128]. If anticonvulsants are ineffective in terminating seizures, neuromuscular blockade is indicated. In this circumstance, continued anticonvulsant therapy and continuous electroencephalographic monitoring are needed to ensure that electrical seizure activity is not occurring.

Extrapolating from experience in animal models, prophylactic administration of an anticonvulsant, either a benzodiazepine or a barbiturate, should be considered in patients at high risk for theophylline-induced seizures (Grade III recommendation). High-risk patients are those with acute overdose and with a serum theophylline concentration greater than or equal to 80 $\mu\text{g/mL}$

(444 $\mu\text{mol/L}$), patients with chronic intoxication who are older than age 60 and with a serum theophylline concentration greater than or equal to 30 $\mu\text{g/mL}$ (167 $\mu\text{mol/L}$), and patients with a history of a seizure disorder or evidence of neuromuscular excitability. Although there is no reported experience in humans to support this practice, pretreatment with anticonvulsants in animal models of acute theophylline intoxication has been shown to be beneficial [128–130]. The use of prophylactic anticonvulsants is not a substitute for and should not result in delay in instituting extracorporeal elimination when the latter is indicated.

Emesis

Emesis must be controlled to administer activated charcoal effectively and to prevent further fluid loss. Control of emesis may be difficult to achieve for most patients with theophylline intoxication [2, 30, 67]. Standard antiemetics, such as phenothiazines, are frequently ineffective [30, 67]. Additionally, phenothiazines may lower the seizure threshold significantly. Ondansetron, a 5-hydroxytryptamine antagonist that acts at the chemoreceptor trigger zone, should be considered to be the antiemetic of choice because it has been shown to reduce theophylline-associated vomiting when other antiemetics have failed [104, 131] (Grade III recommendation). Ranitidine is an important adjunct because it decreases theophylline-induced gastric hypersecretion [66] and does not inhibit cytochrome P-450 enzymes. Ranitidine has been shown to be effective in controlling emesis when used alone [132].

Enhancement of Elimination

There are three main modalities for enhanced elimination of theophylline: multiple-dose activated charcoal (MDAC), charcoal hemoperfusion, and hemodialysis.

Multiple-dose activated charcoal has been shown to reduce theophylline half-life in a case series of intoxicated patients and in human

experimental models of theophylline intoxication [133–141]. In one series of five infants, MDAC reduced the expected half-life of theophylline from 25 h to between 6.5 and 12.6 h [140]. Similarly, in a human volunteer trial, the half-life of theophylline was reduced from 6.4 to 3.3 h when MDAC was administered [142].

The optimal regimen for MDAC has been studied in human volunteers who received 6 mg/kg of aminophylline intravenously. Frequency of administration was found to be more important than the total amount of charcoal given. Administering activated charcoal every 2 h maximally increased clearance of theophylline [143]. The recommended regimen is 25 g of activated charcoal administered every 2 h until the serum theophylline concentration has declined to a level associated with clinical improvement [144]. Activated charcoal should not be used if the patient has an ileus or any other abnormality in bowel motility. As with single-dose AC, MDAC use may be limited by emesis in a patient with methylxanthine toxicity. Ranitidine may decrease some of the gastric acid hypersecretion that contributes to the vomiting in theophylline toxicity and facilitate administration of MDAC [132]. Ondansetron has been reported to be effective in one theophylline toxicity case requiring MDAC and whole-bowel irrigation [104]. If emesis is not quickly controlled, MDAC can be expeditiously administered through a naso- or orogastric tube. When MDAC is administered, it is crucial to avoid using cathartics with each dose because these may lead to life-threatening volume depletion and electrolyte abnormalities. The activated charcoal should be administered as an aqueous suspension. Suggested indications for enhanced elimination are given in Table 4. When giving MDAC, patients should undergo serial abdominal examinations to assess for the presence of intestinal pseudo-obstruction and charcoal bezoar, as these have been described in case reports as complications of MDAC therapy [145].

Extracorporeal drug removal (ECR) may be beneficial for selected patients. Acceptable ECR modalities include hemodialysis and charcoal hemoperfusion [146]. Triple-volume exchange

Table 4 Indications for enhanced elimination

Executive summary of recommendations	
1) General statement:	ECTR is recommended in severe theophylline poisoning (1C)
2) Indications of ECTR:	
ECTR is recommended for:	
[Theophylline] > 100 mg/L (555 μ mol/L) in acute exposure (1C)	
Seizures (1D)	
Life-threatening dysrhythmias (1D)	
Shock (1D)	
Rising serum [theophylline] despite optimal therapy (1D)	
Clinical deterioration despite optimal therapy (1D)	
ECTR is suggested for:	
[Theophylline] > 60 mg/L (333 μ mol/L) in chronic exposure (2D)	
Age <6 months or > 60 years old and [theophylline] > 50 mg/L (278 μ mol/L) in chronic exposure (2D)	
Gastrointestinal decontamination unable to be administered (2D)	
3) Cessation of ECTR:	
Recommended when clinical improvement is apparent OR the [theophylline] < 15 mg/L (83 μ mol/L) (1D)	
4) Choice of ECTR:	
Intermittent hemodialysis is the preferred recommended ECTR (1C)	
The following are acceptable alternatives if hemodialysis is not available:	
Hemoperfusion (1C)	
CRRT (3D)	
Exchange transfusion is an alternative to hemodialysis in neonates (2D)	
5) Miscellaneous:	MDAC should be continued during ECTR (1D)

Adapted from Ref. [153]

transfusion was used successfully in a premature infant [147, 148], but may be impractical in an adult patient, especially when other ECR modalities are available. Peritoneal dialysis removes theophylline but too slowly to have a role in the treatment of theophylline intoxication [149]; however, it has been used in premature neonates when vascular access for hemodialysis (HD) is impractical [149]. The molecular adsorbent recirculating system (MARS(tm)) has been reported in one case to be associated with increased clearance. Ideally, ECR should begin before LTEs fully evolve because numerous case series and case reports have shown that ECR does not reliably terminate LTEs once they begin [1, 2, 30, 146, 147,

150]. Patients have died or experienced significant neurologic disability despite the institution of ECR [1, 2, 30, 151].

Important differences exist between hemodialysis and hemoperfusion. Historically, hemoperfusion is associated with a higher rate of clearance than hemodialysis. Hemoperfusion has been shown to decrease the elimination half-life of theophylline to 1.23 ± 0.31 h versus 2.39 ± 1.14 h for hemodialysis [146]. This difference may now be obviated by the availability of high-flux hemodialysis cartridges; however, this issue has not been formally studied. Hemoperfusion has many disadvantages, however. It is not available in all centers and is associated with complications such as bleeding, thrombocytopenia, and hypocalcemia in 40–60% of patients undergoing the procedure [152, 153]. In contrast, hemodialysis is readily available at most centers and has a lower complication rate [147, 153]. ECR is discussed in more detail in ► Chap. 12, “Extracorporeal Substance Removal.” Saturation of the hemoperfusion cartridge may require the use of multiple cartridges to treat a single patient. As an illustrative case, one report describes theophylline toxicity in a 61-year-old male treated with two rounds of multidose activated charcoal, intermittent HD, whole-bowel irrigation, two sessions of sustained low-efficiency dialysis (SLED), and continuous venovenous HD (CVVHD) over the course of 48 h [154]. The authors describe theophylline clearance of 88–103 ml/min on HD (blood flow 250 ml/min) and 53–71 ml/min on SLED (blood flow 180 ml/min).

In 2012, the Extracorporeal Treatment in Poisoning (EXTRIP) working group convened, representing a collaboration across the fields of medical toxicology, clinical pharmacology, nephrology, and critical care medicine. The intent of this group was to critically assess the literature on the use of extracorporeal therapies for drug removal in poisoning. Extracorporeal therapies for methylxanthine poisoning were compared and extensively reviewed in 2015 [153]. Both caffeine and theophylline are small, 50% protein-bound, small-Vd molecules. These properties make

methylxanthines amenable to hemodialysis. With high-efficiency membranes, clearance of theophylline by hemodialysis can increase from 30 to 150 ml/min compared with endogenous clearance [153]. Extracorporeal techniques should be considered for any patient who is at high risk for LTEs (see Table 4). As previously discussed, in an acute ingestion, high-risk patients include patients with a theophylline serum concentration greater than 100 µg/mL (444–555 µmol/L). In chronic intoxication, patients who are older than age 60 or younger than 6 months and who have supratherapeutic levels are at risk. A summary of EXTRIP recommendations is listed in Table 4.

Although hemoperfusion is more efficient than hemodialysis at removing theophylline, it has not been shown to be better at improving clinical outcome. In the only study to compare clinical outcomes of theophylline-poisoned patients treated with either hemoperfusion or hemodialysis, there was no significant difference in the numbers of patients who had major toxicity during or after the procedure [146]. This study must be interpreted with some caution because patients were not assigned randomly to treatment groups, and it had limited power.

It seems reasonable to have a low threshold to perform hemodialysis for high-risk patients given the risks of hemoperfusion, the poor specificity of risk factors, and the lack of demonstrable benefit between hemodialysis and hemoperfusion. For patients who are already manifesting LTEs, however, hemoperfusion is the best choice given its higher clearance. If hemoperfusion is not immediately available, hemodialysis should be instituted promptly.

Common Errors in the Treatment of Methylxanthine Poisoning

Not instituting hemodialysis in a patient experiencing a life-threatening event if hemoperfusion is unavailable

Not monitoring serum concentrations closely (every 2 h)

Not monitoring serum concentrations for 24 h after an overdose of a sustained-release preparation

Other Methylxanthines: Caffeine and Pentoxifylline

Caffeine is found in numerous prescription and nonprescription products. Chronic ingestion may produce caffeinism, a symptom complex consisting of irritability, insomnia, anxiety, and chronic abdominal pain. In contrast to theophylline, life-threatening toxicity has not been reported after chronic ingestion of caffeine. Clinical effects after acute overdose of caffeine however are similar to symptoms of acute theophylline toxicity. Metabolic acidosis [155], seizures [155, 156], and ventricular arrhythmias [155, 157] all have been reported. Caffeine poisoning also has been associated with excessive catecholamine release similar to that seen with theophylline poisoning [75]. Fatal oral doses of caffeine have ranged from 5–50 g [158–160]. Fatalities have been associated with serum caffeine concentrations ranging from 80–1560 µg/mL [161], although concentrations of 297 µg/mL have been associated with survival after hemoperfusion [157].

Treatment of acute caffeine overdose is similar to that for theophylline intoxication. Several case reports have shown that caffeine is removed effectively by hemoperfusion [157, 161]. A serum concentration level greater than or equal to 120 µg/mL has been cited as a criterion for extracorporeal removal. Since serum caffeine measurement is not performed by most hospital laboratories and requires sending a sample to a reference laboratory, the decision to perform hemodialysis for caffeine poisoning is usually based on the patient's clinical picture.

Pentoxifylline is a xanthine derivative used in the treatment of peripheral vascular disease. Experience in overdose is limited. Acute overdose has been associated with hypokalemia, hyperglycemia, atrioventricular block, and hypotension [162–165]. Death has occurred after massive overdose [166]. Toxicity from chronic use has not been reported. Treatment is primarily supportive. Hypotension may be treated with crystalloid and seizures treated with benzodiazepines or phenobarbital. In one case of massive pentoxifylline ingestion resulting in shock, dialysis clearance was calculated at 154 ml/min. The patient survived without sequelae [167].

Special Populations

In older children and adults, 90% of theophylline is metabolized, and 10% is excreted unchanged in the urine. In neonates and young children, 50% of theophylline is hepatically metabolized with the remainder excreted unchanged in the urine [33]. Unlike adults, in neonates theophylline does have some methylation to caffeine during biotransformation, and this mechanism matures at 50–55 weeks postconceptional age [168, 169]. Theophylline has a prolonged half-life in patients at extremes of age. The half-life in neonates is 25 h, and the half-life in adults older than age 60 years is 10 h. The half-life for patients 16–60 years old is 8 h.

An 11-week pregnant female patient with intentional theophylline overdose received and tolerated hemodialysis followed by extended dialysis. Theophylline clearance was approximately 40 ml/min. Obstetrical examination prior to hospital discharge revealed a normal fetus; however, the patient terminated the pregnancy electively, as this was the original intent of her overdose [170].

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Part VI

Medications: Psychotropic

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The discovery of chlorpromazine and other traditional antipsychotic agents in the early 1950s revolutionized the management of schizophrenia and led to a dramatic reduction in the number of hospitalizations necessary for patients with psychosis. Shortly after their introduction, however, it was noted that these agents often produced disabling neurological side effects (e.g., sedation, extrapyramidal side effects [EPS], tardive dyskinesia [TD]) and were ineffective against the negative symptoms (e.g., anhedonia, apathy, inactivity, poverty of thought, social withdrawal) and neurocognitive deficits of schizophrenia. Initially, it was thought that EPS were linked inextricably to antipsychotic drug action. The introduction of clozapine in 1990 and other so-called atypical agents shortly thereafter has further revolutionized the management of schizophrenia. Compared with traditional antipsychotics, atypical agents produce minimal EPS at clinically effective antipsychotic doses and seem to be more effective for the negative symptoms and neurocognitive deficits of schizophrenia. This chapter describes in detail the pharmacology and toxicology of traditional and atypical antipsychotic agents.

The antipsychotics commonly are referred to either as *neuroleptics*, owing to their propensity to cause EPS, or as *major tranquilizers*, owing to their ability to cause sedation. These terms are misleading, however, because they refer to non-essential features of these agents. The newer atypical agents separate therapeutic from adverse effects; they are more likely to produce antipsychotic effects without producing EPS or sedation. The term *antipsychotic* is preferred by some experts but also is misleading [1]. Although these agents are used primarily to treat schizophrenia and other psychotic disorders, they also are used to facilitate induction of general anesthesia and to treat the manic phase of bipolar illness, agitated behavior, drug-associated hallucinations and delirium, migraine and tension headaches, nausea and vomiting, intractable hiccoughs, pruritus, and many extrapyramidal movement disorders (e.g., tics, chorea). Currently, the terms *neuroleptic* and *antipsychotic* may be used interchangeably to classify these agents.

Poisoning by antipsychotic agents may occur after therapeutic doses or accidental or intentional overdose. Toxicity often results from an extension of pharmacological actions and primarily manifests as neurological and cardiovascular abnormalities. Antipsychotic agents have a wide therapeutic index; death after overdose is rare, particularly if medical care is initiated in a timely manner. Death most commonly occurs when antipsychotics have been coingested with other agents, although relative rates may be higher when certain agents such as chlorpromazine or thioridazine are ingested alone or in combination with alcohol [2–4]. It has been estimated that the most toxic antipsychotic agents cause 1 death from poisoning for every 1000 patient-years of use [2]. Of 2,275,141 human drug exposures reported to the National Poison Data System in 2012, antipsychotics were among the top 5 substance classes most frequently cited (6.05%), with sedatives/hypnotics/antipsychotics implicated in 405 fatalities [5].

Classification

Currently, more than 40 antipsychotics are clinically available worldwide, and numerous others are in various stages of development. Antipsychotics are classified most commonly by structure, pharmacological profile, and whether they are typical (traditional, conventional) or atypical (novel, second-generation). Antipsychotics are a structurally diverse group of heterocyclic compounds, with at least 14 different classes and derivatives available worldwide (Table 1). The phenothiazine and thioxanthene agents are subdivided further into three groups (aliphatic, piperidine, and piperazine) based on side-chain substitution of the central ring (Fig. 1). The nature of the substitution influences pharmacological activity. Compared with the piperazine subclass, aliphatic (e.g., chlorpromazine) and piperidine (e.g., thioridazine) phenothiazines have lower antipsychotic potency and a lower incidence of EPS but have a higher incidence of sedation, hypotension, and anticholinergic effects [6]. Aside from the phenothiazine class,

Table 1 Antipsychotic agents

Structural class	Generic name (trade name)	Affinity of antipsychotic agent for D ₂ -dopamine receptor (potency) ^a	Daily dose range (mg)
Typical agents			
Butyrophenone	Droperidol (Inapsine)	3+	1.25–30
	Haloperidol (Haldol)	2+	1–30
Dihydroindolone	Molindone (Moban) Oxypertine ^b	1+	15–225
Diphenylbutylpiperidine	Pimozide (Orap) Fluspirilene ^b	2+	1–20
Phenothiazine Aliphatic	Chlorpromazine (Thorazine) Promazine (Sparine)	2+	25–2000 50–1000
	Promethazine (Phenergan)	2+	25–150
	Levomepromazine ^b	2+	
	Triflupromazine (Vesprin)		5–90
Piperazine	Acetophenazine (Tindal)		40–400
	Fluphenazine (Prolixin)	3+	0.5–30
	Perphenazine (Trilafon)	3+	4–64
	Prochlorperazine (Compazine)	2+	10–150
	Trifluoperazine (Stelazine)	3+	2–40
	Thiethylperazine (Torecan)		10–30
Piperidine ^c	Mesoridazine (Serentil)	2+	30–400
	Thioridazine (Mellaril, Miltazine)	2+	20–800
Thioxanthene	Chlorprothixene (Taractan)	2+	30–600
	Cloperthixol ^b	3+	
	Flupentixol ^b	3+	
	Thiothixene (Navane)	3+	6–60
	Zuclopenthixol (Clopixol) ^b	3+	
Atypical agents			
Benzamides	Amisulpride	2+	100–1200
	Raclopride	3+	5–8
	Remoxipride	1+	150–600
	Sulpiride	2+	100–1600
	Sultopride		
Benzisothiazole	Ziprasidone (Geodon)	3+	40–160
	Lurasidone (Latuda)	3+	20–160
Benzisoxazole	Risperidone (Risperdal)	3+	2–16
	Paliperidone (Invega)	3+	6–12
	Iloperidone (Fanapt)	3+	2–24
Dibenzodiazepine	Clothiapine ^b		
	Clozapine (Clozaril, Leponex)	1+	150–900

(continued)

Table 1 (continued)

Structural class	Generic name (trade name)	Affinity of antipsychotic agent for D ₂ -dopamine receptor (potency) ^a	Daily dose range (mg)
Dibenzoxazepine	Loxapine (Loxitane)	1+	20–250
	Savoxepin ^b		
Dibenzothiazepine	Quetiapine (Seroquel)	1+	300–600
	Zotepine ^b	2+	150–300
Imidazolidinone	Sertindole (Serlect) ^b	3+	12–24
Quinolinone	Aripiprazole (Abilify)	2+	10–30
Thienobenzodiazepine	Olanzapine (Zyprexa)	2+	5–20
Dibenzo-oxepino pyrrole	Asenapine (Saphris)	2+	10–20

Adapted from Ref. [6]

^aA higher numerical value indicates greater binding affinity (greater antagonism) at D₂-receptor. Binding affinity (potency) at D₂-receptor correlates with daily dose range. 0 = minimal to none; 1+ = low; 2+ = moderate; 3+ = high to very high

^bNot currently available for clinical use in the United States

^cWithdrawn from market in many countries, including the United States

structure-activity relationships have not been elucidated for most antipsychotics. Antipsychotic classification based on chemical structure has little clinical utility.

It is more useful to classify antipsychotics based on relative receptor binding profiles (Table 2). Because clinical toxicity is often the result of exaggerated pharmacological activity, knowledge of an antipsychotic's relative receptor binding can be used to predict adverse effects that will occur after therapeutic doses and overdose [7–9].

Clinically, agents are considered atypical if they

1. Produce minimal EPS at clinically effective antipsychotic doses
2. Have a low propensity to cause TD with long-term treatment
3. Are effective for treating the positive (delusions, disorganized behavior, hallucinations) and negative symptoms of schizophrenia [1, 7–9, 17, 18]

Clinical Pharmacology

D₂-dopaminergic receptor antagonism (Fig. 2) seems to be necessary for antipsychotic effects; currently, there is no effective antipsychotic

devoid of this property [1, 6–8]. Antipsychotics bind to and antagonize presynaptic (autoreceptor) and postsynaptic D₂-receptors [6]. Initially, this antagonism stimulates dopamine neurons to synthesize and release more dopamine. With continued antipsychotic treatment, however, depolarization inactivation occurs, and decreased production and release of dopamine occur along with continued postsynaptic D₂-receptor antagonism [6, 18].

For most antipsychotics, the affinity (potency) for the D₂-receptor correlates with the daily dose used to treat schizophrenia and the likelihood of producing EPS [1, 8, 20]. Antagonism of mesolimbic D₂-receptors is believed to mediate antipsychotic effects (positive symptom amelioration). Based on in vivo radioligand binding studies with positron emission tomography (PET), the therapeutic effects of antipsychotics correlate with 70% or greater mesolimbic D₂-receptor occupancy [7, 21]. Simultaneous antagonism of mesocortical D₂-receptors, however, is believed to exacerbate cognitive impairment and the negative symptoms of schizophrenia [22]. Blockade of nigrostriatal D₂-receptors produces EPS (e.g., acute dystonia, parkinsonism, akathisia, and tardive dyskinesia). Agents with high affinity for D₂-receptors (e.g., fluphenazine, thiothixene, haloperidol) have a high likelihood of

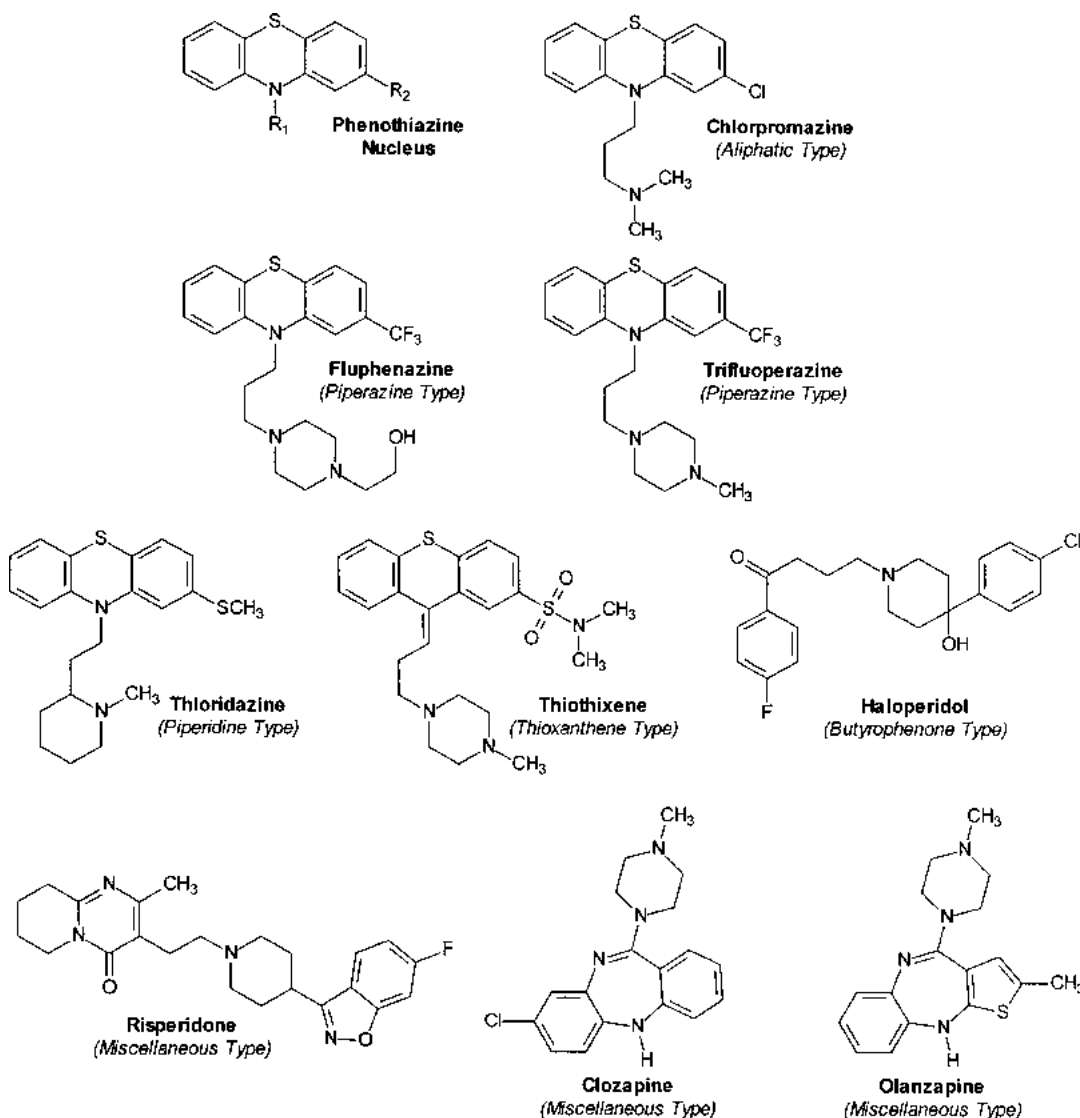


Fig. 1 Chemical structures of representative antipsychotic agents

producing EPS [7]. Agents with low D_2 -receptor affinity (e.g., clozapine, quetiapine) or agents that selectively antagonize limbic D_2 -receptors over receptors in the nigrostriatum (e.g., sulpiride, remoxipride, raclopride) are less likely to produce EPS [1, 8, 9, 17, 18]. Data from PET studies show that EPS are seen with nigrostriatal D_2 -receptor occupancy at 80% or greater [7, 21]. At therapeutic doses of most conventional antipsychotics, there is minimal separation of D_2 -receptor

occupancies in the mesolimbic and nigrostriatal areas [21].

Blockade of D_2 -receptors in the area postrema (chemoreceptor trigger zone) of the medulla oblongata mediates the antiemetic action of antipsychotics. Antagonism of D_2 -receptors in the anterior pituitary (tuberoinfundibular pathway) stimulates prolactin secretion and may result in galactorrhea, gynecomastia, menstrual changes, and sexual dysfunction [7]. D_2 -receptor blockade

Table 2 Relative neuroreceptor affinities for antipsychotics^a

	Receptor						
Antipsychotic agent						Other receptor	EPS
	H ₁	α ₁	α ₂	M ₁	5-HT _{2A}	Binding	Risk ^b
Typical agents							
Chlorpromazine	2+	3+	0	1+	3+	D ₁ , D ₃ , D ₄	1+
Fluphenazine	0	0	0	0	0		3+
Haloperidol	0	1+	0	0	1+	D ₁ , D ₄ , σ	3+
Loxapine	3+	3+	0	2+	3+	D ₄ , blocks NE reuptake	1+
Mesoridazine	3+	3+		1+			1+
Molindone	0	0	1+	0	0		3+
Perphenazine	1+	1+		0	3+		3+
Pimozide	0	1+		0	1+		3+
Prochlorperazine	1+	1+		0	0		3+
Thioridazine	2+	3+	0	3+	2+		1+
Thiothixene	0	0	0	0	0		3+
Trifluoperazine	0	1+		0	1+		3+
Atypical agents							
Amisulpride	0	0	0	0	0	D ₃	1+
Aripiprazole	1+	1+	0	0	3+	D ₃ , 5-HT _{2C} , 5-HT ₇	0
Asenapine	3+	3+	3	0	3+	D ₁ , D ₂ , D ₄ , 5-HT _{1A} , 5-HT _{1B} , 5-HT _{2B} , 5-HT _{2C} , 5-HT _{5A} , 5-HT ₆ , 5-HT ₇ , H ₂ D ₁ , D ₄ , M ₂ , M ₃ , M ₄ , M ₅ , 5-HT _{2C} , 5-HT _{2D} , 5-HT ₃ , 5-HT ₆ , 5-HT ₇ ; blocks NE reuptake	0
Clozapine	3+	3+	+	3+	3+		0
Iloperidone	1+	3+	0	0	3+	D ₃ , D ₄ , 5-HT ₆ , 5-HT ₇ D ₁ , D ₃ , D ₄ , M ₂ , M ₃ , M ₄ , M ₅ , 5-HT _{1C} , 5-HT ₃ , 5-HT ₆	1+
Olanzapine	2+	2+	0	3+	3+		0
Paliperidone	1+	3+	2	0	3+	5-HT _{1A} , D ₁	1+
Quetiapine	3+	3+	+	3+	1+		0
			0				
Remoxipride	0	0		0	0	Σ	1+
Risperidone	0	2+	1+	0	3+	D ₁ , D ₄	1+
Sertindole	0	1+	0	0	3+	5-HT _{1C} , 5-HT _{2C}	
Ziprasidone	0	3+	0	0	3+	5-HT _{1A} , 5-HT _{1C} , 5-HT _{1D} , 5-HT _{2C} , D ₁ ; blocks NE, 5-HT reuptake	0
Zotepine	2+	0	2+	0	3+	D ₁ , D ₃ , D ₄ , 5-HT _{2C} ; blocks NE reuptake	1+
			+				

Adapted from Refs. [6–16], and respective package inserts

EPS extrapyramidal side effects, NE norepinephrine

^aRelative neuroreceptor affinity (neuroreceptor affinity at receptor X/dopamine D₂-receptor affinity) indicates relative receptor antagonism at therapeutic (D₂-blocking) antipsychotic doses. 0 = minimal to none; 1+ = low; 2+ = moderate; 3+ = high; 4+ = very high

^bA higher M₁ and 5-HT₂ relative neuroreceptor affinity confers a lower EPS risk

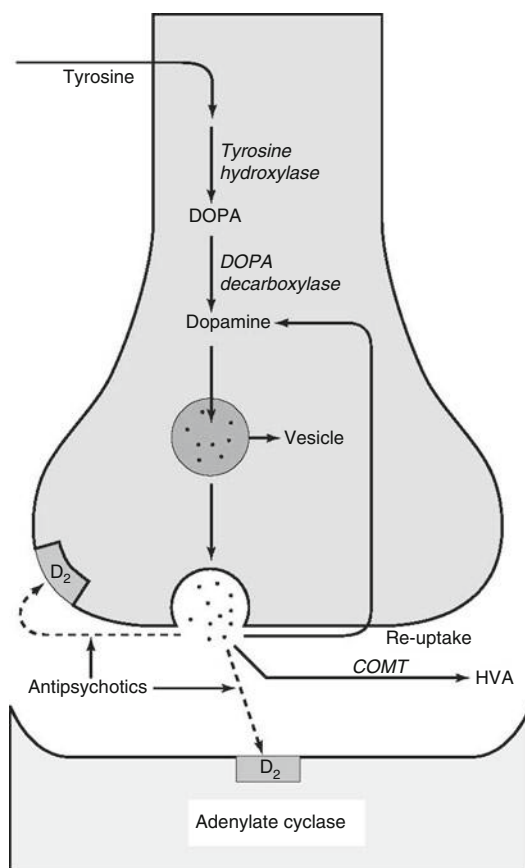


Fig. 2 The release and inactivation of dopamine and blockade of the D₂-receptor by antipsychotics. *COMT* catechol O-methyltransferase, *HVA* hydroxyvanillic acid (From Brody et al. [19])

in the anterior hypothalamus impairs temperature regulation and may result in hypothermia or hyperthermia, depending on ambient temperature [6]. D₂-receptor antagonism in the hypothalamus and nigrostriatum mediates the neuroleptic malignant syndrome (see ► Chap. 31, “**Neuroleptic Malignant Syndrome**”), a rare hyperthermic condition associated with antipsychotic therapy.

A novel class of antipsychotic agents, called dopamine system stabilizers, has recently emerged. These agents (e.g., aripiprazole) function as partial agonists of the D₂ and 5-HT_{1A}

receptors with antagonism of the 5-HT_{2A} receptor. They reduce dopaminergic neurotransmission when such activity is excessive and enhance dopaminergic activity when such activity is deficient. They work to restore dopamine neurotransmission to the normal range and provide antipsychotic effects while minimizing adverse effects from excessive D₂-receptor antagonism [23, 24].

Antipsychotics are competitive antagonists at a wide variety of neuroreceptors; each agent has a unique pharmacological profile that determines its clinical profile. Because D₂-receptor potency closely correlates with the dose used to treat psychosis, the likelihood of effect from other neuroreceptors at a given dose depends on their binding affinity relative to that of the D₂-receptor (see Table 2) [7, 25]. Relative binding affinity data can be used to predict adverse effects at therapeutic doses and overdose. Relative binding affinity data can be used to predict adverse effects in overdose, which are typically an extension of effect at therapeutic doses. Agents with high relative α_1 -adrenergic antagonism (e.g., aliphatic and piperidine phenothiazines, clozapine, olanzapine, risperidone, ziprasidone, sertindole) are likely to produce orthostatic hypotension, reflex tachycardia, miosis, and nasal congestion. High relative α_2 -adrenergic receptor antagonism (e.g., clozapine, risperidone) may result in sympathomimetic effects (i.e., tachycardia). High relative H₁-histamine receptor binding (e.g., aliphatic and piperidine phenothiazines, clozapine, loxapine, olanzapine, quetiapine) produces central nervous system (CNS) depression, appetite stimulation, and hypotension. Agents with high relative M₁-muscarinic receptor binding (e.g., aliphatic and piperidine phenothiazines, clozapine, olanzapine) produce central and peripheral anticholinergic stigmata (e.g., agitation, blurred vision, delirium, dry skin and mucous membranes, hallucinations, ileus, mydriasis, tachycardia, urinary retention). Sialorrhea, a feature unique to clozapine, likely is mediated by its partial agonism at M₁- and M₄-receptors [7]. High relative potencies at M₁-receptors and 5-HT_{1A}- and

3. D₂-receptor, 5-HT_{1A}-receptor partial agonists, 5-HT_{2A}-receptor antagonists (e.g., aripiprazole), also called *serotonin-dopamine system stabilizers*
4. Broad-spectrum, multireceptor antagonists (e.g., clozapine, olanzapine, quetiapine) [9, 31]

Characteristics Associated with Atypical Behavior of Antipsychotics

Low D₂-receptor potency (high milligram drug dosing)

Low D₂-receptor occupancy (<70%) by positron emission tomography in mesolimbic and nigrostriatal areas at therapeutic drug doses

High affinities for M₁-, D₁-, 5-HT_{1A}-, and 5-HT_{2A}-receptors relative to D₂-receptors

Selective mesolimbic D₂-receptor antagonism

Broad multireceptor antagonism

Partial agonist activity at D₂- and 5-HT_{1A}-receptors

Minimal propensity to elevate serum prolactin concentrations

Adapted from Refs. [7–9, 17, 18, 21, 26, 27].

Antipsychotics with a high relative 5-HT_{2A} binding affinity (5-HT_{2A}-to-D₂-receptor binding ratio >1) have a lower likelihood of producing EPS and mitigate the negative symptoms of schizophrenia by disinhibiting the dopamine system in the striatum and prefrontal cortex (see Fig. 3) [26–28]. Normally, dopamine neurons in the nigrostriatum and prefrontal cortex are inhibited by serotonin heteroreceptors. 5-HT₂-Receptor antagonism releases dopamine neurons from this inhibition (disinhibition) and ameliorates the effects of D₂-receptor blockade. 5-HT_{1A}-Autoreceptor agonism produced by certain atypical antipsychotics (e.g., aripiprazole, clozapine, ziprasidone) or stabilizers (e.g., aripiprazole) additionally releases dopamine neurons from this inhibition and mitigates EPS (see Fig. 3) [18, 26, 27]. 5-HT_{2A}-Receptor antagonism in the limbic system seems to have an independent antipsychotic effect [18, 22]. Serotonin-dopamine

antagonists (e.g., amperozide, clozapine, olanzapine, risperidone, sertindole, ziprasidone) may be given at smaller doses and produce a lower incidence of EPS while maintaining clinical effectiveness.

Pathophysiology of Therapeutic and Toxic Effects

The aliphatic and piperidine phenothiazines (e.g., chlorpromazine, thioridazine, mesoridazine) have a direct negative inotropic action and quinidine-like (type IA) antiarrhythmic effect on the heart [6]. These agents bind to inactivated fast-sodium channels responsible for membrane depolarization and potassium channels responsible for membrane repolarization [32–34]. This sodium channel blockade is voltage and rate dependent; block is enhanced greatly at less negative membrane potentials and faster heart rates [32]. Conduction disturbances are more apparent for drugs that also produce a tachycardia (e.g., drugs with anticholinergic properties). Potassium channel blockade is concentration, voltage, and reverse frequency dependent; block is enhanced at higher concentrations, at less negative membrane potentials, and at slower heart rates [33, 34]. Drugs that prolong cardiac repolarization commonly do so by blocking the *HERG*-encoded delayed rectifier, voltage-gated potassium channel. This mechanism has been demonstrated in vitro and correlated clinically with QT prolongation with pimozide, thioridazine, and sertindole and is suspected to be at play with numerous other antipsychotics [33]. While most QT prolonging drugs inhibit I_{Kr}, the potency of this inhibition does not clearly correlate with degree of QT prolongation or risk of developing ventricular dysrhythmia (torsades de pointes) [34].

Certain antipsychotics (e.g., haloperidol, mesoridazine, pimozide, and thioridazine) also are calcium channel antagonists [35, 36]. Pimozide is known to antagonize calmodulin and T-type calcium channels [37]. Electrophysiological effects variably include a depressed rate of phase 0 depolarization, depressed amplitude and duration of phase 2, and prolongation of phase

3 repolarization. Early afterdepolarizations that result from blockade of rectifying potassium channels may trigger ventricular arrhythmias, particularly torsades de pointes.

Antipsychotics produce hypotension from depressed peripheral vasomotor tone (from α_1 -adrenergic blockade), central vasomotor reflex depression, and direct myocardial depression. Hypotension is most commonly orthostatic and occurs during initial therapeutic dosing or shortly after acute overdose with certain agents.

Antipsychotics produce dose-related electroencephalographic (EEG) changes and are believed to lower the threshold for new-onset seizures and recurrent seizures in epileptic patients [38–41]. The seizures are dose related [39–41]. For most antipsychotics, however, the risk of seizures is low, even after overdose [3]. Clozapine, loxapine, and chlorpromazine are the antipsychotics most commonly associated with seizures after therapeutic doses and overdose [38–42]. Clozapine and chlorpromazine also induce the most striking EEG alterations when schizophrenic patients are given antipsychotics in therapeutic doses [38–41]. The mechanisms by which antipsychotics lower the seizure threshold are not well understood. GABA_A-receptor antagonism, norepinephrine reuptake inhibition, and membrane-destabilizing activity (altered ionic flow through channels) may mediate seizures for certain agents. The GABA_A antagonists clozapine and loxapine (the latter from its active metabolites, amoxapine and hydroxymoxapine) also produce dose-related inhibition of norepinephrine reuptake, which may account partly for the high incidence of seizures with these agents.

Normal extrapyramidal motor function requires a balance among the excitatory nigrostriatal dopaminergic neurons and inhibitory intrastriatal cholinergic neurons, raphistriatal and raphe nigral serotonergic neurons, and GABAergic striatonigral neurons (see Fig. 3) [18, 26–29]. Numerous other neurotransmitter pathways (e.g., noradrenergic, σ , D₁, dopaminergic, and *N*-methyl-D-aspartate [NMDA] glutamatergic) converge on various basal ganglia nuclei to modulate extrapyramidal movement

further [18, 29]. All antipsychotics seem to produce EPS by nigrostriatal D₂-receptor blockade [7]. This blockade leads to striatal cholinergic excess and signs and symptoms of EPS [43, 44]. Any agent that prevents cholinergic excess by balancing D₂-receptor blockade with M₁-receptor blockade at therapeutic doses is less likely to induce EPS (less relative dopamine antagonism in the nigrostriatum) [7]. Similarly, agents with high relative 5-HT₂ antagonism or 5-HT_{1A} agonism release the nigrostriatal dopamine system from inhibition, prevent cholinergic excess, and ameliorate EPS [18, 26–28]. Agents with low D₂-receptor potency in the nigrostriatum are unlikely to result in depolarization inactivation, receptor alterations, and signs of acute and chronic EPS [18]. σ - and NMDA-receptor antagonism modulates the dopaminergic-cholinergic balance to increase the likelihood of acute dystonia, whereas α -adrenergic and D₁ antagonism seem to protect against the development of acute dystonia [18, 29, 45].

Although parkinsonism is known to result from decreased nigrostriatal dopaminergic activity, the pathophysiology of other extrapyramidal syndromes has not been elucidated fully [46]. Akathisia is possibly the manifestation of mesocortical D₂-receptor blockade [46]. Similar to parkinsonism, acute dystonic reactions (DRs) may result from decreased dorsal striatal dopaminergic activity. Paradoxically, acute DRs alternatively may result from increased nigrostriatal dopaminergic activity that occurs as a compensatory response to antipsychotics [46, 47]. Acutely, postsynaptic D₂-receptor blockade produced by antipsychotics is matched by increased presynaptic dopamine synthesis and release (see Fig. 2). As midbrain concentrations of the antipsychotic decline hours to days after a dose, a state of dopamine excess develops, and sustained muscular contraction (dystonia) occurs [44, 45]. TD is likely a compensatory response to prolonged D₂-receptor antagonism by antipsychotics. Upregulated postsynaptic processes create a state of dopamine supersensitivity and an exaggerated response despite smaller quantal releases of dopamine [6, 46, 47]. An alternative theory postulates that TD results from the neurotoxic effects of free radicals, which are produced by increased

dopamine metabolism associated with chronic antipsychotic D₂-receptor blockade [48].

Pharmacokinetics

The pharmacokinetics of antipsychotics are complex. Although the pharmacokinetic parameters are similar for most classes of agents, there is substantial interindividual variability. Absorption is nearly complete after oral administration, but bioavailability is erratic and unpredictable (range, 10–70%) as a result of extensive first-pass hepatic metabolism and interactions of intestinal transport proteins such as P-glycoprotein [49, 50]. Bioavailability is increased four to ten times after intramuscular administration. Plasma concentrations peak 1–6 h after oral therapeutic dosing, 0.5–1 h after immediate-release intramuscular administration, and within 24 h of intramuscular administration of sustained-release preparations [49, 50]. Oral inhalation of loxapine results in rapid absorption with peak serum concentrations at 2 min [51]. Sustained-release (depot) preparations are made by esterifying the hydroxyl group of an antipsychotic (e.g., fluphenazine, haloperidol) with a long-chain fatty acid (e.g., enanthate or decanoate). After oral overdose, absorption occurs more rapidly, but peak plasma concentrations are delayed; clinical effects occur sooner and last longer.

Most antipsychotics are highly lipophilic, are highly protein bound (75–99%), and accumulate in the brain and other tissues [6, 49, 50]. Volumes of distribution are large, and plasma concentrations after therapeutic doses are low (less than one to several hundred nanograms per milliliter). These pharmacokinetic characteristics make significant extracorporeal removal by hemodialysis and hemoperfusion impossible. Most antipsychotics readily cross the placenta to enter the fetal circulation and are secreted into breast milk. All antipsychotics are eliminated predominantly by hepatic metabolism. The main routes of metabolism are oxidation by cytochrome P-450 mixed-function oxidases (CYP) or flavin-containing monooxygenase (FMO), hydroxylation, sulfoxidation, *N*-dealkylation, and

conjugation [50, 52]. Metabolites commonly are active and metabolized further in the liver or excreted in the urine or bile. Large interindividual variation in the biotransformation of antipsychotics results in substantial differences in steady-state plasma concentrations with fixed therapeutic dosing [6, 49, 50, 52, 53]. In addition, many antipsychotics have metabolites that are not readily measured but are pharmacologically active. There is often little correlation among antipsychotic dose, serum concentrations, and clinical effects [49, 50, 52, 53]. Elimination half-lives typically range from 18 to 40 h and allow for once-daily dosing for many antipsychotics. Depot preparations have elimination half-lives of 7–21 days [49] (Table 3).

Drug Interactions

When antipsychotics are coadministered with other drugs, clinically significant interactions may occur [54]. Interactions may be additive or antagonistic and pharmacodynamic or pharmacokinetic. These interactions are most likely to be of clinical concern when therapy is begun or discontinued. The CNS and respiratory depressant effects of antipsychotics may be potentiated by alcohols, antihistamines, antidepressants, opiates, and sedative-hypnotics. Fatal cardiorespiratory arrest has been reported to occur when therapeutic doses of clozapine have been taken with diazepam and lorazepam [55, 56]. Exaggerated anticholinergic effects may occur when certain antipsychotics are coadministered with tricyclic antidepressants, antihistamines, antiparkinsonian agents, and certain skeletal muscle relaxants (e.g., cyclobenzaprine). The hypotensive effects of antipsychotics with α_1 -antagonist properties may be potentiated when coadministered with antihypertensives (e.g., prazosin) with similar pharmacological properties. The dopamine receptor-blocking effects of antipsychotics antagonize the effects of levodopa and dopamine agonists used to treat patients with Parkinson's disease. Mesoridazine or thioridazine may potentiate the cardiotoxicity of other type IA antiarrhythmic agents (e.g., quinidine, tricyclic

Table 3 Pharmacokinetics of commonly used antipsychotics

Antipsychotic Agent	t_{\max} (hr)	$t_{1/2}$ (hr) (mean)	Protein Binding (%)	V_d (L/kg)	Route of metabolism	Active metabolite
Typical agents						
Chlorpromazine	2–4	8–35	90–95	7–20	CYP2D6	Yes (7-hydroxychlorpromazine, others)
Haloperidol	1–6	17–36	92	10–35	CYP2D6, CYP3A4	Yes (reduced haloperidol, others)
Fluphenazine	2–5	5–27 (13)	90–95	220	Hepatic	Yes (7-hydroxyfluphenazine, others)
Flupenthixol	2–6	22–36	90–93	12–24	Hepatic	No
Loxapine (PO) Loxapine (oral inhaled)	1–6 2 min	2–8 (3.4) 6–9 (7.6)	– 97	– –	CYP1A2, CYP2D6, CYP3A4 CYP1A2, CYP2D6, CYP3A4	Yes (amoxapine, 7-hydroxyloxapine, others) Yes (amoxapine, 7-hydroxyloxapine, others)
Perphenazine	2–6	8–21	90–95	10–35	CYP2D6	No
Pimozide	6–8	28–214	99	11–62	CYP3A4, CYP1A2	Yes
Thioridazine	2–4	9–36	99	18	CYP2D6	Yes (mesoridazine, sulforidazine, ring sulfoxide)
Thiothixene	1–3	12–36	90–95	–	Hepatic	No
Atypical agents						
Aripiprazole	3–5	31–146 (75)	>99	4.9	CYP2D6, CYP3A4	Yes (dehydroaripiprazole)s
Asenapine Clozapine	1 1–4	24 10–105 (16)	95 92–95	20–25 2–5	CYP1A2, hepatic CYP1A2, CYP3A4	Yes (norclozapine)
Olanzapine	5–6	20–70 (30)	93	10–20	CYP1A2, CYP2D6	No
Paliperidone Quetiapine	24 1–2	23 4–10 (7)	74 83	487 10	CYP2D6, CYP3A4 CYP3A4	No Yes (7-hydroxyquetiapine)
Remoxipride	1–2	4–7	80	0.7	Hepatic, renal	No
Risperidone	1–1.5	3–24 (3.6)	90	1–1.5	CYP2D6	Yes (9-hydroxyrisperidone)
Sertindole	10	24–200 (55–90)	>99	20–40	CYP3A4, CYP2D6	Yes (dehydrosertindole)
Sulpiride	3–6	5–14 (6.8)	40	2.7	Hepatic, renal	No
Ziprasidone	5	4–10 (NA)	>99	2	CYP3A4	No

Pharmacokinetic data obtained from Refs. [6, 8, 11, 12, 17, 50, 52]

NA data not available, $t_{1/2}$ half-life, t_{\max} time to peak plasma concentration, V_d volume of distribution

antidepressants) and vice versa. Certain antipsychotics (e.g., haloperidol, sertindole, thioridazine) may potentiate the QT prolongation produced by other cardioactive agents.

The addition of selective serotonin reuptake inhibitors (e.g., fluoxetine) to patients taking antipsychotics may precipitate EPS. When combined with antipsychotics, lithium may precipitate a toxic syndrome that resembles neuroleptic malignant syndrome [54].

The principal pharmacokinetic interactions that occur between antipsychotics and other drugs result from hepatic CYP P-450 enzyme induction and inhibition (Table 4) [50, 52, 54, 57]. Because many antipsychotics are metabolized by CYP2D6 and CYP1A2 enzymes, their clearance may be decreased significantly when coadministered with inhibitors of these enzymes, such as fluoxetine or paroxetine. Although these interactions occur frequently and often go unnoticed, they occasionally may result in clinically significant effects. Clozapine toxicity has been reported after coadministration with the CYP1A2 inhibitors cimetidine, erythromycin, and fluvoxamine [58–61]. Clarithromycin, a CYP3A4 and CYP1A2 inhibitor, can increase plasma concentrations of pimozide and can result in significant increases in the QT_c interval in human volunteers given a single dose of pimozide [62]. Selective serotonin reuptake inhibitors block CYP2D6 and may precipitate aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine, perphenazine, risperidone, quetiapine, and thioridazine toxicity [50, 52, 54, 57, 63]. In particular, selective serotonin reuptake inhibitors may precipitate thioridazine cardiotoxicity by increasing plasma concentrations of the unchanged parent drug and shunting metabolism to the cardioactive ring-sulfoxide metabolite. Conversely, the clearance of many antipsychotics may be increased significantly when coadministered with certain CYP isoenzyme inducers. Anticonvulsants (e.g., carbamazepine, phenytoin, phenobarbital) stimulate CYP3A4 and may decrease plasma concentrations of clozapine, olanzapine, and quetiapine. Cigarette smoking induces CYP1A2 and increases clearance of chlorpromazine, clozapine, fluphenazine, haloperidol, olanzapine, and numerous other antipsychotics [50]. Knowledge of

the receptor profile and pharmacokinetic parameters of a drug facilitates recognition and treatment of clinically significant drug interactions.

Clinical Presentation

Overdose

After accidental or intentional overdose, most patients remain asymptomatic or develop only mild toxicity [5]. Toxic effects are commonly an exaggeration of pharmacological effects. Clinical effects typically begin within 30–90 min of ingestion and include CNS and consequent respiratory depression, miosis or mydriasis, hypertension or orthostatic hypotension, sinus tachycardia, agitation, confusion, delirium, anticholinergic stigmata, myoclonic jerking, seizures, hyperthermia or hypothermia, cardiac conduction disturbances, and atrial and ventricular arrhythmias. Rarely, pulmonary edema may occur [64, 65]. Peak toxic effects are usually evident within 2–6 h, and resolution of serious toxicity usually occurs by 24–48 h. CNS depression is the most frequent clinical finding in overdose [3, 66–70]. CNS effects may range from lethargy, slurred speech, ataxia, and confusion in mild poisoning to deep coma with apnea and loss of brainstem and deep tendon reflexes in severe poisoning. Anticholinergic manifestations are frequent after overdoses with chlorpromazine, clozapine, mesoridazine, olanzapine, and thioridazine. Rarely, a post-injection delirium/sedation syndrome (PDSS) has been described shortly after injection of long-acting intramuscular olanzapine pamoate. It is characterized by sedation, confusion, slurred speech, ataxia, or coma, effects consistent with those demonstrated following olanzapine overdose. It is rare (observed in 0.07% of injections), occurs within seconds to 5 h (median onset time of 25 min) of injection, and is presumed to occur due to unintended intravascular injection of a portion of the olanzapine dose [71–73]. Sinus tachycardia is a frequent finding with chlorpromazine, clozapine, mesoridazine, olanzapine, quetiapine, risperidone, and thioridazine. Miosis is more likely to occur in severely poisoned patients; it has been

Table 4 Pharmacokinetic drug interactions of antipsychotics

Antipsychotic		Interacting drug(s)	Drug effect
<i>Atypical</i>	<i>Typical</i>		
Clozapine Olanzapine Quetiapine Ziprasidone	Loxapine Pimozide	Cimetidine Clarithromycin Erythromycin Fluvoxamine Fluoroquinolones Isoniazid Paroxetine	Elevated plasma antipsychotic concentrations from CYP1A2 inhibition
Clozapine Olanzapine Quetiapine Risperidone Sertindole	Chlorpromazine Fluphenazine Haloperidol Loxapine Perphenazine Thioridazine	Amiodarone Chloroquine Cimetidine Fluoxetine Paroxetine Propafenone Propoxyphene Propranolol Quinidine Risperidone Sertraline Tricyclic antidepressants	Elevated plasma antipsychotic concentrations from CYP2D6 inhibition
Clozapine Olanzapine Quetiapine Sertindole Ziprasidone	Haloperidol Pimozide	Amiodarone Antifungals (azoles) Cimetidine Clarithromycin Cyclosporine Erythromycin Fluoxetine Nefazodone Protease inhibitors Zafirlukast	Elevated plasma antipsychotic concentrations from CYP3A4 inhibition
Clozapine Olanzapine Quetiapine Sertindole Ziprasidone	Haloperidol Pimozide	Carbamazepine Dexamethasone Phenytoin Phenobarbital Primidone Rifampin	Decreased plasma antipsychotic concentrations from CYP3A4 induction
Clozapine Olanzapine Quetiapine Ziprasidone	Loxapine Pimozide	Carbamazepine Cigarettes Phenobarbital Phenytoin Rifampin Ritonavir Omeprazole	Decreased plasma antipsychotic concentrations from CYP1A2 induction
Clozapine Olanzapine Quetiapine Risperidone Sertindole	Chlorpromazine Fluphenazine Haloperidol Loxapine Perphenazine Thioridazine	Carbamazepine Phenobarbital Phenytoin Rifampin Ritonavir	Decreased plasma antipsychotic concentrations from CYP2D6 induction
Quetiapine	Chlorpromazine	Cigarettes	Decreased plasma antipsychotic concentrations
	Haloperidol		
	Fluphenazine		
	Haloperidol	Fluvoxamine	Elevated plasma antipsychotic concentrations
Quetiapine		Thioridazine	Decreased plasma antipsychotic concentrations

described in greater than 70% of patients poisoned with phenothiazines and has been noted frequently in patients poisoned with clozapine, olanzapine, and quetiapine (agents with greater alpha blockade relative to antimuscarinic activity) [67, 68, 70, 74]. Although acute EPS are often idiosyncratic reactions that follow therapeutic antipsychotic doses, these effects also may be dose related and have occurred after overdose with many antipsychotics [66, 75, 76]. EPS may be the presenting manifestation in a child after accidental antipsychotic poisoning [75–77]. Sialorrhea, a feature unique to clozapine, has been observed in 13% of patients poisoned with this agent [67, 75]. Acute pulmonary edema has been described after overdose of chlorpromazine, clozapine, haloperidol, and perphenazine [64, 65]. Rhabdomyolysis, myoglobinuria, and acute renal failure have occurred in patients with repetitive seizures after loxapine overdose [42, 78].

Antipsychotics have a relatively high therapeutic index, particularly when compared with certain other psychotropic medications, such as tricyclic antidepressants. Overdoses of antipsychotics are rarely fatal [5]. Death most frequently results from respiratory arrest (before medical intervention), arrhythmias, or aspiration-induced respiratory failure [6]. The toxic and lethal doses are highly variable and depend largely on agent identity, the presence of coingestants, age and habituation of the patient, and time to treatment. Children and nonhabituated adults are more sensitive to the toxic effects of these agents than individuals who have taken the agents on a long-term basis before an acute overdose. Higher-potency antipsychotics (e.g., fluphenazine, thiothixene, haloperidol) are safer after overdose than low-potency, multireceptor agents (e.g., chlorpromazine, thioridazine, clozapine). These latter agents are more likely to produce respiratory depression, seizures, and cardiovascular toxicity. The ingestion of a single tablet of chlorpromazine, clozapine, loxapine, mesoridazine, olanzapine, or thioridazine may cause serious toxicity in a toddler. Coma and respiratory arrest have been reported after the ingestion of 100 and 200 mg of clozapine, respectively, in toddlers [75]. Pronounced CNS sedation and anticholinergic delirium have

occurred after the ingestion of 7.5–15 mg of olanzapine in children [79, 80]. Death of an infant was reported after the ingestion of 350 mg of chlorpromazine [81]. Adult fatalities have been reported after the ingestions of 2 g of chlorpromazine and clozapine, 2.5 g of loxapine and mesoridazine, 600 mg of olanzapine, and 1.5 g of thioridazine [81–83]. Other patients have survived much larger ingestions.

Cardiovascular Toxicity

Orthostatic hypotension and sinus tachycardia are frequent clinical manifestations [3, 66, 67, 69, 70, 75, 76, 79–81]. Electrocardiogram (ECG) abnormalities include prolongation of the PR, QRS, and QT intervals; T-wave and U-wave abnormalities (blunting, notching, inversion); ST-segment depression; rightward axis of the terminal 40 msec of the QRS; atrioventricular, bundle-branch, fascicular, and intraventricular conduction disturbances; and supraventricular and ventricular tachyarrhythmias [3, 84–90]. These cardiac effects are observed most commonly with aliphatic and piperidine phenothiazines. Thioridazine is perhaps the most cardiotoxic agent. In one study of 299 patients with antipsychotic overdose, thioridazine had a significantly greater incidence of prolonged QT_c interval (60%), prolonged QRS interval (23%), and arrhythmia (5%) than chlorpromazine (34%, 15%, and 0%, respectively) and other antipsychotics (19%, 6%, and 0%, respectively) [3]. ECG changes and arrhythmias occasionally have been described after overdose of the newer atypical antipsychotics [66, 67, 91–96].

Repolarization abnormalities are the earliest and most common abnormalities noted on the ECG of patients with antipsychotic poisoning [84–86, 89]. Although observed with therapeutic doses, repolarization abnormalities are dose and concentration dependent and more prevalent in overdose. Prolongation of the QT interval has been observed with aliphatic and piperidine phenothiazines, droperidol, haloperidol, loxapine, pimozide, quetiapine, sertindole, risperidone, and ziprasidone [3, 42, 92, 94–102]. Therapeutic

doses of sertindole have been associated with a mean QT_c interval increase of 21 msec in one premarketing trial and a QT_c interval greater than 500 msec in 50% of patients in another trial [91, 103]. The manufacturer withdrew its new drug application in the United States due to fear of polymorphic ventricular tachycardia from this agent. Torsades de pointes has been described after overdose with droperidol, haloperidol, mesoridazine, pimozide, sertindole, and thioridazine [104]. This complication is particularly important to the intensivist who uses haloperidol to sedate agitated patients in the intensive care unit. In one study, torsades de pointes occurred in 3.6% of hospitalized critically ill patients who received intravenous haloperidol for sedation [141]. The incidence of torsades de pointes was increased significantly when greater than 35 mg of haloperidol was administered in less than 6 h (64%) and when the QT_c interval was greater than 500 msec (84%). No patient who had a QT_c interval less than 500 msec developed torsades de pointes.

Ventricular tachyarrhythmias may underlie sudden death that has been associated with therapeutic doses of phenothiazines [105–107]. Thioridazine is likely the most dangerous. In one case series of 49 deaths associated with therapeutic doses of antipsychotics, more than half of the cases were associated with thioridazine [106].

Seizures

Although all antipsychotics are considered to lower the seizure threshold and produce dose-related EEG abnormalities, seizures occur uncommonly [38, 39]. Generalized and partial seizures have been reported, but generalized major motor seizures predominate. Seizures are most likely to occur in patients with one or more risk factors, at higher therapeutic doses, and after overdose with certain agents (e.g., chlorpromazine, clozapine, loxapine) [38–42]. Risk factors for seizures include organic brain disease, epilepsy, a history of electroconvulsive therapy, abnormal baseline EEG, polypharmacy, large drug doses, and initiation or rapid dose escalation of antipsychotics [38,

41]. Seizures have been reported to occur in 2.4% of patients taking clozapine and 1.2% of patients taking phenothiazines [38, 40]. The incidence of seizures rises, however, to 4.4% for patients taking greater than 600 mg of clozapine daily and 9% for patients taking greater than 1 g of chlorpromazine daily [39, 40]. Seizures are unlikely to occur when certain traditional agents (e.g., fluphenazine, haloperidol, molindone, pimozide) and newer atypical agents are used; these agents have a seizure incidence comparable to placebo (<1%) during therapeutic dosing [38]. Overall the incidence of seizures is low after antipsychotic overdose. In one study of 299 patients with antipsychotic overdose, the incidence of seizure was only 1% [3]. For clozapine and loxapine, however, the risk is much higher. Seizures have occurred in 10% of clozapine overdoses reported in the literature [67]. There is an estimated 10% cumulative risk of seizure after 3.8 years of therapeutic use. The risk of seizures with clozapine appears to be dose dependent and is greatest with high-dose therapy (greater than 600 mg/day) [40]. In one series of ten patients with loxapine overdose, seizures occurred in 6 (60%) and were often multiple [42].

Hepatotoxicity

Asymptomatic elevations of hepatic transaminases have occurred during treatment with most antipsychotics [108, 109]. These abnormalities commonly are noted during the first 3 months of therapy and are self-limiting. The incidence is variable according to agent; incidences of 37%, 20%, and 16% have been described for clozapine, chlorpromazine, and haloperidol, respectively [108, 109]. Clinically significant hepatotoxicity occurs in a small proportion of patients. Hepatotoxic reactions are idiosyncratic and not observed with acute antipsychotic overdose. Chlorpromazine carries an incidence of overt liver disease of 0.1–1% [108, 110]. Cholestatic jaundice is the characteristic pattern of injury. In support of a hypersensitivity mechanism, the injury most often occurs within 1 month of therapy onset, is characterized by a rash and eosinophilia in most cases, and is not dose related [108, 111]. Cholestatic jaundice also has been

associated rarely with haloperidol and risperidone therapy. Chlorpromazine and clozapine also may cause direct hepatocyte cytotoxicity [108].

Blood Dyscrasias

Agranulocytosis (absolute neutrophil count $<500/\text{mm}^3$ [3]) is a life-threatening idiosyncratic reaction that rarely may occur with phenothiazine and clozapine therapy. It occurs in approximately 1 in 10,000 patients receiving chlorpromazine, usually within the first 8–12 weeks of treatment [112, 113]. The incidence is higher with clozapine (1–2%) and, as for chlorpromazine, usually occurs within the first 3 months of therapy [114, 115]. Mortality rates range from 30% to 85% when agranulocytosis occurs [115]. The risk of clozapine-associated agranulocytosis is minimized by weekly white blood cell count monitoring. With regular monitoring, the incidence (cumulative risk 0.8% at 1 year) of and mortality (4%) from agranulocytosis have been reduced [114, 115]. The mechanism of clozapine-associated agranulocytosis has not been determined but is likely to result from immune-mediated and direct drug-induced myelotoxicity [116]. Granulocyte colony-stimulating factor has shortened recovery time significantly when administered to patients with antipsychotic-associated granulocytopenia [117].

Extrapyramidal Syndromes

EPS are a group of sustained-movement disorders that occur in approximately 30% of patients treated with antipsychotics and often lead to medication noncompliance, inadequate treatment, and an exacerbation of the symptoms of schizophrenia [118]. New-generation atypical antipsychotics are associated with a significantly lower incidence and severity of EPS; rates not significantly different from placebo have been found with clozapine, olanzapine, quetiapine, and sertindole [10, 103, 119]. EPS may occur within hours to days (e.g., acute DRs, akathisia), days to months (e.g., akathisia, parkinsonism), or months to years

(e.g., TD) from the initiation of therapy and may be reversible or irreversible. The neuroleptic malignant syndrome, a severe EPS, rarely may occur during treatment and is discussed in the chapter devoted to that syndrome.

Acute DRs are reversible motor disturbances that occur soon after initiation of antipsychotic therapy or after an increase in dose. Of acute DRs, 50% occur within 48 h, and 90% occur within 5 days of antipsychotic treatment [120, 121]. Peak incidence occurs when antipsychotic concentrations are declining in the serum. Acute DRs are characterized by sustained muscle contractions resulting in abnormal posturing of the eyes, face, tongue, jaw, neck, back, abdomen, and pelvis. Clinical manifestations include facial grimacing, trismus, oculogyric crisis, blepharospasm, tongue protrusion, buccolingual dyskinesias, dysarthria, swallowing difficulties, retrocollis, torticollis, opisthotonos, tortipelvis, gait disturbance, and, rarely, stridor from laryngospasm. Impaired respiration caused by dystonia of laryngeal and pharyngeal muscles rarely may result in death [122]. Acute DRs are characterized by a patient who is awake and alert. The overall prevalence of acute DRs is approximately 2%, but the incidence varies according to individual susceptibility (presence of risk factors), agent identity, dose, and duration of therapy [118]. Patient-related risk factors include male sex, young age (5–45 years old), a personal or family history of acute dystonia, and recent alcohol or cocaine use [118–121, 142, 144]. High-potency D_2 -receptor antagonists cause acute DRs more frequently than do low-potency agents. Acute DRs have been reported to occur in 25% of patients treated with intramuscular fluphenazine, 16% of patients treated with haloperidol, 8% of patients taking thiothixene, 3.5% of patients taking chlorpromazine, and 1% or less of patients treated with atypical agents [10, 43, 119–121]. Clozapine is the only known atypical antipsychotic that does not induce acute dystonia. Although previously considered an idiosyncratic reaction, acute DRs are more likely to occur with larger drug doses and frequently have been described after acute antipsychotic overdose [66, 75–77].

Akathisia is the subjective sensation of motor restlessness that occurs within hours to days of the initiation of antipsychotic therapy [10, 119]. Akathisia is characterized by a compelling need to move and the inability to maintain a stable position or posture for several minutes. Patients may be irritable and anxious; have difficulty concentrating; and often constantly move their legs, rock, pace, or shift their weight from foot to foot. Vital signs are normal. Akathisia occurs in approximately 30% of patients taking antipsychotics [10, 119]. In one study, akathisia developed in 44% of patients within 1 h after taking a single 10-mg intravenous dose of prochlorperazine [123]. Akathisia occurs more commonly in women and is more prevalent with high-potency antipsychotics.

Parkinsonism is a reversible, intermediate-stage extrapyramidal syndrome that often occurs 5–30 days after starting antipsychotic therapy [10, 119]. In a study of 1559 patients treated with antipsychotics, parkinsonism was noted in 66% of patients [118]. Parkinsonism is characterized by bradykinesia (slow movement) or akinesia, masked facies, muscular rigidity (e.g., cogwheeling), tremor (e.g., pill rolling), gait and postural instability, bradyphrenia (slow thinking), and cognitive impairment. The risk of drug-induced parkinsonism is greatest in the elderly, patients with organic brain injury, patients taking high-potency agents, and patients receiving long-term antipsychotic therapy [118].

TD is a late-appearing, potentially irreversible movement disorder that occurs in approximately 20% of patients who receive long-term antipsychotic treatment and 50% of high-risk individuals (e.g., the elderly) [10, 119]. With conventional antipsychotic therapy, an annual incidence of 3–5% for TD has been reported. Atypical antipsychotics have a lower propensity to cause TD, with an annual incidence of less than 2% [10, 119]. It has been associated with all antipsychotics except clozapine. TD is characterized by stereotyped, involuntary, repetitive, painless movements of the face, eyelids, mouth, tongue, extremities, or trunk. Clinically, patients show chewing, tongue protrusion, lip smacking and puckering, rapid eye blinking, facial

grimacing, grunting, and, occasionally, slow choreoathetosis of the arms and legs. Orofacial movements are the earliest and most frequent clinical manifestations. The risk of developing TD is greatest in the elderly, patients with organic brain injury, patients taking high-potency agents, and patients receiving long-term antipsychotic therapy [124].

Diagnosis

The diagnosis of antipsychotic poisoning is based on a history of ingestion; suggestive physical findings; and corroborating evidence from ECG, laboratory, and other adjunctive tests. A history that suggests poisoning includes report of antipsychotic exposure by the patient or an acquaintance, a medication list that includes an antipsychotic, known history of psychosis or treatment with an antipsychotic, and the discovery of an antipsychotic near the patient before or on hospital arrival. The presence of CNS or respiratory depression, anticholinergic stigmata (see ► Chap. 23, “Anticholinergic Syndrome”), miosis, sinus tachycardia, hypotension, and EPS on physical examination suggests antipsychotic poisoning. An ECG that shows repolarization abnormalities (e.g., nonspecific ST-T changes, QT interval prolongation) with or without sinus tachycardia is consistent with antipsychotic exposure. An abdominal radiograph may show radiopaque densities with phenothiazine and butyrophenone poisoning. The absence of this finding, however, does not rule out poisoning with these agents. Chlorpromazine, mesoridazine, quetiapine, and thioridazine often produce false-positive results for tricyclic antidepressants on immunoassay screens. When necessary, toxicological screening by gas chromatography–mass spectrometry or high-performance liquid chromatography may be used to confirm the presence of some antipsychotics. Quantitative drug concentrations may be obtained but are not helpful in guiding therapy; they generally are not available in a timely manner and do not correlate well with clinical toxicity [49, 50, 52].

Differential Diagnosis

Poisoning by antipsychotics may mimic the neurological and cardiovascular effects produced by alcohols, antiarrhythmics, anticholinergics, antiepileptics, antihistamines, barbiturates, cyclic antidepressants, opiates, and sedative-hypnotics. Specifically, mesoridazine and thioridazine toxicity may be clinically indistinguishable from that produced by tricyclic antidepressants. CNS infection, occult trauma, cerebrovascular accident, and metabolic abnormalities always should be considered in the differential diagnosis and ruled out by appropriate testing. Acute dystonic reactions must be differentiated from alkalosis/hypocarbica; anticholinergic, antiepileptic, and strychnine poisoning; cerebrovascular accident; CNS and oropharyngeal infections; conversion disorder; hypocalcemia; hypomagnesemia; and joint dislocations. In addition, numerous drugs other than antipsychotics may produce acute DRs. Akathisia often may be misinterpreted as acute anxiety or agitation. Parkinsonism produced by antipsychotics may be indistinguishable from that produced by cerebrovascular accidents; CNS infection and trauma; and poisoning by carbon disulfide, carbon monoxide, cyanide, manganese, methanol, metoclopramide, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and reserpine.

Treatment

Overdose

Treatment for antipsychotic overdose is primarily supportive. Endotracheal intubation and assisted ventilation should be instituted for patients with significant CNS or respiratory depression. All patients should have an intravenous line established, an ECG performed, and continuous monitoring of cardiac and respiratory function. Serum glucose measurement and administration of naloxone, oxygen, or thiamine should be considered in patients with coma or seizures. Patients with mild-to-moderate CNS depression who do not initially require endotracheal intubation should be placed in the lateral decubitus, head-

down position to minimize the risk of aspiration (III). Arterial blood gas; urinalysis; and measurements of serum creatine phosphokinase, calcium, and magnesium additionally should be obtained for patients with seizures, hyperthermia, or severe toxicity. A complete blood count should be obtained for any patient who presents with fever while taking clozapine or chlorpromazine. Serial evaluations of mental status and vital signs are important to determine the course of poisoning and the need for further testing and intervention.

Hypotension should be treated initially with Trendelenburg's position and rapid intravenous crystalloid infusion (i.e., 10–40 mL/kg normal saline or lactated Ringer's solution). Refractory hypotension should be treated with inotropes or vasopressors. Preferred first-line vasopressors include either norepinephrine or epinephrine infusions, whose direct alpha-adrenergic agonist effects can overcome the alpha-adrenergic antagonist effects of many antipsychotics (III). Central venous and peripheral arterial monitoring may be needed for patients who require significant doses of pressors to maintain perfusion.

Indications for ICU Admission in Antipsychotic Poisoning

Significant central nervous system depression (unresponsive to verbal stimuli)

Significant central nervous system agitation (requiring chemical or physical restraint)

Respiratory depression ($PCO_2 > 45$ mmHg)

Hypoxia or respiratory failure (adult respiratory distress syndrome)

Need for endotracheal intubation

Hypotension (systolic blood pressure ≤ 80 mmHg) not immediately responsive to crystalloid

Multiple seizures with altered mental status

Nonsinus cardiac rhythm

Acute overdose with $QRS > 120$ msec or $QT_c > 500$ msec

Second-degree or third-degree atrioventricular block associated with poisoning

(continued)

Need for invasive hemodynamic monitoring (e.g., pulmonary artery catheter, arterial line)

Extremes of temperature (e.g., $\geq 40^{\circ}\text{C}$ or $\leq 32^{\circ}\text{C}$)

Significant acid–base or metabolic disturbances requiring close monitoring or aggressive correction

Initial diagnosis of neuroleptic malignant syndrome

Adapted from Brett et al. [125].

Sinus tachycardia does not require specific treatment. Supraventricular tachycardias may be treated according to standard advanced cardiac life-support guidelines. Ventricular tachyarrhythmias may be treated with standard doses of lidocaine and electrical cardioversion, depending on the hemodynamic stability of the patient. Sodium bicarbonate (1–2 mEq/L intravenous boluses) is indicated as first-line therapy for ventricular or wide-complex tachycardias associated with mesoridazine, thioridazine, and, rarely, other agents (III). Type IA (e.g., procainamide), type IC (e.g., propafenone), and type III (e.g., amiodarone) antiarrhythmic agents are not recommended and are potentially dangerous; these agents may impair cardiac conduction further. Torsades de pointes should be treated by standard methods (see ► Chap. 21, “Cardiac Conduction and Rate Disturbances”) [126–129].

Seizures generally are treated best with benzodiazepines (e.g., diazepam, lorazepam) followed by barbiturates (e.g., phenobarbital), as necessary. The efficacy and safety of phenytoin has not been established for antipsychotic-associated seizures and is not recommended (see ► Chap. 20, “Toxicant-Induced Seizures” for a fuller discussion of this point). Patients with recurrent seizures (e.g., loxapine poisoning) rarely may require neuromuscular paralysis and endotracheal intubation to prevent rhabdomyolysis and myoglobinuric renal failure. Continuous EEG monitoring is required for these patients to determine the efficacy of antiepileptic therapy (see ► Chap. 20, “Toxicant-Induced Seizures”).

Physostigmine may be used to control agitation and reverse delirium in patients who have

significant anticholinergic toxicity (II-3). Its duration of action is less than 1 h, however, so repeat dosing may be necessary. Physostigmine is generally safe. Caution has been suggested if the ECG shows cardiac conduction delays; [130] however, this should not be considered an absolute contraindication. It has been used successfully to reverse the anticholinergic syndrome associated with chlorpromazine, clozapine, olanzapine, and thioridazine [130, 131]. Physostigmine should be given slowly intravenously (0.02 mg/kg in children or 2 mg in adults) over 2 min (see ► Chap. 161, “Physostigmine” for a full discussion of the clinical pharmacology of this antidote). Physostigmine-treated patients should be observed closely for at least 15 min for evidence of cholinergic excess. Alternatively, agitated behavior associated with the anticholinergic effects of antipsychotics may be treated with benzodiazepines. Of note, the anticholinergic effects of these agents manifest early and can be prolonged. Patients may demonstrate anticholinergic delirium when they emerge from coma following resolution or other neuroreceptor effects that potentiated early coma in the overdose patient.

Activated charcoal adsorbs antipsychotic agents effectively; however, its efficacy in altering the clinical course or outcome in these patients is unknown. Because patients ingesting these agents may develop a decrease in mental status or seizures, activated charcoal should be used cautiously, if at all. It is unlikely to alter drug absorption if given after an hour post ingestion. Gastric lavage is not recommended (see ► Chap. 3, “Therapeutic Approach to the Critically Poisoned Patient”). Multiple-dose activated charcoal has no proven clinical benefit for antipsychotic poisoning and is not recommended. Because antipsychotics have large volumes of distribution, have high protein binding, and are metabolized predominantly in the liver, their elimination is not enhanced by hemodialysis, hemoperfusion, forced diuresis, or urinary alkalinization techniques [132–134]. Urinary alkalinization is reserved for patients with rhabdomyolysis that may result from antipsychotic-associated seizures or hyperthermia.

Acute Dystonic Reactions

Treatment of acute dystonic reactions (DRs) may rarely require supplemental oxygen and assisted ventilation for patients with respiratory distress from laryngeal and pharyngeal dystonia. Pharmacological therapy with a parenteral anticholinergic dopaminergic (antiparkinsonian) agent is highly effective and usually provides relief within 10 min of administration [143]. Benztropine, which is a potent inhibitor of dopamine uptake (0.02–0.05 mg/kg) or diphenhydramine (1 mg/kg), may be given intramuscularly or slowly intravenously over 2 min. Repeat dosing may be necessary for complete resolution of acute DRs. Resistant cases may respond to diazepam (0.1 mg/kg intravenously) or lorazepam (0.05–0.1 mg/kg intravenously). A search for other underlying illnesses should be sought whenever acute DRs are resistant to antiparkinsonian treatment. After parenteral therapy, an oral antiparkinsonian agent should be administered for 48–72 h to prevent acute DR recurrence [135]. When continued antipsychotic therapy is necessary, patients also should be maintained on an antiparkinsonian agent or switched to an antipsychotic with lower EPS liability [119].

Akathisia

Although recommended as initial therapy, anticholinergic/antiparkinsonian agents often are ineffective for the treatment of akathisia [119]. These agents seem to be effective, however, when administered prophylactically. Pretreatment with diphenhydramine significantly decreases the incidence of akathisia that follows a single therapeutic dose of prochlorperazine [136]. Treatment with a benzodiazepine, propranolol (20 mg orally twice daily), or clonidine (0.1 mg orally three times daily) may be beneficial [137, 138]. When continued antipsychotic therapy is necessary, akathisia may be minimized by reducing the antipsychotic dose, adding an anticholinergic agent, or switching to an antipsychotic with lower EPS liability [119].

Parkinsonism

Parkinsonism effects may be minimized by using low doses of traditional antipsychotics, switching to an atypical agent, or adding an anticholinergic/antiparkinsonian agent (e.g., benztropine, biperiden, diphenhydramine, or trihexyphenidyl) or an agent that enhances dopaminergic activity (e.g., amantadine) [119].

Tardive Dyskinesia

Tardive dyskinesia (TD) is often irreversible and has no consistently effective treatment. The best treatment for TD is to minimize its risk of occurrence. The best preventive practice is to use the minimal effective dose of an antipsychotic for long-term therapy and to discontinue treatment when it is no longer medically necessary [119]. An alternative option is to treat patients with atypical agents, which have a lower propensity to induce TD with long-term treatment. Some atypical agents are antidyskinetic (e.g., clozapine, olanzapine, quetiapine, risperidone); the severity of TD is reduced after a change in regimen to these agents from a traditional antipsychotic [119].

Disposition

For all antipsychotics, signs and symptoms develop rapidly (within 4 h) after acute ingestion. After an initial treatment and observation period in the emergency department, clinical reassessment can reliably identify patients who are at high risk for complications and require intensive care and patients who may be medically discharged. Most patients with pure antipsychotic overdose develop only mild toxicity and are medically safe for psychiatric evaluation and disposition after an observation period of 4–6 h in the emergency department. Patients who manifest persistent mild toxicity (e.g., ataxia, lethargy, sinus tachycardia, repolarization abnormalities on ECG) should be admitted to a monitored bed for continued observation. Patients with moderate

to severe toxicity (e.g., moderate-to-severe CNS or respiratory depression, hypotension, seizures, marked agitation, acid–base disturbances, arrhythmias other than mild sinus tachycardia, and cardiac conduction disturbances) should be admitted to an intensive care unit for aggressive supportive care. Admission to a monitored bed also is recommended for patients who take phenothiazines on a long-term basis and have incidental ECG abnormalities (e.g., prolonged QRS or QT_c intervals); these patients are considered at risk for sudden phenothiazine death. When the appropriate disposition of a patient is in question, consultation with a medical toxicologist or poison control center is recommended.

Special Populations

Patients with Renal Impairment

Because most antipsychotics are metabolized extensively in the liver before excretion, they are not affected significantly by changes in renal function. Normally, small amounts (1–3%) of a parent drug are excreted unchanged by the kidney [49]. Aside from the benzamide derivatives (e.g., remoxipride, sulpiride, and risperidone), these drugs commonly do not require dose alteration for patients with renal impairment [50]. Even when clearance is prolonged due to renal dysfunction, clinical toxicity is unlikely to be lengthened appreciably after overdose in this patient population.

Patients with Hepatic Impairment

Most patients with hepatic disease (e.g., cirrhosis, hepatitis) and conditions that decrease hepatic blood flow (e.g., congestive heart failure) have decreased antipsychotic clearance from plasma and require dose adjustment with long-term therapy [50]. After acute overdose, antipsychotic clearance may be prolonged but is unlikely to delay clinical recovery significantly.

Infants, Children, and Elderly Patients

Compared with normal adults, fetuses, infants, and elderly patients have a diminished capacity to metabolize and eliminate antipsychotics [6]. Children commonly metabolize these drugs more rapidly than adults. Compared with normal adults, plasma clearances of antipsychotics are reduced by 30–50% (elimination half-lives doubled) in the elderly [49, 50]. In general, elderly individuals are more sensitive than young adults to the effects of antipsychotics; they have decreased CNS, hepatic, renal, and cardiac function and have a greater tendency to develop anticholinergic stigmata, EPS (e.g., parkinsonism, TD), sedation, confusion, cardiac conduction abnormalities, and postural hypotension from these agents. Elderly patients ≥ 65 years old treated with antipsychotic agents for dementia-related psychosis are at greater risk for sudden death. The United States Food and Drug Administration has issued a black box warning for all antipsychotic agents used in this patient population. The relative risk of mortality with atypical antipsychotics is 1.6–1.7 times as compared to placebo; the relative mortality risk is even higher with traditional antipsychotic agent use [139, 140].

The safety and efficacy of most antipsychotics have not been established in pediatric patients. Similar to elderly patients, children may be more sensitive than normal adults to the CNS and respiratory depressant effects of these drugs. In addition, children are more likely to develop an acute DR than other age-groups.

Patients of Different Races and Ethnic Groups

Genetic polymorphisms of hepatic CYP isoenzymes often are associated with race or ethnic group variations. These polymorphisms result in large interindividual differences in antipsychotic steady-state plasma concentrations and clearance [51]. CYP isoenzyme differences become clinically important with long-term dosing or when

other CYP isoenzyme substrates are ingested concomitantly. Genetic polymorphisms of CYP2D6 may result in different concentrations of aripiprazole and thioridazine despite similar therapeutic doses in otherwise similar individuals [51]. Poor metabolizers at CYP2D6 are at greater risk for cardiovascular side effects from thioridazine and its metabolite mesoridazine. These individuals attain much higher plasma concentrations of unchanged thioridazine and the cardioactive ring sulfoxide metabolite [52]. The latter metabolite is CYP2D6 independent and preferentially formed when CYP2D6 activity is low.

Pregnant and Breast-Feeding Patients

There are no adequate, well-controlled studies in pregnant women that establish the safety of antipsychotics for the developing fetus. Most antipsychotics should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Because most antipsychotics are secreted in breast milk and their safety to infants is not established, breast-feeding is not recommended for women taking antipsychotics.

Key Points in Antipsychotic Poisoning

1. Toxic effects are often an exaggeration of pharmacological effects.
2. For all antipsychotics, clinical effects occur rapidly (within a few hours) of acute ingestion.
3. The presence of central nervous system and respiratory depression, anticholinergic toxicity, miosis, sinus tachycardia, hypotension, and extrapyramidal side effects on physical examination should suggest antipsychotic poisoning.
4. Timely supportive care should prevent death in most patients with antipsychotic poisoning.
5. An electrocardiogram should be obtained for all symptomatic patients with

antipsychotic poisoning and cardiac monitoring instituted.

6. After an acute antipsychotic overdose, patients may be medically discharged if they remain asymptomatic after an observation period of 4–6 h; symptomatic patients should be observed until they are alert and electrocardiogram abnormalities resolve.

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Prescription anxiolytic/sedative-hypnotic (ASH) drug toxicity, and withdrawal, is commonly encountered by health care providers in many clinical settings. Although the pharmacokinetic and epidemiologic characteristics of the agents involved have changed over several decades, the essential features of ASH poisoning (and withdrawal) remain unchanged since the introduction of chloral hydrate (CH) in the mid-nineteenth century. Today, ASH drugs are ubiquitous and used for numerous indications by inducing anxiolysis and sedation that result in drowsiness or sleep. Overall, this drug group consists of benzodiazepine (e.g., diazepam) and benzodiazepine-like drugs (e.g., zolpidem), barbiturate (e.g., butalbital) and barbiturate-like drugs (e.g., meprobamate), and drugs (e.g., dexmedetomidine) with different mechanisms of action. The toxic effects of barbiturates are discussed in detail in another chapter (► Chap. 46, “Barbiturates”). Other agents, such as dexmedetomidine, are discussed in greater detail elsewhere (see ► Chap. 35, “Alpha-2 Adrenergic and Imidazoline Receptor Agonists: Clonidine, Dexmedetomidine, and Related Antihypertensives, Decongestants, and Sedatives”).

Prescription drugs with ASH activity possess significant abuse potential. The objectives of intentional misuse include achievement of a euphoric state, attenuation of undesirable side-effects of other drugs (e.g., methamphetamines), relief of withdrawal symptoms, and criminal acts (e.g., sexual assault) after surreptitious administration. Evidence is gathering that ASH agents, particularly when co-prescribed with opioid analgesics, convey greater risk of death compared to population matched controls [1, 2]. As a result of the

development of pharmacodynamic tolerance, chronic abuse of these agents causes a characteristic withdrawal syndrome after abrupt discontinuation. The resulting effects are very similar to the withdrawal syndrome associated with ethanol (see ► Chap. 27, “Withdrawal Syndromes”).

Benzodiazepines are one of the most widely prescribed class of drugs worldwide. Many other prescription ASH, including chloral hydrate (‘Mickey Finn’), glutethimide (Doriden®), (Current and past trade names of these agents as marketed in the United States are given. These may be different in other countries) ethchlorvynol (Placidyl®), and methaqualone (Quaalude®) are historically important sources of abuse and poisoning. There has been a marked decline in the reported exposures to these older agents in the United States from 7.5% to <1% of the ASH category over 30 years [3, 4]. However, some of these medications remain available in non-US markets and, because of their limited use, are briefly summarized in this chapter.

Biochemistry and Clinical Pharmacology of Benzodiazepines

The structures of representative sedative-hypnotic drugs are shown in Fig. 1. Except for clorazepate, whose bioavailability requires gastric decarboxylation to nordiazepam, benzodiazepines are well absorbed following oral administration [5]. Other relevant pharmacokinetic properties of benzodiazepines, including a high degree of protein binding (60–95%), are summarized in Table 1. The

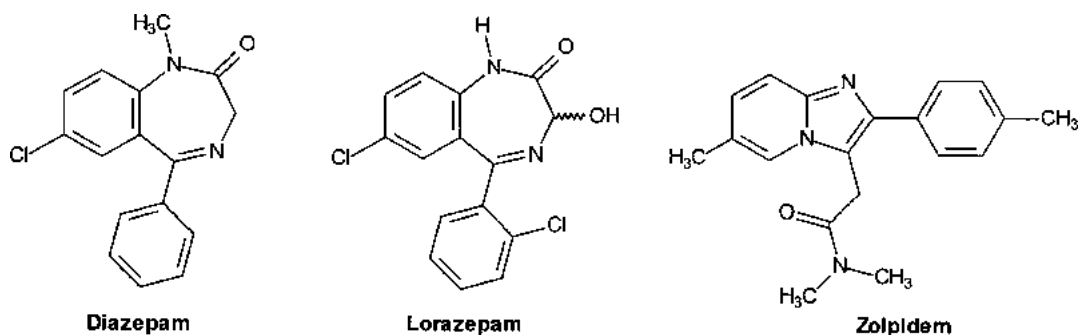


Fig. 1 Chemical structures of representative benzodiazepine and benzodiazepine-like drugs

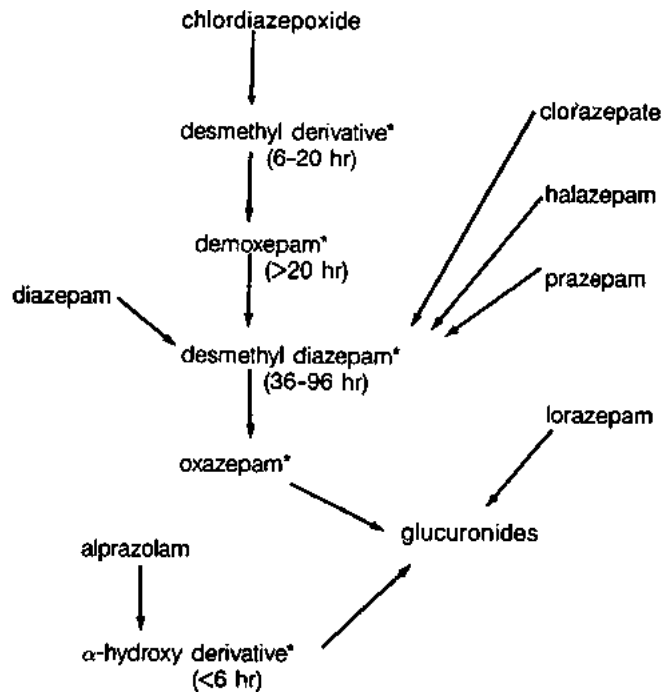
Table 1 Benzodiazepines and Benzodiazepine-like drugs

Generic drug (trade name)	Estimated equivalency (mg)	Half-life parent compound (hr)	Estimated duration (hr) ^a
Onset: 2–3 h			
Halazepam (Paxipam)	20	14–15	Long ^b
Oxazepam (Serax)	20	3–25	Intermediate
Prazepam (Centrax)	20	Prodrug	Long ^b
Temazepam (Restoril)	15	5–20	Intermediate
Zolpidem (Ambien)	10	1.4–4.5	Short
Onset: 1–2 h			
Alprazolam (Xanax)	0.75	6.3–26.9	Intermediate
Chlordiazepoxide (Librium*)	25	5–48	Long ^b
Clonazepam (Klonopin)	2	18–50	Long ^b
Estazolam (ProSom)	2	10–34.6	Intermediate
Flurazepam (Dalmane)	15	Prodrug	Long ^b
Lorazepam (Ativan)	1	10–20	Intermediate
Quazepam (Doral)	15	25–53	Long ^b
Triazolam (Halcion)	0.375	1.5–5.5	Short
Onset: <1 h			
Clorazepate (Tranxene)	15	Prodrug	Long ^b
Diazepam (Valium)	10	20–80	Long ^b
Midazolam (Versed)	0.035	1.5–12	Intermediate
Flunitrazepam (Rohypnol)	1	10–30	Intermediate

^aArbitrarily based on mean half-life of parent compound: half-life <4 h = short; half-life ≤24 h = intermediate; half-life >24 h = long duration

^bDue to presence of active metabolite with a long half-life

Fig. 2 Metabolism of selected benzodiazepines
(From Rech [127])



related metabolic pathways of select benzodiazepines are shown in Fig. 2.

Unless occurring in combination with other central nervous system (CNS) depressants, benzodiazepine overdose, even in large amounts, rarely results in life-threatening respiratory or hemodynamic manifestations. The wide margin of safety of benzodiazepines has made them appealing for the management of anxiety disorders, agitation, and substance abuse and withdrawal. Relatively newer additions to the market (zolpidem, zalepon and eszopiclone) also mediate their effects through CNS benzodiazepine receptors [6]. Their clinical pharmacology and toxicology are similar to those of benzodiazepine drugs.

Benzodiazepines primarily undergo hepatic metabolism with some drugs (e.g., chlordiazepoxide and diazepam) having active metabolites with slower elimination than their parent compound. Pre-existing liver disease or concurrent use of agents that inhibit hepatic metabolism (e.g., CYP3A4 inhibitors, such as selected macrolide antibiotics) may result in prolonged clinical effects.

Pathophysiology of Toxic Effects

The sedative and anticonvulsant effects of benzodiazepine (like) drugs result from activity on two CNS inhibitory neurotransmitters. Agonism of γ -aminobutyric acid (GABA) neuronal receptors enhances the binding of GABA to postsynaptic chloride (GABA_A) channels (Fig. 3). Benzodiazepine compounds also inhibit the presynaptic uptake of adenosine, which exerts a negative modulatory effect on the presynaptic release of glutamate, an excitatory neurotransmitter in the CNS [7]. These actions result in an increased postsynaptic influx of negatively charged ions (Cl^-), and decreased glutamate-stimulated postsynaptic influx of positively charged ions (Na^+ and Ca^{2+}). The end effect is widespread postsynaptic neuronal hyperpolarization and suppression of electrical impulse propagation.

Clinical Presentation and Life-Threatening Complications

The clinical manifestations of acute and chronic benzodiazepine overdose range from mildly depressed sensorium to coma. Impaired psychomotor skill, somnolence, dysarthria, nystagmus, ataxia, hyporeflexia, and respiratory depression are common features of intoxication [5, 8]. In general, the severity and duration of these effects increase with age, which is explained on the basis of age-related changes in drug disposition and neuropharmacologic actions (see ► Chap. 8, “Geriatric Poisoning”). If respiratory failure occurs, it suggests the presence of another CNS depressant agent or underlying disease (e.g., chronic obstructive pulmonary disease).

Retrograde and anterograde amnesia occur after therapeutic and supratherapeutic doses of benzodiazepines, which are advantageous during uncomfortable medical procedures. The acute ingestion of benzodiazepines will raise the seizure threshold and offer prophylactic anticonvulsant effects, particularly after an overdose involving a proconvulsant agent (e.g., bupropion).

Anxiolytic/Sedative-Hypnotic Drug Withdrawal

Long-term administration of any ASH (or GABA-agonist) medication may result in pharmacodynamic tolerance and a potentially life-threatening withdrawal syndrome if the agent(s) is abruptly stopped. Tolerance to these agents is due to the down-regulation of neuroinhibitory cell membrane receptor expression or functional activity [9]. The abrupt cessation triggers a sudden imbalance in CNS excitatory neurotransmission. The clinical result of this CNS hyperactivity is similar with most of these agents except in terms of the timing of onset (based on the half-life of the involved drug) and intensity (based on the amount used on a regular basis).

The temporal course of ASH withdrawal depends on the elimination rate of the parent

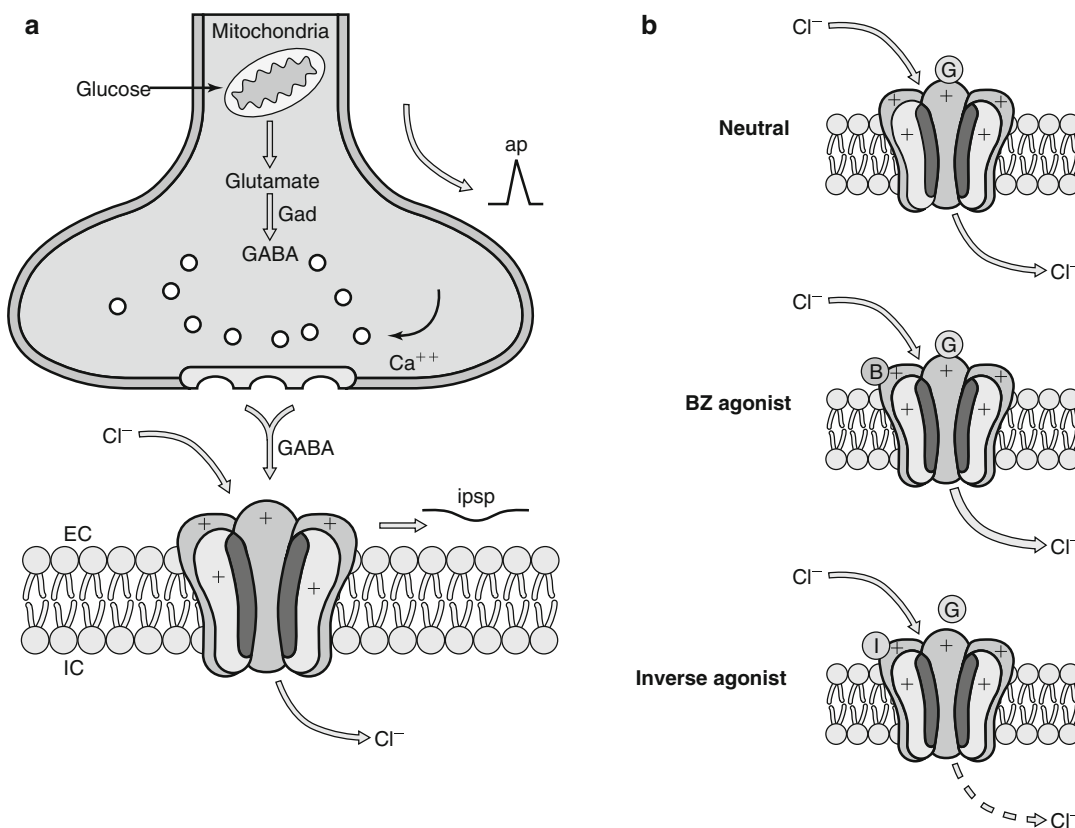


Fig. 3 Idealized model of γ -aminobutyric acid (GABA)-benzodiazepine (BZ)-chloride (Cl^-) channel at axosomatic (postsynaptic) inhibitory synapses. **a** Presynaptic and postsynaptic elements. *ap* action potential, *Gad* glutamic acid decarboxylase, *EC* extracellular, *IC* intracellular, *ipsp* inhibitory postsynaptic potential. **b** GABA-BZ receptor interactions influencing permeability of chloride channels.

Neutral: GABA receptor binds GABA (G) with moderate affinity in the absence of BZ ligand. BZ agonist: Direct BZ agonist (B) enhances GABA affinity for its receptor, resulting in maximal chloride permeability. Inverse agonist: Inverse agonist bound to BZ receptor results in poor GABA affinity and markedly reduced chloride permeability (From Rech [127])

drug involved and whether it is metabolized to active compounds. These metabolites may have longer half-lives (e.g., desmethyldiazepam, half-life ~100 h; diazepam, half-life ~45 h). Withdrawal begins more rapidly with compounds having shorter elimination rates. Following an abrupt stoppage of use, withdrawal starts within 24 h for short-acting benzodiazepines, 24–36 h for carisoprodol/meprobamate, and 4–8 days for long-acting benzodiazepine compounds.

In contrast to the relatively more benign clinical effects of opioid withdrawal, acute withdrawal from sedative-hypnotic agents can be life-

threatening. Symptoms and signs of withdrawal range from relatively minor (e.g., restlessness, tremor, and insomnia), to more severe (e.g., agitated delirium, psychosis, hyperthermia, tachyarrhythmias, and seizures) [10]. Hypertension, tachypnea, mydriasis, and diaphoresis are commonly seen but also occur in withdrawal for any GABA-agonist agent.

A complete differential diagnosis for ASH withdrawal includes both toxicological and non-toxicological diseases that may be indistinguishable from one another based on presenting clinical features. This differential includes

sympathomimetic (e.g., amphetamines) and methylxanthine (e.g., caffeine) toxicity; thyrotoxicosis; hypoglycemia; and neurosepsis. Anticholinergic poisoning, with the exception of anhidrosis and specific neurobehavioral features (e.g., mumbling speech and carphologia; see ► Chap. 23, “Anticholinergic Syndrome”), also presents with similar features.

Special Agents

Dexmedetomidine

Dexmedetomidine (DXM) is a centrally acting α_2 agonist which decreases release of catecholamines resulting in sedation and, at higher doses, bradycardia and hypotension; it may also have mild analgesic properties [11, 12]. It has been successfully used for pediatric sedation via oral and intranasal administration [13, 14]. Dexmedetomidine is indicated for short term weaning of mechanical ventilation, but has been used for procedural sedation and as an adjunct for GABA-agonist withdrawal [15, 16]. However, while it does assist in controlling signs of GABA withdrawal’s hyperadrenergic state it does little to prevent seizures and should not be used as a sole agent [16]. Its volume of distribution in healthy volunteers is <1 L/kg but can be larger in critically ill patients [17]. The terminal half-life is approximately 1.8 h, and an infusion rate of 0.7 $\mu\text{g/kg/h}$ will maintain steady state concentrations in most patients [18]. Although it causes less respiratory depression than other sedative agents, at higher doses the most common side effects are bradycardia and hypotension [19]. Treatment of these effects includes stopping the infusion and supportive care.

Propofol

Propofol is a GABA_A agonist and NMDA antagonist that, at high concentrations, can directly open chloride channels. It also results in minor dopamine release from nigral pathways and

possible dopamine agonism at D2 receptors. It is unclear, however, if these effects are clinically significant in humans. Propofol is used for induction of anesthesia and is now one of the most commonly used parenteral anesthetics. It is also used for sedation of ventilated patients, procedural sedation and treatment of status epilepticus. Sedative effects are achieved within seconds after administration and rapidly resolves (after discontinuation) after use of short periods of time. The intravenous induction dose is around 2 mg/kg and an infusion of 0.2 mg/kg/min will usually maintain anesthesia. Sedating doses of propofol may result in myocardial depression, hypotension and respiratory depression. Propofol is formulated in a soybean oil emulsion which can support bacterial growth if not used promptly after opening.

Higher doses of propofol, typically infused for longer than 48 h, may result in a propofol infusion syndrome. This syndrome includes cardiovascular instability, metabolic acidosis, rhabdomyolysis and renal insufficiency. Prolonged sedation after termination of the infusion and deaths have been reported.

Ramelteon

Ramelteon, a newer sedative agent, is an agonist at melatonin (MT1 and MT2) receptors. These are G protein-linked receptors primarily in the suprachiasmatic nucleus. Agonism at these receptors increases sleep length and decreases sleep latency [20]. The therapeutic half-life is about 1.5 h [21]. Limited data on clinical effects report fatigue, CNS depression, dizziness and headache [22]. Episodes of sleep-walking (and other parasomnias) are possible; a withdrawal syndrome has not been reported.

Suvorexant

Suvorexant, another newer medication, antagonizes orexin receptors. Sleep-wake cycle signals originate in the lateral hypothalamus and then project into several brain nuclei where orexin receptors are located. By antagonizing these

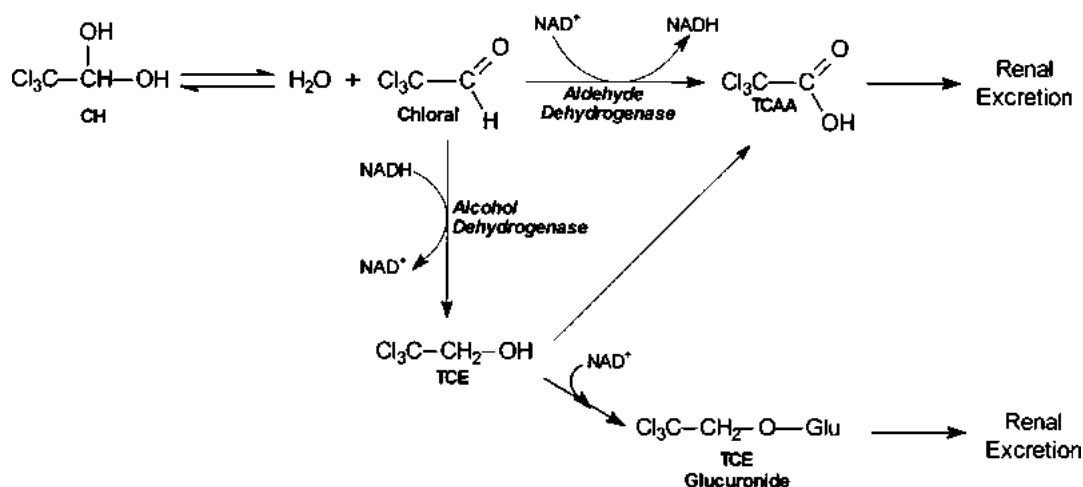


Fig. 4 Metabolism of chloral hydrate (CH). TCAA trichloroacetic acid, TCE trichloroethanol

receptors, signals for wakefulness are inhibited [23]. Reported adverse effects in therapeutic dosing include hallucinations, somnolence, headache, abnormal dreams and dizziness [24, 25].

Chloral Hydrate

Chloral hydrate was introduced into clinical medicine by Liebreich in 1869 and, shortly thereafter, used maliciously by adding it to alcoholic drinks and being referred to as a “Mickey Finns” or “knockout drop.” CH is available as a liquid, capsule, or rectal suppository. The recommended and most commonly reported doses used for pediatric outpatient sedation range from 25 to 100 mg/kg [26]. There has been much work published on the use of CH for procedural sedation, with mixed results and recommendations [27]. Several recent studies have shown CH to be safe [28–30]. There are, however, rare reports of death following CH-induced sedation [31, 32]. Newer, more predictable sedative agents should increasingly take the place of CH in clinical medicine [31].

After complete absorption from the gastrointestinal (GI) tract, CH is metabolized rapidly in the liver, brain, and red blood cells to trichloroethanol (TCE) and trichloroacetic acid (TCAA) [33–35]. Rapid nicotinamide adenine dinucleotide (NADH)-dependent enzymatic reduction of

CH by alcohol dehydrogenase (ADH) produces the active metabolite TCE, which has two fates: hepatic glucuronidation to urochlorallic acid with subsequent renal (major) and bile (minor) excretion, or oxidation to TCAA (Fig. 4) [36–38].

The coadministration of ethanol, with CH, competitively inhibits the metabolism of TCE and (via its metabolism by ADH) results in a changed redox potential and net increase in the NADH-to-NAD ratio, which effectively drives primary CH metabolism to TCE (Fig. 5) [35, 39, 40]. Simultaneous increase in TCE production and its reduced metabolism result in a rapid development of peak plasma concentrations of TCE, which, combined with TCE-mediated inhibition of ethanol metabolism through ADH, are thought to explain the rapid and profound onset of CNS depression that are characteristic of a ‘Mickey Finn.’

Because the hepatic enzymatic elimination of CH in normal healthy adults and older children is rapid (half-life 4 min), the rate of detection of the parent compound in urine in most clinical situations is low, limiting the utility of toxicologic assay for the parent compound itself. [37, 42] The relatively more prolonged hypnotic effects of CH are attributed to the active metabolite TCE (half-life >6 h) [37, 42, 43]. With concurrent ethanol administration or after CH overdose, the elimination half-life of TCE reportedly has increased to greater than 30 h [44].

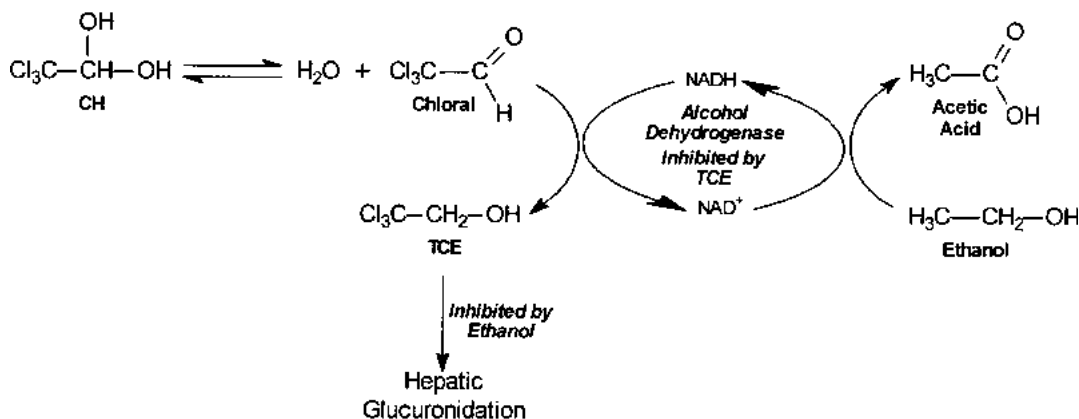


Fig. 5 Metabolic interaction of ethanol and chloral hydrate. *NAD* nicotinamide adenine dinucleotide, *NADH* nicotinamide adenine dinucleotide, reduced form; *TCE* trichloroethanol

The precise mechanism of action for CH is unknown. Several lines of evidence, including the demonstration of CH's rapid bioconversion, suggest that the dose-dependent hypnotic and sedating effects of CH are due in large part to its active metabolite, TCE [41–43, 45]. In addition, there is evidence to support TCE's indirect agonist actions at GABA_A chloride channels in a manner similar to that of barbiturates [46, 47]. Several mechanisms of CH-induced myocardial toxicity have been postulated, including sensitization of the myocardium to the dysrhythmogenic effects of catecholamines (similar to other halogenated hydrocarbons); reduction in myocardial contractility; and shortening of the refractory period of the myocardial action potential [37, 48, 49].

Mild sedation (drowsiness) occurs at low CH doses (250 mg in adults; 8 mg/kg in children), with hypnotic responses seen at moderate doses (500–1,000 mg in adults; 25–50 mg/kg in children). At therapeutic doses of CH, there is minimal depression of cardiovascular and respiratory function with maintenance of intact airway reflexes. Higher doses (>50 mg/kg in children) may produce more profound depression of respiratory and vasomotor functions. These effects develop within 1 h of oral or rectal administration.

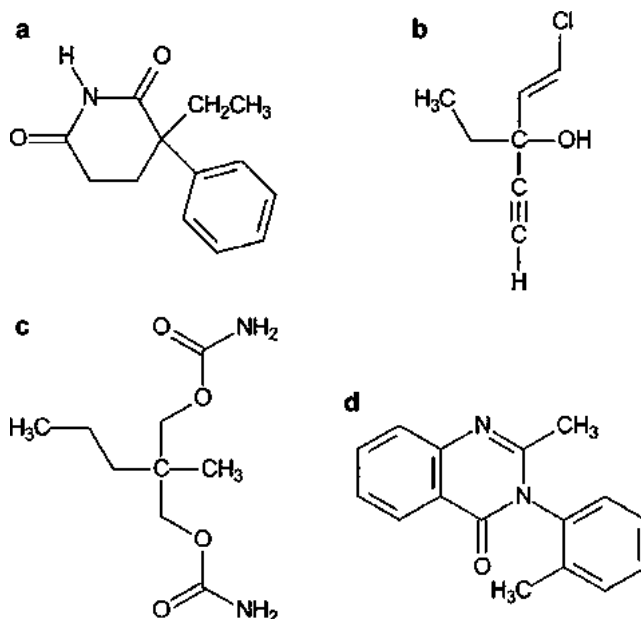
Physiologic tolerance after long-term administration of CH has been in rare cases and is plausible based on its effects on GABA transmission [50, 51]. There is minimal risk for withdrawal following limited use for medical procedures [52].

The acute lethal dose of CH is variable, with death reported after ingestion of 4 g in one case and survival reported after ingestion of 30 g in another [53]. Although excessive depression in level of consciousness and attendant respiratory compromise are the most commonly occurring and anticipated toxic effects of CH overdose, most deaths reported after CH overdose usually occurred after development of cardiovascular shock and malignant cardiac dysrhythmias [54–57].

Reported dysrhythmias include premature ventricular beats, ventricular tachycardia, ventricular fibrillation, bigeminy, accelerated junctional rhythm, torsades de pointes, and asystole. Severe irritant GI injuries have been reported, including upper GI hemorrhage, perforation, and esophagitis with stricture formation [54, 58–62]. A case series involving accidental intravenous administration of CH with skin sloughing and cyanosis illustrates the soft tissue effects of direct exposure [63].

Chloral hydrate has been associated with hypersensitivity reactions as well as "DRESS" (drug reaction with eosinophilia and systemic symptoms) [64, 65]. The coadministration of CH and furosemide has been associated with adverse events, including hot flashes, diaphoresis, nausea, tachycardia, and alterations in blood pressure (hypertension and hypotension) [66, 67]. Typically, these clinical manifestations have been encountered shortly after intravenous furosemide

Fig. 6 Chemical structures of older sedative-hypnotic agents **a** Glutethimide, **b** Ethchlorvynol, **c** Meprobamate, **d** Methaqualone



administration in patients who had previously received CH. A toxicologic mechanism for these occurrences has not been established. Case reports suggest that these effects do not occur when furosemide is administered more than 24 h after the last dose of CH. A retrospective study documented the occurrence of transient (<20 min) flushing-type reactions in 3 of 43 patients (7%) who received intravenous furosemide after CH [68]. There is also a case report of an adverse drug interaction involving CH and methotrexate [69].

Older, Less Used Sedative-Hypnotics

Glutethimide, ethchlorvynol, meprobamate, and methaqualone (Fig. 6) are sedative-hypnotic drugs that have fallen out of common use, having been replaced largely by benzodiazepine and benzodiazepine-like drugs. For example, only one of these, meprobamate, is still available on the U.S. Food and Drug Administration (FDA) regulated pharmaceutical market and only as a U.S. Drug Enforcement Agency (DEA) schedule III (some abuse potential, but not as much as a schedule 1 or 2 drug, and low to moderate

likelihood of dependence) drug. Meprobamate is the major active metabolite of a widely prescribed, non-DEA-scheduled, centrally acting muscle relaxant, carisoprodol (see ► Chap. 58, “Centrally Acting Muscle Relaxants”).

A marked decline in the availability, prevalence, and therapeutic use of these older sedative-hypnotics is reflected in the marginal incidence of poisonings attributed to their continued use. In 2013, the American Association of Poison Control Centers reported a total of less than 50 exposures and no deaths attributed to glutethimide, ethchlorvynol, meprobamate, and methaqualone out of a sedative-hypnotics/antipsychotics category total of greater than 150,000 exposures and 363 deaths [4]. Because these drugs continue to exhibit persistent availability they are briefly discussed.

Glutethimide

Glutethimide was introduced in the mid-1950s and became widely known in the 1970s for its abuse potential, especially when combined with opioid drugs, such as codeine. Glutethimide is a compound of relatively low water solubility that

exhibits slow, erratic gastrointestinal absorption; is distributed relatively broadly (volume of distribution 2.7 L/kg); and undergoes inducible biotransformation and elimination through cytochrome P-450 pathways to active metabolites (e.g., 4-hydroxyglutethimide and 2-phenylglutarimide) with an elimination half-life that ranges from 5 to 22 h [70].

Structurally similar to phenobarbital, glutethimide has sedative-hypnotic effects that are similar to the effects of barbiturates, but it lacks anticonvulsant properties. It also possesses potent antimuscarinic activity (see ► Chap. 23, “Anticholinergic Syndrome”), including anhidrosis and pupillary mydriasis. Acute toxicity from glutethimide is complicated by slow, erratic absorption and redistribution from tissues, resulting in a cyclic pattern of coma, convulsions, hypotension, and respiratory failure; pulmonary edema and renal failure also have been reported [71–73]. The close structural similarity of glutethimide to phenobarbital also explains the occurrence of false-positive results on urine immunoassays for barbiturates after glutethimide administration.

Aggressive life support is the essence of the intensive care management after glutethimide overdose. Initial enteral administration of activated charcoal in the patient with a protected airway to prevent further absorption may be of benefit, given the potential for delayed gastric emptying associated with a drug that possesses anticholinergic and barbiturate-like depressant properties. However, activated charcoal has not been shown to alter the outcome of these patients. There is no clinical benefit from the use of extracorporeal clearance modalities (e.g., hemodialysis) in the management of glutethimide poisoning [73, 74].

Ethchlorvynol

Ethchlorvynol was initially marketed in the 1950s as a hypnotic agent and formulated in a capsule containing a liquid form of ethchlorvynol and polyethylene glycol diluent. These capsules are noted for the characteristic vinyl (plastic-like)

odor and reported to occur on the breath of the overdose patients. A highly lipophilic and volatile compound, ethchlorvynol has a rapid absorption and onset of action with the latter typically occurring before peak post absorption serum concentrations are reached (1–1.5 h). Because of its absorption kinetics and volume of distribution (~2.8 L/kg), a second, post-redistribution peak concentration is seen about 10 h following ingestion [70, 75]. Hepatic metabolism is extensive, with less than 1% urinary excretion occurring as the parent compound; elimination half-life ranges from 10 to 25 h at therapeutic doses to greater than 100 h after overdose.

The pharmacologic properties of ethchlorvynol are similar to those of barbiturates, including the capability for anticonvulsant and sedative-hypnotic actions. Prolonged (>10 days) coma, respiratory failure, bradycardia, hypotension, hyporeflexia, and hypothermia are characteristic of the clinical presentation after oral overdose. Pulmonary edema occurs more frequently after parenteral overdose and probably results from an increase in pulmonary alveolar membrane permeability as an effect of the drug itself, rather than the coformulate excipient [76, 77]. Bullous skin lesions and rhabdomyolysis are relatively common, although nonspecific, peripheral organ system complications of ethchlorvynol overdose, particularly in cases in which initial clinical discovery is delayed [75]. Given the potential for an extended period of severe intoxication after ethchlorvynol overdose, prolonged supportive care in an intensive care unit is required.

Meprobamate

Meprobamate was introduced in the 1950s and used widely for sedation and anxiolysis until it was recognized to be highly addictive and relatively lethal in overdose. Carisoprodol, its metabolic precursor, continues to be marketed as a muscle relaxant (Soma[®]) and continues to be associated with risks of toxicity, abuse, tolerance, and withdrawal (see ► Chap. 58, “Centrally Acting Muscle Relaxants”) [4, 78–80].

Meprobamate absorption, similar to that of carisoprodol, has been characterized in some cases of overdose as erratic or prolonged, and may reflect formation of gastric concretions [81, 82]. Although there is (very limited) clinical data supporting the use of repeat administration of activated charcoal, this is not routinely indicated [83, 84]. Activated charcoal administration has not been shown to alter the outcome in these patients. Because of the possibility of obtundation of mental status activated charcoal should be given cautiously, if at all, in the non-intubated patient. Coma, clonus, seizures, profound and protracted hypotension, pulmonary edema, and cardiac dysrhythmias all have been reported after massive meprobamate overdose [82]. Cardiovascular depression may occur at doses responsible for coma. Although unproven, theoretical support for the use of hemodialysis to enhance meprobamate elimination includes its known low molecular weight and volume of distribution (0.7 L/kg), and degree of protein binding (20%) [70]. In addition, due to a risk of delayed or recurrent clinical deterioration after acute overdose, intensive monitoring and care should be maintained for 24 h following recovery from significant clinical effects.

Methaqualone

Methaqualone was withdrawn from the regulated U.S. market in 1983 after it was found to be relatively ineffective as a long-term maintenance drug in the treatment of anxiety and sleep disorders and developed widespread notoriety as a substance of abuse. It is pharmacologically similar to glutethimide and ethchlorvynol, with a slow biphasic pattern of elimination and prolonged duration of CNS depression following overdose. As a result of its selective inhibition of polysynaptic spinal reflexes, toxicity is notable for coma plus hyperactive motor dysfunction, clinically manifested as increased muscle tone, hyperreflexia, clonus, and myoclonus [85–87]. Another structurally related compound, methyl-methaqualone, has been reported to result in similar clinical effects [88]. It has been

suggested that case reports of retinal and gastrointestinal hemorrhage may be explained on the basis of drug-induced effects on platelet dysfunction and coagulation factors [89, 90].

Aggressive supportive care of severe methaqualone toxicity should be directed at control of motor hyperreactivity (e.g., intravenous benzodiazepines or neuromuscular blockade or both). If paralytic agents are used, continuous electroencephalogram should be considered.

Diagnosis

As with many drug-induced illnesses, the history of use or abuse of a sedative-hypnotic is often a starting point for patient evaluation and management. Important historical questions include: What medications is the patient taking? How much and for how long was the patient taking the medication? What medications did they have access to?

The laboratory detection and identification of benzodiazepines in blood and urine can be challenging based on the available assays. The relatively low sensitivity and specificity of immunoassay methods (e.g., enzyme multiplied immunoassay technique) and limited ability to detect benzodiazepines in biologic matrices by more specific methods (e.g., gas chromatography/mass spectrometry) are explained by the low concentrations of some drugs in urine and the excretion of conjugated metabolites [5, 7, 8]. Routine urine drug screening may include false positive or false negative results. And although specific drug testing methods are often valuable during forensic investigations, they rarely change initial patient management. In some circumstances, checking other drug concentrations (e.g., ethanol, phenytoin, phenobarbital) may assist in diagnosing (or ruling out) other drug causes for the patient's condition.

The diagnosis of sedative-hypnotic withdrawal is primarily determined by the presence of signs and symptoms of GABA-agonist withdrawal in a patient with a history of long-term use or abuse. An agitated patient who responds minimally to escalating doses of a rapidly acting

benzodiazepine (e.g., diazepam) is also suggestive of sedative-hypnotic withdrawal. This diagnosis is further supported by the presence of a causative agent (or metabolite) on routine or comprehensive toxicologic testing; though limitations of such testing must be appreciated.

Chloral hydrate toxicity may be signaled by the pear-like odor associated with its use, which may alert the clinician to the diagnosis. CH tablets are radiopaque on an abdominal x-ray. Because CH's metabolite, TCE, has a long half-life and is detectable in blood and urine, it can be tested for in suspected exposures [91].

Treatment

The management of acute benzodiazepine toxicity is mainly supportive. Other causes for altered sensorium (e.g., hypoglycemia) should always be investigated. Appropriate initial intervention include cardiopulmonary (with pulse oximetry and perhaps end tidal CO₂) monitoring, and based on the patient's clinical status, supplemental oxygen, intravenous fluids and dextrose. Naloxone administration should be considered in patients with hypoventilation (Level of Evidence (LoE) I). The potential for aspiration should remain a concern as long as the patient is comatose. If clinical presentation occurs within one hour of ingestion, oral (voluntary) administration of a single dose of activated charcoal may be considered (LoE I). However, activated charcoal has not been shown to alter the outcome in these overdoses and should be given cautiously to non-airway protected patients who have taken a drug that might obtund their mental status.

Flumazenil is a competitive antagonist at the benzodiazepine binding site of GABA_A receptors and reverses the CNS depressant effects of benzodiazepines. (LoE I) Flumazenil should also reverse the effects of benzodiazepine-like agents (e.g., zolpidem) as well [6, 92]. The degree and duration of effect of flumazenil on benzodiazepine-induced respiratory depression may be limited, however.

The use of flumazenil is safest in cases of acute, isolated benzodiazepine toxicity (e.g., in young

children after an exploratory ingestion and patients not on chronic benzodiazepine therapy and in whom there is a low suspicion for coingestants). Successful reversal of CNS depression in these instances does not obviate the need for further close monitoring because re-sedation may recur. Continuous infusion of flumazenil (in appropriate patients) has been reported but is not routinely recommended. The indiscriminant use of flumazenil may precipitate seizures, cardiac arrhythmias and/or acute withdrawal [93]. The chapter on flumazenil provides a more detailed discussion regarding the mechanism of action, contraindications, and administration of this antidote..

Because uneventful recovery from acute benzodiazepine toxicity usually occurs within 24 h after supportive care, extracorporeal enhancement of drug elimination is not indicated. Hemodialysis would not be expected to change clinical outcome for several reasons, including benzodiazepines' high degree of protein binding.

Treatment: Chloral Hydrate

All CH overdose patients should be observed closely on a cardiac monitor for at least 3 h after ingestion and for at least 24 h if they develop clinical toxicity. (LoE II-3) Appropriate supportive measures, including endotracheal intubation, mechanical ventilation, and intravenous fluid volume replacement, should be provided as they are clinically indicated. Tachydysrhythmias induced by CH poisoning should be treated with a β -adrenergic receptor antagonist. (LoE III) Numerous case reports document the successful use of propranolol (1 mg intravenous bolus followed by an infusion of 3 mg/h) or other β -blocker, such as metoprolol (5 mg intravenous bolus), in the treatment of CH-induced dysrhythmias [63, 94–97]. β -Blocker use often has been reported to be successful after failure to control the dysrhythmia with other drugs, such as lidocaine, procainamide, sodium bicarbonate, or magnesium. Continuous cardiac monitoring is warranted, and repeated dosing of the β -blocker may be required. Cardioversion or defibrillation

also has been employed to terminate dysrhythmias associated with CH poisoning [96]. The administration of nonselective adrenergic agonists (e.g., dopamine, norepinephrine) to CH-poisoned individuals has been associated with an increase in dysrhythmias [37, 96, 98]. These agents should be used with caution or avoided in favor of α -selective agonists (e.g., phenylephrine) in the treatment of CH-induced hypotension.

Case reports suggest that the use of flumazenil in CH overdose may reverse CH-induced sedation as well as precipitate ventricular dysrhythmias [99, 100]. The induction of acute withdrawal states by naloxone or flumazenil administration may increase the risk of TCE-induced dysrhythmias by increasing the release of endogenous catecholamines [63]. (LoE III) Naloxone and flumazenil should not be used in the management of CNS depression associated with CH overdose.

Several reports show favorable outcomes after the use of hemodialysis in severe CH-induced toxicity, including a pregnant patient with malignant cardiac dysrhythmias [44, 54, 96, 101, 102]. (LoE III) There is no published clinical trial evidence to support outcome benefit, but it seems reasonable to recommend hemodialysis when the CH poisoning is severe, prolonged, or refractory to other therapeutic interventions.

Treatment: Acute Sedative-Hypnotic Withdrawal

Appropriate management of acute sedative-hypnotic withdrawal should focus on the use of GABA-agonists. It should be remembered that patients may have a broad cross-tolerance among different drugs within the sedative-hypnotic class, depending on their mechanism of action. Rational choices of treatment are based on the relative safety and reliability of systemic administration, speed of therapeutic onset, and duration of effect. In general, agents with a rapid onset and long half-life (with or without active metabolites), such as diazepam, are pharmacologically desired. The optimal end point of pharmacotherapeutic titration with an intravenous benzodiazepine (e.g.,

diazepam) is resolution of sympathetic hyperactivity to the point of mild, rather than profound, sedation. The dose required to achieve this is highly variable and should be based on the closely monitored clinical response to incremental enteral or parenteral administration. The frequency of drug administration is based on the patient's clinical status. Patients with significant neurological and cardiovascular signs of sedative-hypnotic withdrawal should be continuously monitored, frequently (e.g., every 15 min) re-assessed and re-dosed as needed. See ► [Chap. 27, “Withdrawal Syndromes”](#) for a more complete and general discussion of drug withdrawal and its management.

The failure of benzodiazepine therapy to reverse sedative-hypnotic withdrawal manifestations may reflect inadequate dosing, inadequate cross-tolerance secondary to differences in GABA_A-receptor subtype affinity or another etiology for the patient's condition.

Long-term treatment of ASH dependence, including detoxification and discontinuation of therapy, can be accomplished safely and reliably using one or a combination of tapering regimens employing the same drug or a long-acting substitute (e.g., phenobarbital) [103–107]. (LoE II-3) Non-GABA-agonist adjunctive therapy is not routinely needed during inpatient treatment. Although this withdrawal state, and treatment, share very similar pathophysiology with alcohol (or any GABA-agonist) withdrawal, there is no consensus on definitive treatment [108]. Optimal management of significant withdrawal requires a facility capable of addressing the medical complications associated with acute or pre-existing co-morbidities (e.g., sepsis, hypertension) and potential complications of treatment (e.g., excessive sedation and loss of airway). Access to psychological and social services resource should also be available for long-term behavioral treatment [109].

Clinically significant benzodiazepine withdrawal may occur within hours of recovery from the acute sedative effects depending on the underlying degree of pharmacodynamic tolerance and the elimination kinetics of the specific drug. Once the patient has returned to baseline status,

maintenance therapy with the same (or other, related) drug is suggested in patients who are chronically taking the medication. Based on available data, all patients should be monitored for evidence for acute withdrawal following a sedative-hypnotic overdose. Although scientific evidence is lacking, anecdotal and our personal experience suggests that withdrawal from some GABA-agonists (e.g., alprazolam and carisoprodol) is best treated with the specific agent.

Special Populations

Pediatric Patients

Children who have received oral or parenteral benzodiazepines for conscious sedation may experience paradoxical reactions consisting of restlessness, disorientation, agitation, and combativeness [8, 110]. These adverse reactions have been observed to occur at relatively low (~1%) frequencies and are even less common in adults. Case experience has shown that flumazenil may be effective in reversing excessive sedation or paradoxical reactions that occurs after iatrogenic benzodiazepine administration [111, 112].

Pregnant and Breast-Feeding Patients

Most benzodiazepines, including alprazolam, and lorazepam, have been classified by the FDA as teratogenicity category D drugs (meaning there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.) but the benefits from use in pregnant women is often acceptable based on the indication and patient's condition or when safer drugs cannot be used or are ineffective. Exceptions to this generalization are triazolam, temazepam, quazepam, estazolam, and flurazepam, which are classified as category X (contraindicated in pregnancy) drugs; zolpidem, zaleplon and eszopiclone are classified as category C (Animal reproduction studies have shown an adverse effect

on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks) [113, 114].

Two neonatal syndromes that have been described after relatively high-dose (>30 mg) or prolonged maternal diazepam administration during labor are floppy infant syndrome (lethargy, hypotonia, sucking difficulties) and withdrawal (tremors, irritability, hypertonicity, vomiting, diarrhea, vigorous sucking) [113, 115]. On the basis of their known excretion into human breast milk and reports of clinical withdrawal and excessive sedation in breast-feeding infants, it is recommended that benzodiazepines be used with caution in breast-feeding women [113, 116].

Elderly Patients

Elderly individuals are at greater risk for more severe or prolonged toxicity as a result of age-dependent differences in pharmacokinetic and pharmacodynamic responses to the administration of benzodiazepines. Drug-drug interactions are also possible in this age group. Flumazenil administration, if done at all, should be done with even more caution.

Special Populations: Chloral Hydrate

The use of CH has been associated with higher rates of adverse effects, including inadequate sedation, excessive sedation in patients with obstructive sleep apnea, wheezing, mental retardation, and diseases of cerebral white matter or the brainstem [117, 118]. A study of 52 pregnant women who received CH while in active labor did not report any adverse maternal or fetal effects [119]. Analysis of fetal (cord) blood revealed significant concentrations of CH, TCE, and TCAA. Low, but measurable concentrations of CH is found in breast milk that may be too low to produce neonatal effects [119–121]. Data suggest that neonates and preterm infants have impaired abilities to metabolize and excrete CH and its metabolites [122]. Reports have documented

significant increases in the half-life of TCE to 40 h in neonates and critically ill children [123, 124]. Published reports indicate the potential for increases in serum bilirubin (direct and indirect) in infants receiving CH [125, 126]. This apparent dose-related phenomenon may reflect competition between CH and CH metabolites and bilirubin for conjugation in the immature liver.

Indications for ICU Admission in Benzodiazepine Toxicity

Established or impending respiratory failure.

Prolonged or profound level of obtundation.

Withdrawal syndrome, refractory to initial treatment.

Reversed coma using flumazenil (necessity of adequate monitoring)

Key Points in Benzodiazepine Toxicity

1. Depressed sensorium without serious respiratory, cardiovascular, or other neurologic manifestations represents the typical clinical presentation of acute or chronic benzodiazepine or benzodiazepine-like drug (e.g., zolpidem) toxicity.
2. Paradoxical neuropsychiatric reactions (e.g., restlessness, agitation) occur uncommonly but with apparently greater frequency in children and elderly individuals.
3. The mainstay of treatment for benzodiazepine toxicity is supportive care.
4. Flumazenil, a benzodiazepine receptor antagonist, should be used selectively and with caution in the management of acute or chronic benzodiazepine and benzodiazepine-like drug toxicity, particularly when pharmacodynamic tolerance to the effects of benzodiazepine receptor agonists or concomitant proconvulsant (e.g., tricyclic antidepressant) intoxication is considered likely.

5. Reinstitution of maintenance regimen doses of benzodiazepine or benzodiazepine-like drugs, particularly drugs with relatively rapid elimination kinetics, should be implemented during the early convalescent phase of acute or chronic poisoning to prevent withdrawal.

Key Points in the Management of Chloral Hydrate Toxicity

1. Monitor closely for signs or symptoms of toxicity for at least 3 h after ingestion.
2. Provide supportive care, including intubation, oxygenation, and ventilation, when clinically indicated.
3. Use a β -adrenergic blocker (e.g., propranolol) for tachydysrhythmias.

Indications for ICU Admission in Chloral Hydrate Toxicity

Neurologic instability (coma, seizures)

Respiratory failure

Cardiac dysrhythmias

Pharmacokinetics of Chloral Hydrate

Volume of distribution: 0.6 L/kg (CH)

Protein binding: TCE, 40%; TCA, 85%

Mechanisms of elimination: CH, <10% excreted unchanged in urine; TCE, renal excretion as urochloralic acid or oxidation to TCAA; TCAA, renal excretion

Plasma half-life: CH, approximately 4 min; TCE, 10 h (can be longer in overdose); TCAA, 67 h (can be longer in overdose)

Metabolites: chloral hydrate (CH) undergoes rapid conversion to two metabolites: trichloroethanol (TCE) (active) and trichloroacetic acid (TCAA) (inactive).

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Barbiturates were originally introduced as sedative-hypnotics and anticonvulsants in the early 1900s. Secondary to the frequency of their prescription and illicit use, unintentional/intentional overdoses and the ensuing toxicities became commonplace. Barbiturates are hazardous and have the highest risk of morbidity and mortality among all sedative-hypnotics [1]. The use of newer, relatively less-toxic medications (such as benzodiazepines) has largely supplanted the routine use of barbiturates. As a result, the incidence of serious toxicity related to barbiturate use has declined. Nevertheless, barbiturates are occasionally used today. Examples include phenobarbital and butalbital, which currently are prescribed for seizure disorders and migraine headaches, respectively [2]. Phenobarbital is also often employed to treat moderate-to-severe γ -aminobutyric acid (GABA)-agonist withdrawal [3]. Primidone, used as an anticonvulsant and in management of GABA-agonist withdrawal, is metabolized to phenobarbital [4]. Barbiturates such as methohexital are used for induction of anesthesia, and pentobarbital is commonly relied on for control of intracranial pressure and status epilepticus in intensive care units [5, 6]. Barbiturates are sometimes used as adjunctive therapy for neonatal hyperbilirubinemia [7]. Illicit drug use also may involve barbiturates because of their high abuse potential. These agents have also been employed in self-harm gestures, particularly in those populations with access to these medications, such as healthcare and veterinary workers.

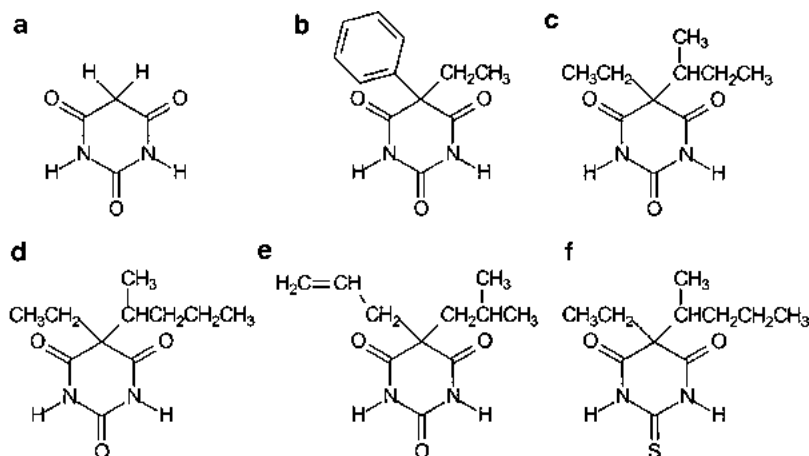
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Fig. 1 Chemical structures of barbituric acid (a), phenobarbital (b), butabarbital (c), pentobarbital (d), butalbital (e), and thiopental (f)



Consequently, clinicians must be aware of the potential toxicities due to accidental or intentional ingestions of barbiturates and remain astute as to the potential addictive properties of barbiturates, with the attendant risk for tolerance and abstinence-induced withdrawal. Finally, secondary to their potent clinical effects, these agents have been employed in criminal poisonings and suicide attempts [8, 9].

Biochemical and Pharmacokinetic Properties

All barbiturates are barbituric acid (2,4,6-trioxohexahydropyrimidine) derivatives (Fig. 1) [10]. Barbiturates have traditionally been classified as short-acting, intermediate-acting, and long-acting based upon their duration of action and hepatic metabolism. These characteristics are influenced primarily by the lipid solubility and consequent distribution into tissues, rather than the actual pharmacologic elimination half-life. Lipid solubility, potency, and onset and duration of action are functions of various substitutions made at different positions on the common barbituric acid structure (see Fig. 1). Agents with long side chains, such as thiopental, tend to display a high degree of lipid solubility and potency, with a rapid onset and short duration of action. In contrast, phenobarbital has a shorter side chain,

which confers a relatively lower lipid solubility, lower potency, slower onset, and longer duration of action. Substitution of a phenyl group at the C5 position results in anticonvulsant activity, as observed with phenobarbital and mephobarbital. In general, the more lipid-soluble the barbiturate compound, the more protein-bound it is in the plasma [11]; for example, thiopental is highly protein-bound, while phenobarbital is less so. Protein binding plays an important role in the ability to remove a barbiturate effectively from the plasma using hemodialysis [12].

Most barbiturates are well absorbed after oral administration and distribute widely to most body tissues, including the placenta and breastmilk, and undergoing nearly complete hepatic metabolism through cytochrome P₄₅₀ systems to inactive compounds, which are subsequently renally excreted [9]. Two barbiturates, mephobarbital and metharbital, are endogenously converted to phenobarbital and barbital [1]. Renal excretion is more important for long-acting barbiturates, with nearly 25% of phenobarbital being excreted unchanged in the urine. Elimination of barbiturates is slower in neonates, elderly patients, and those with hepatic and renal dysfunction; pregnancy may increase the half-life of a barbiturate, owing in part to an expanded volume of distribution Table 1.

Several noteworthy drug interactions occur with barbiturate administration. The sedative-hypnotic effects of barbiturates may be enhanced with

Table 1 Pharmacokinetics of Barbiturates

Barbiturate	Duration of action (hr)	pKa	Protein binding (%)	Elimination route	V _d (L/kg)
Ultra-short-acting					
Thiopental (Pentothal)	0.3	7.60	80	Hepatic	1.3–6.9
Methohexital (Brevital)	0.3	7.90	73	Hepatic	1.1–2.6
Short-acting					
Pentobarbital (Nembutal)	3	7.96	40–70	Hepatic	0.65–1.2
Secobarbital (Seconal)	3	7.90	52–57	Hepatic	1.5
Butalbutal (Fiorinal)	3–4	7.6	NA	Hepatic	NA
Intermediate-acting					
Amobarbital (Amytal)	3–6	7.75	60	Hepatic	1.0–1.27
Aprobarbital (Alurate)	3–6	NA	NA	Hepatic	NA
Butabarbital (Butisol)	3–6	7.74	NA	Hepatic	0.78
Long-Acting					
Phenobarbital (Luminal)	6–12	7.24	51	Renal (25–30%)	0.5–0.7
Mephobarbital (Mebaral)	6–12	7.8	40–60	Renal (35–40%)	2.8
Primidone (Mysoline)	6–12	13.0	19	Renal (15%)	1.0

NA, not available; V_d, volume of distribution

concomitant administration of other sedative agents such as ethanol or benzodiazepines. Repeated administration of barbiturates may induce hepatic CYP₄₅₀ 3A4, enhancing the metabolism of oral contraceptives, warfarin, vitamin D, tricyclic antidepressants, sulfonamides, doxycycline, corticosteroids, phenytoin, and barbiturates themselves [4].

Pathophysiology of Therapeutic and Toxic Effects

Barbiturates generate their sedative-hypnotic effects in the central nervous system via several mechanisms. They promote GABA binding to the GABA_A chloride channel complex, increasing the duration of chloride channel opening. At high concentrations, they may directly open the GABA_A chloride channel [13, 14]. The result of these actions is increased chloride content in the nerve cell, hyperpolarizing the membrane and depressing neuronal electrical activity [15]. Barbiturates also can reduce excitatory α -amino-3-hydroxy-5-methyl-4-isoxazole propionate glutamate-induced depolarization [13].

Barbiturates may inhibit nicotinic neurotransmission in autonomic ganglia. Other effects of barbiturates include depression of the medullary respiratory center, inhibition of myocardial contractility and conduction as a result of their “membrane-stabilizing” actions (i.e., fast sodium channel blockade), and suppression of gastrointestinal motility [13].

Long-term barbiturate use may produce tolerance to its sedative-hypnotic effects. This phenomenon is related partially to barbiturate induction of hepatic microsomal enzymes (pharmacokinetic tolerance). Additionally, GABA_A receptor downregulation occurs with chronic use, which progressively increases as the drug dose increases (pharmacodynamic tolerance) [16].

Clinical Presentation and Life-Threatening Complications

The clinical presentation of the acutely barbiturate-poisoned patient may vary depending on the patient’s age and duration of use of the drug. A given dose of barbiturate may cause severe toxicity in a first-time user but only minor

impairment in the long-term user because of the latter's pharmacodynamic tolerance to the drug. Barbiturate overdose management decisions should be based primarily on the clinical status of the patient and, to a lesser degree, to the serum barbiturate concentration, if available.

In general, acute intoxication with barbiturates may be clinically indistinguishable from that caused by other central nervous system depressant and sedative-hypnotic compounds, such as ethanol or benzodiazepines. These clinical manifestations center around central nervous system depression; somnolence, ataxia, slurred speech, and incoordination are often considered cardinal signs of barbiturate toxicity. Vital sign stability and deep tendon reflexes may be preserved in mild barbiturate poisoning. Moderate or severe poisoning frequently progresses to lethargy, bradypnea, hypopnea, and diminished deep tendon reflexes [17].

Patients with severe barbiturate intoxication classically present with coma, hypothermia, and circulatory collapse. Neurologic findings may include nonreactive pupils, loss of other brainstem reflexes (corneal, oculovestibular), absent deep tendon reflexes, and presence of pathologic reflexes (i.e., Babinski sign) [17]. These manifestations mimic and can easily be mistaken for clinical brain death, which may be further suggested by isoelectric electroencephalogram tracings. Skin bullae may be present but are nonspecific findings and are occasionally observed as a complication of other central nervous system depressant poisonings. Deleterious effects from other ingested toxins, anoxia, trauma, aspiration pneumonia, and rhabdomyolysis all may compound the initial insult and may cloud the clinical picture.

Patients who chronically use or abuse barbiturates may experience withdrawal symptoms during the recovery phase of an acute poisoning episode or during other periods of medication abstinence. The severity of the withdrawal syndrome is a function of the daily dose of barbiturate and the degree of dependence [16]. This clinical syndrome, similar to withdrawal from other

GABA agonist agents, typically manifests within 24 h and peaks depending on the elimination half-life and duration of effect of the barbiturate used. Early signs and symptoms may include restlessness, anxiety, confusion, tremor, nausea, abdominal cramps, tachycardia, and diaphoresis. Progression to more severe signs and symptoms may occur and can include increased muscular tone, delirium, and seizures. In addition, progressive autonomic dysfunction and cardiovascular collapse may occur in severe cases. Short-acting barbiturates such as secobarbital tend to be associated with onset of withdrawal symptoms within the first 48–72 h of their discontinuation, while withdrawal from long-acting barbiturates, such as phenobarbital, typically peaks in approximately 1 week. The abstinence syndrome usually clears within 14 days [1]. This syndrome may be seen in the intensive care unit in patients receiving continuous barbiturate administration for sedation [18].

Chronic adverse effects of barbiturates include induction of several enzyme systems, including hepatic microsomal CYP₄₅₀ 3A4, the mitochondrial enzyme aminolevulinic acid synthetase, and the cytosolic enzyme aldehyde dehydrogenase [13]. Induction of aminolevulinic acid synthetase may precipitate exacerbations of underlying porphyria because of enhanced porphyrin synthesis [13].

Anticonvulsant hypersensitivity syndrome is a well-recognized pharmacogenetic and idiosyncratic reaction to anticonvulsant therapy with aromatic-ring-containing agents such as phenobarbital, phenytoin, primidone, and carbamazepine. The pathogenesis of this syndrome is thought to stem from formation of reactive metabolic intermediates (arene oxides) through the actions of hepatic microsomal enzymes. If these arene oxides are not sufficiently detoxified by epoxide hydrolase, they may covalently bind to cell membrane constituents to form neoantigens that trigger hypersensitivity reactions. The clinical manifestations of anticonvulsant hypersensitivity syndrome arise most frequently on first exposure

to the drug and occur usually within several days to weeks of initiation (earlier in previously-sensitized patients). Fever, malaise, pharyngitis, cervical lymphadenopathy, atypical lymphocytosis, eosinophilia, and cutaneous eruption are typically part of the initial clinical presentation of the hypersensitivity syndrome. The rash may range from an exanthemous eruption to Stevens-Johnson syndrome or toxic epidermal necrolysis. Additional visceral organ involvement may include hepatitis, myocarditis, pericarditis, nephritis, pneumonitis, and thyroiditis [19].

Diagnosis

Laboratory tests obtained for a patient with suspected barbiturate intoxication should include a finger-stick blood glucose, electrolyte panel, serum creatine phosphokinase, and an electrocardiogram. If there is concern for the possibility of acute overdose, it is advisable also to screen for acetaminophen and salicylate poisoning. Urine immunoassay tests, such as enzyme-magnified immunoassay techniques, readily detect many barbiturates at plasma concentrations associated with toxicity. Drugs such as glutethimide, a nonbarbiturate sedative-hypnotic, may cause false-positive results [4]. In addition, barbiturates other than phenobarbital cross-react with the latter compound in some immunoassays [20]. Gross crystalluria has been reported with primidone toxicity; this drug is an anticonvulsant that undergoes biotransformation to phenobarbital and involves renal tubular precipitation of the parent compound [4].

Serum barbiturate concentrations do not always correlate with toxicity, particularly in the barbiturate-dependent patient. Prognostic or forensic information may be provided by serum drug concentrations; however, in barbiturate-poisoned patients, values greater than 35 mg/L of short-acting barbiturates such as secobarbital and greater than 80 mg/L (approx 350 $\mu\text{mol/L}$) of long-acting barbiturates

such as phenobarbital are potentially lethal [1]. In addition, serial serum barbiturate concentrations may assist in determining the need for continuing medical treatment or in the declaration of brain death after initial biologic detection of barbiturates.

Treatment

Standard treatment of acute barbiturate poisoning begins with aggressive airway management and ventilatory support as clinically indicated. Careful attention to hemodynamic monitoring is crucial. If hypotension occurs and persists despite aggressive fluid volume resuscitation, the addition of intravenous vasopressors such as norepinephrine may be required to achieve hemodynamic stability. Forced diuresis is not recommended because of the attendant risks of sodium and fluid overload and probable lack of efficacy. Severe hypothermia should be treated by vigorous rewarming measures.

If a patient presents early after acute oral overdose, administration of a single dose of activated charcoal may be considered. However, it should be administered with caution in a nonintubated patient as the barbiturate may cause a lessening of their level of consciousness during activated charcoal administration, thus enhancing the risk of aspiration. Multiple doses of activated charcoal may reduce the duration of coma in an acutely phenobarbital intoxicated patient (Level of Evidence: II-1) [21–23]. Caution is advised with this intervention because bowel motility may be compromised in a barbiturate-toxic patient. Multi-dose activated charcoal (MDAC) administration must be performed prudently to minimize the risk of aspiration, which generally requires airway-protective measures and oronasogastric tube placement in comatose patients. There is no evidence to support the use of MDAC and urinary alkalization with short- or medium-acting barbiturates.

Indications for ICU Admission in Barbiturate Poisoning

Hemodynamic instability
 Requirement for mechanical ventilation
 Coma
 Severe hypothermia
 Presence of comorbid medical conditions that may complicate therapy (e.g., severe coronary artery disease, congestive heart failure, renal failure)
 Requirement for hemodialysis
 Severe electrolyte disturbances or acidemia
 Actively suicidal patient requiring close observation beyond general hospital floor capability
 Increasing barbiturate level despite aggressive therapy
 Significant withdrawal syndrome

Alkalinization of the urine has been shown to enhance clearance of phenobarbital (Level of evidence: I), which has a pK_a of 7.2. The clearance of barbiturates with higher pK_a values has not been shown to increase in this manner [16]. Administration of sodium bicarbonate intravenously at dosages of 50–100 mmol of sodium bicarbonate in 1 L of 5% dextrose in water infused at 150–250 mL/h, maintaining the serum pH at a level of approximately 7.5–7.55, may effectively promote formation of phenobarbital's ionized form. [1] The rationale behind alkalinization is that because ionized molecules are poorly reabsorbed in the kidney, phenobarbital is ion-trapped under alkaline conditions in the renal tubule and is unable to be efficiently reabsorbed, thereby enhancing elimination. The goal of urinary alkalinization is the maintenance of a urine pH of 7–8 (Level of Evidence: III) [12]. Urinary alkalization may be beneficial in treatment or prevention of accompanying rhabdomyolysis (Level of Evidence: III) [4]. Urinary alkalization to a pH of 8 or above should be done with caution because it may promote hypoventilation.

Hemodialysis and hemoperfusion also can be employed to enhance elimination of long-acting

barbiturates. These drugs are less protein-bound and less lipid-soluble than short-acting barbiturates and can be cleared effectively from the plasma by extracorporeal removal techniques. Indications include severely poisoned patients who are not responding adequately to the aforementioned supportive measures and patients who cannot excrete the barbiturate effectively because of oliguric/anuric renal failure. In addition, the Extracorporeal Treatments in Poisoning work-group provides guidelines for use of extracorporeal removal of barbiturates. These consensus guidelines state that the use of extracorporeal removal techniques should be restricted to cases of severe long-acting barbiturate poisoning. The indications for extracorporeal removal in this setting are the presence of prolonged coma, respiratory depression necessitating mechanical ventilation, shock, persistent toxicity, or increasing or persistently elevated serum barbiturate concentrations despite treatment with multiple-dose activated charcoal. Intermittent hemodialysis is the preferred mode of extracorporeal removal therapy, and multiple-dose activated charcoal treatment should be continued during extracorporeal removal. Cessation of such therapy is indicated when clinical improvement is apparent [37]. Several case reports have shown apparent clinical effectiveness of extracorporeal removal of phenobarbital in patients not responding to other supportive measures [24–27]. Exchange transfusion has been reported as an effective intervention for phenobarbital intoxication in neonates being treated for hyperbilirubinemia [7].

Criteria for ICU Discharge in Barbiturate Poisoning

Mechanical ventilation no longer required as coma resolves or mental status improves
 Vasopressors discontinued
 Hemodynamic stability
 Resolution of coma
 Normothermia
 Resolution of metabolic disturbances
 Decreasing serum barbiturate concentrations

Key Points in the Treatment of Barbiturate Poisoning

1. Aggressive airway management and ventilatory support are key.
2. Administer intravenous fluid (1–2 L) if hypotension is present; if no response, initiate vasopressors (norepinephrine preferred) to maintain systolic blood pressure >90 mmHg and adequate urine output.
3. Perform vigorous rewarming measures for severe hypothermia.
4. Consider administration of one or multiple enteral dose(s) of activated charcoal.
5. Consider urinary alkalization (target urine pH 8) for moderate-to-severe phenobarbital overdose.
6. Consider serial barbiturate levels.
7. If the patient is clinically unstable or has rising serum barbiturate levels despite above measures, hemodialysis or hemoperfusion should be considered.
8. The presence of rhabdomyolysis should be determined.
9. Skin bullae require local wound care; consider tetanus immunization.
10. Consider gastric stress ulcer and deep venous thrombosis prophylaxis in critically ill patients.

Barbiturate Withdrawal

The prevention and management of the barbiturate withdrawal syndrome primarily include gradual tapering of the previously administered medication regimen and institution of the same or a cross-tolerated sedative-hypnotic. In the critical care setting, discontinuation of a short-acting barbiturate such as pentobarbital may be accomplished safely and effectively after initiation of a long-acting barbiturate such as phenobarbital [18]. Withdrawal also may be managed by the administration of a benzodiazepine, such as

diazepam or lorazepam, to control the sympathetic hyperactivity to the point of mild sedation, with care taken not to cause respiratory compromise. Gentle, incremental dose titration may be required at the patient's bedside. When control of withdrawal signs and symptoms is attained, further treatment may entail reintroduction of the barbiturate, depending on the clinical situation [4].

Special Populations**Pediatric Patients**

Neonatal exposure to barbiturates can occur in a variety of clinical scenarios, including administration during delivery or in the intensive care unit and maternal use during pregnancy. Pharmacologic effects of barbiturates in neonates are similar to those in adults, but strict adherence to drug doses and dosing intervals must be maintained because of relatively low levels of phase I enzyme activity in neonates [28]. In addition, phenobarbital has been associated with neonatal hemorrhage owing to a decrease in vitamin K-dependent clotting factors II, VII, IX, and X [28].

Because barbiturates cross the placenta freely, neonatal withdrawal may be encountered. Signs of withdrawal in neonates usually begin 4–7 days after birth and may include overactivity, restlessness, insomnia, hyperphagia, tremor, and vasomotor instability. These signs may persist for weeks to months [16].

Fetal abnormalities also have been reported with use of barbiturates during pregnancy, in a manner similar to that associated with use of phenytoin, trimethadione, and valproic acid. The name *fetal hydantoin syndrome* may be a misnomer because the etiologies of this syndrome also seem to include barbiturates. Clinical manifestations of this syndrome may include facial dysmorphism, prenatal and postnatal growth deficiency, and developmental delay. More recently, the notion of drug-specific syndromes has been

supplanted by the term *fetal antiepileptic drug syndrome* [29, 30].

Pregnant and Breastfeeding Patients

Pregnancy is a multifaceted clinical arena because barbiturate use during this time may affect the mother and the fetus. Barbiturate toxicity in pregnant women may be associated with deleterious effects in the developing fetus, secondary to impaired maternal physiology (e.g., hypotension or hypoxemia). Resuscitation of the mother is the primary goal of the critical care provider.

Barbiturates may be employed in the treatment of pregnant women with epilepsy. Approximately one-third of women with seizure disorders experience escalating seizure frequency when gravid; generalized motor seizures during pregnancy generate fetal bradycardia, decelerations, decreased variability, and intracranial hemorrhage [30]. As a result, optimal seizure control in a pregnant patient is essential to maintenance of fetal health. Although phenobarbital is considered a US Food and Drug Administration pregnancy category D drug (evidence of human fetal risk, but benefit may be acceptable despite potential risk), the risk to the mother and fetus may be greater if seizure control is lost. The lowest amount of drug required to control seizures should be used, and frequent monitoring of drug levels should be maintained [31, 32].

Phenobarbital is excreted in breastmilk, and reports of both infant intoxication and withdrawal have been described. Breastfeeding women prescribed phenobarbital should be instructed to monitor their infant(s) for sedation, and infant phenobarbital levels should be monitored if toxicity is suspected [31].

Elderly Patients

Adverse drug reactions are commonplace in the elderly, who take an average of four or five prescribed medications and two over-the-counter medications [33]. In addition, alterations in the GABA-benzodiazepine receptor complex

associated with aging may make older patients more sensitive to barbiturates [34]. Elderly patients also may have significant comorbid medical conditions that not only can lead to serious problems with medication compliance (e.g., excessive administration of sedative-hypnotics) but also may confound clinical presentation. Not only may the toxicity of the barbiturates be compounded in an elderly patient already taking other sedative-hypnotics or antihistamine medication, but also the diagnosis may be delayed or missed in patients with other medical illnesses clouding the clinical picture.

No specific data are available regarding the absorption, volume of distribution, protein binding, half-life, or changes in metabolism of phenobarbital in the geriatric patient. It has been shown, however, that phenobarbital clearance was reduced in patients aged greater than 40 years when compared with younger patients, and a reduction in maintenance dose was required in the older patients to maintain the same plasma phenobarbital concentration [35]. Decline in renal clearance associated with aging might lead to increased plasma phenobarbital concentrations at the same dose [35].

Veterinary Medicine Professionals

Veterinarians and animal handlers may present a specialized circumstance with respect to sedative-hypnotics. Barbiturates such as pentobarbital are among the common pharmaceuticals used for euthanasia of animals. Additionally, many brand-name agents have been and continue to be employed for this purpose, such as Beuthanasia-D Special[®] (Brand names given here are sold in the USA and are given as examples. These may vary in other countries) (pentobarbital, phenytoin, propylene glycol, and alcohol), Repose[®] (secobarbital, mephensin, and propylene glycol), and Socumb[®] (pentobarbital, isopropanol, and propylene glycol). One of the most popular veterinary euthanasia drugs historically employed was termed T-61[®], a combination agent containing embutramide, mebezonium, and tetracaine solubilized in *N,N*-dimethylformamide. This agent is

still available for veterinary use in many countries. Several case reports of humans using these agents for self-harm exist in the literature [8, 36]. As in other cases of sedative-hypnotic toxicity, aggressive supportive care is the mainstay of therapy in overdose situations involving these agents. In cases of T-61[®] overdose, seizures have been reported to be benzodiazepine-responsive. Pyridostigmine may be effective in cases of skeletal muscle paralysis from this agent, and intubation/ventilatory support addresses the profound respiratory depression from the embutramide component of this agent [8].

Key Points in Barbiturate Poisoning

1. Assessment and treatment should be based primarily on the patient's clinical status, not just serum drug concentrations.
2. Barbiturates can cause isoelectric electroencephalogram (EEG) patterns; the diagnosis of brain death should not be made based on the EEG when these patterns are present.
3. Patients who are taking barbiturates on a long-term basis may develop a severe withdrawal syndrome if they are stopped abruptly.
4. There is no role for forced diuresis.

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Bupropion is an atypical antidepressant primarily used for the treatment of depression and as an adjunct for smoking cessation. The United States Food and Drug Administration approved bupropion for the treatment of depression in 1985, but the drug was withdrawn prior to marketing after seizures were reported in four of 55 nondepressed bulimic patients who received it [1]. It was later reported that the risk of seizures with bupropion was comparable to that of other antidepressants, provided the daily dose did not exceed 450 mg, and the drug was reintroduced in 1989 [2, 3]. Today, bupropion is available as immediate-release, sustained-release, and extended-release formulations [4]. It is generally well tolerated at therapeutic doses, with common side effects including insomnia, agitation, dry mouth, and nausea [5]. Given its unique pharmacologic properties, adverse effects frequently encountered with other antidepressants (such as sexual dysfunction, weight gain, and sedation) are rarely seen with bupropion [5]. In overdose, however, bupropion can exhibit significant toxicity, and bupropion abuse is increasingly recognized as an evolving concern. This chapter focuses on the pharmacological and toxicological properties of bupropion, with particular attention to its pharmacokinetics, the clinical manifestations of overdose, and recommendations for management.

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Biochemistry and Clinical Pharmacology

Bupropion hydrochloride and its metabolites inhibit the reuptake of norepinephrine and dopamine and antagonize neuronal nicotinic acetylcholine receptors [6]. Bupropion's action as a norepinephrine and dopamine reuptake inhibitor is thought to explain its mechanism in the treatment of depression, which is further substantiated by animal models demonstrating a reduction in antidepressant effects of bupropion in the face of administration of dopamine or norepinephrine antagonists [5]. Inhibition of dopamine reuptake confers anticraving and antiwithdrawal effects, which underlie its role in smoking cessation [5, 6]. Bupropion also exhibits similarities to amphetamine (Fig. 1). Structurally, bupropion contains a phenylethylamine skeleton. In animal models, it produces stimulant effects related to conditioned behaviors similar to other psychostimulants: increases locomotor activity, decreases core body temperature, and reduces food consumption

[6]. These similarities underlie the misuse of bupropion for recreational purposes.

In addition to its effects on neuronal tissue, in overdose bupropion can interfere with cardiac conduction. In a guinea pig heart model, bupropion exhibits weak blockade of the delayed inward rectifier potassium channel (I_{Kr}) at supratherapeutic concentrations ($IC_{50} \sim 34 \mu\text{M}$ (9.38 mg/L) – therapeutic range 0.18–0.36 μM or 0.05–0.1 mg/L [7]. This finding is consistent with the observation that prolongation of the QT interval is seen more often in the setting of overdose than with therapeutic use [7, 8]. Bupropion has also been shown to cause widening the QRS interval at very high concentrations (10 μM ; 2.78 mg/L). This effect is not explained by sodium channel blockade, but rather by inhibition of intercellular gap junction communication in the cardiac conduction system [7].

The pharmacokinetic properties of bupropion are summarized in Table 1. Following ingestion, bupropion absorption is not appreciably influenced by food. It distributes extensively

Fig. 1 Molecular structures of amphetamine and bupropion

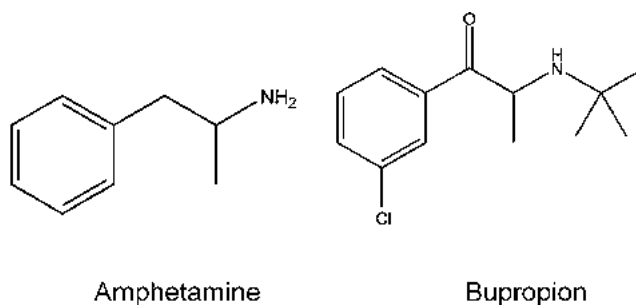


Table 1 Pharmacological properties of bupropion hydrochloride

	Molecular weight	Volume of distribution	Protein binding	Water soluble	Time to peak	Elimination half-life
	276 daltons	19 L/kg	82–88%	No	Immediate release: 1.5 h	Parent bupropion: 21 h
Bupropion hydrochloride				(log P 3.47)	Sustained release: 3 h	Metabolites:
					Extended release: 5 h	Hydroxybupropion: 20 h
						Threohydrobupropion: 33 h
						Erythrohydrobupropion: 37 h

throughout the body, with a volume of distribution of 19 L/kg and protein binding ranging from 82% to 88% [9]. The time to peak concentration is dependent on the formulation. The immediate-release tablet achieved peak concentrations at 1.5 h [9], but modified-release formulations prolong absorption by design. The sustained-release formulation incorporates bupropion into a methylcellulose matrix, while the extended-release formulation consists of a core of bupropion surrounded by controlled release and moisture barrier coatings. Following therapeutic doses, these delivery systems result in peak concentrations at 3 h and 5 h, respectively [9]. Limited evidence suggests that these kinetics can be altered following overdose. One report of a large overdose (5.7 g) of sustained-release bupropion observed a time to peak concentration of more than 8 h post-ingestion, with no history of any co-ingestants [10]. Another report involving an unknown amount of extended-release bupropion observed peak levels 13 h after presentation [11]. In this case, however, the comprehensive toxicology screen was also positive for chlorpheniramine [11] which may have delayed absorption. Pharmacobezoar formation has also been postulated as a mechanism for delayed absorption [12].

The three major metabolites of bupropion are hydroxybupropion, threohydrobupropion, and erythrohydrobupropion [6]. The formation of hydroxybupropion is mediated primarily by CYP2B6, with other CYP isoforms playing minor roles [6, 9]. Threohydro- and erythrohydrobupropion formation result from the activity of carbonyl reductase, a family of nonmicrosomal enzymes found in liver and intestinal tissue [6, 9]. All three major metabolites are pharmacologically active. Hydroxybupropion demonstrates 50% of the antidepressant activity of the parent bupropion, while threohydro- and erythrohydrobupropion are approximately 20% as effective as an antidepressant [6, 9]. The hydroxybupropion and threohydrobupropion metabolites accumulate to a greater extent than the parent compound at steady state, and in a mouse model, all three metabolites were shown to be more proconvulsant than the parent compound [13]. The $t_{1/2}$ of bupropion, hydroxybupropion,

threohydrobupropion, and erythrohydrobupropion are 21 h, 20 h, 33 h, and 37 h, respectively [9]. Bupropion is extensively metabolized by the liver, with less than 0.5% of the parent compound excreted unchanged in urine and less than 10% in feces [6, 9]. In addition to being a substrate for CYP2B6, bupropion has been shown to be a strong inhibitor of CYP2D6 [6].

The clinical significance of hepatic and renal impairment on the disposition of bupropion and its metabolites is uncertain. In an open-label study, the elimination half-life of the hydroxybupropion metabolite was 32.2 h in patients with alcoholic liver disease, as compared to 21.1 h in healthy volunteers; however, there were minimal differences in half-lives of the parent compound and the threohydro- and erythrohydrobupropion metabolites [14]. A separate study found no differences in pharmacokinetic parameters in nine patients with mild to moderate cirrhosis compared to healthy volunteers [9]. In a study involving eight hemodialysis patients, concentrations of bupropion and its metabolites were measured serially over 7 days following a 150 mg dose. Bupropion concentrations were similar regardless of renal function; however, the concentration of metabolites was two to threefold higher in patients with renal impairment [15]. Predictably, this study also demonstrated that dialysis has little influence on bupropion clearance, in keeping with the drug's lipophilicity and large volume of distribution [9].

Clinical Presentation

Therapeutic Dose

At therapeutic doses, bupropion is relatively well tolerated. Common adverse effects include nausea, xerostomia, agitation, and insomnia [9]. Compared to other antidepressants, bupropion has little effect on serotonergic transmission. Consequently, many of the undesirable effects of conventional antidepressants such as weight gain, sexual dysfunction, and sedation are uncommon during treatment with bupropion. Indeed, in some instances, bupropion has been used to counter

Table 2 Summary of case series examining bupropion overdose

Study	Design	Formulation	Number of cases	Median age	Cases with seizure	Mean dose for seizure	Mean time of seizure onset	Seizure onset time range	Deaths
Spiller et al. (1996) [16]	3-year retrospective case series	Immediate release, IR	58	30 y	21%	3,078 g	3.7 h	1–8 h	0
Shepherd et al. (2004) [17]	2-year retrospective case series analysis	Sustained release, SR (75% of cases)	385	29 y	11%	n/a (Range 600 mg to 18 g)	4.3 h	1–14 h	2
Starr et al. (2009) [18]	1-year retrospective and 2-year prospective case series	Extended release, XL	117	25.8 y	31.6%	4.35 g ^a	7.3 h	0.5–24 h	1

y years of age, g grams, h hours

^aThis dose applies to patients over the age of 12 years

these effects [5]. Even at therapeutic doses, bupropion demonstrates a dose-dependent risk for seizures with a rate of 0.1% at doses up to 300 mg/d and 0.4% at doses up to 450 mg/d [2, 9].

Overdose

Bupropion overdose is often accompanied by serious neurologic and cardiovascular toxicity. Most of our understanding of the natural history of bupropion overdose derives from case reports and case series.

Neurologic Toxicity

Several case series demonstrate that seizures are a hallmark of bupropion overdose. A large retrospective review of nearly 7,400 single-agent bupropion exposures found that seizures occurred in 15% of patients [4]. A major limitation of this study was the lack of information regarding doses ingested. Three other case series have further characterized the clinical manifestations of bupropion overdose (Table 2).

A retrospective case series of bupropion ingestions reported to five regional poison centers from 1989 to 1991 identified 58 bupropion-only

ingestions, all involving immediate-release formulation [16]. The mean toxic dose producing seizure was 3,078 mg. Seizures occurred in 12 of 58 (21%) patients, with a mean time to onset of 3.7 h. Among patients who seized, the dose ranged from 575 mg to 6,000 mg, and two of 12 patients who seized had multiple seizures. Other neurologic symptoms included lethargy, tremor, confusion, hallucinations, and paresthesias [16].

A subsequent retrospective case series from the Texas Poison Center Network identified 358 cases of bupropion overdose from 1998 to 1999 [17], the majority of them involving sustained-release formulations. Seizures occurred in 41 of 358 (11%) patients, with doses ranging from 600 mg to 18,000 mg, and a time to seizure onset ranging up to 14 h. Multiple seizures were documented in 9 of 41 patients. Two deaths were reported, although in one case it was difficult to definitively ascribe death to bupropion, because of co-ingestants [17].

A final case series identified 117 overdoses of extended-release bupropion [18]. Seizures developed in 37 of 117 (31.6%) patients, 18 of whom had multiple seizures. In some instances, seizure onset was delayed up to 24 h post-ingestion. The range of ingested doses was 600 mg to 54,000 mg,

with an average dose of 4,350 mg. Other clinical effects included tremor, agitation, and tachycardia. The sole reported death in this study was a 16-month old who ingested 143 mg/kg of bupropion and developed multiple seizures, followed by ventricular fibrillation and cardiac arrest [18].

Cardiovascular Toxicity

Sinus tachycardia is the most common cardiac finding in bupropion overdose [16–18]; however, several case reports describe QRS widening and QT interval prolongation [11, 19–23]. While many cases are obfuscated by co-ingestants or lack of serum bupropion concentrations, one case report in which serum bupropion concentrations were measured demonstrated that the QRS widening and QT interval prolongation coincided with the peak concentration of the parent compound and that these findings normalized once bupropion concentrations fell [11]. QRS widening is not due to cardiac sodium channel blockade, which explains why sodium bicarbonate fails to reliably influence QRS width in case reports [11, 19, 21]. Rather, bupropion is believed to widen the QRS by inhibiting intercellular gap junctions, which normally allow electrical communication between myocytes allowing for propagation of excitation [7]. The clinical significance of QT interval prolongation due to bupropion is unknown; to date, no cases of Torsades de Pointes have been reported, despite reports of QT intervals up to 600 ms [22, 23]. A prospective case series found that 13 of 17 patients with bupropion overdose had a QTc interval exceeding 440 ms; however, no arrhythmias were reported. The investigators postulated that the prolonged QT interval was not due to cardiac disease but rather formulaic overcorrection due to tachycardia [23]. In severe cases, patients can present with cardiogenic shock with global cardiac dysfunction [20] and in some cases cardiac arrest [21].

Brain Death mimic

Rare case reports describe bupropion overdose mimicking brain death [24, 25]. One case report

described a 29-year-old woman with fixed, dilated pupils, absent brain stem reflexes, no spontaneous respiration, and a burst suppression pattern on EEG. Not initially recognized as an overdose, these findings resolved completely within 36 h of presentation [25]. In patients exhibiting such findings in the setting of possible bupropion overdose, sufficient time for drug clearance should be afforded prior to declaration of brain death.

Death

Although deaths were uncommon in the case series noted above [17, 18], fatalities from bupropion overdose have been reported. A series of five fatalities documented serum bupropion concentrations ranging from 3.1 to more than 20 mg/L, with four patients having ingested the extended-release formulation [26]. This series also identified retained pill fragments in the stomach of four patients on autopsy. In light of very elevated bupropion concentrations, it has been postulated that these may represent “ghost pills” from which the active compound had been released, leaving only residual matrix behind [26].

Recreational Abuse and Misuse

Recreational abuse of bupropion is a relatively new but growing phenomenon. Bupropion has amphetamine-like properties and is easily obtained by patients under the pretense of seeking an antidepressant or smoking cessation aid [27, 28, 29]. People who misuse bupropion report experiencing a mild cocaine-like “high” [27, 29]. Reported routes of misuse include oral [30], intravenous [27, 28, 31], and nasal insufflation [29, 32–37]. A recent case series involving 67 cases of bupropion insufflation reported to the California Poison Control System identified 20 patients who experienced seizures but none with a second or delayed onset seizure [38]. The lack of delayed or multiple seizures, as often seen following oral bupropion overdose, reflects disruption of the modified-release formulations intended to slow gastrointestinal absorption.

Consequently, patients who abuse bupropion via non-oral routes may not require the same duration of monitoring as those who ingest large amounts. Other adverse effects resulting from non-oral administration include dramatic tissue necrosis and secondary infections [27], as well as epistaxis following insufflation [29]. These can represent clinical clues of misuse in the appropriate context.

Bupropion abuse has also been identified as a growing problem in correctional facilities [39]. Some users report first learning to misuse bupropion while incarcerated [29, 39]. Additionally, Internet forums exist, providing instruction on recreational misuse of bupropion [28].

Diagnosis

Bupropion overdose is a clinical diagnosis based on a history of exposure in the context of corresponding symptoms and signs. Given the drug's widespread availability, bupropion toxicity should be suspected in patients with otherwise unexplained seizures. Although serum bupropion concentrations have been measured in case reports, they are not readily available in most settings and unlikely to aid in management. Urine immunoassays do not detect bupropion *per se*, but given its phenylethylamine skeleton, false-positive screens for amphetamine can serve as a potential clue to bupropion toxicity [16, 22].

In addition to a history of new-onset seizures, other relevant associated signs include tremors, agitation, and hallucinations. While these findings may presage seizures [16–18], patients with bupropion toxicity may seize despite the absence of such features [18].

Patients with bupropion toxicity can range from lucid to seizing or post-ictal and can even display features suggestive of brain death [24, 25]. The presence or absence of tachycardia is helpful, as case series demonstrate that nearly all patients with bupropion-induced seizures were tachycardic [16–18]. Given the risk of seizures and the associated complications, the authors

recommend a low threshold for mechanical airway protection in all cases. Other aspects of the physical examination that may provide clues to abuse include a nasal airway exam to identify bleeding or injury from insufflation, as well as a dermatologic exam looking for track marks at injection sites or evidence of ulcers, tissue necrosis, or cellulitis [27, 29].

The presence of QRS widening and/or QT interval prolongation, particularly in the absence of other contributing causes, should raise the possibility of bupropion toxicity, particularly when a urine drug screen is positive for amphetamine. In a series of more than 10,000 urine drug screens obtained from emergency department patients, 362 tested positive for amphetamine using the EMIT II assay. However, in 128 (35%) of cases, no amphetamine was detected on gas chromatography. In nearly half of such cases, records documented bupropion use only [40].

Treatment

The treatment of bupropion overdose is primarily supportive. Treatment recommendations are informed by available case series rather than by high-quality evidence.

Supportive Care

Patients with suspected bupropion overdose should be cared for in a monitored setting, with particular attention to neurologic and cardiovascular status. Due to the delayed presentation of seizures, the authors recommend that patients suspected of bupropion overdose – especially those with ingestions of modified-release formulations – be monitored for a minimum of 24 h (Grade III recommendation).

In addition to routine investigations and telemetry, serial electrocardiograms are advisable, particularly following large ingestions and those in which QT prolongation or QRS widening are anticipated. As described above, a false-positive

urine drug screen for amphetamines may reflect the presence of bupropion.

Decontamination

In patients with bupropion overdose who present to hospital within 2 h of ingestion, the authors recommend the administration of activated charcoal (1 g per kilogram) (Grade III recommendation). However, due to variability in gastric emptying time, amount ingested, and potential co-ingestions, no absolute cut-off time can be recommended for activated charcoal. Although no data demonstrate that activated charcoal improves clinical outcomes in patients with bupropion overdose, it is a relatively safe intervention expected to reduce bupropion absorption. The primary hazard associated with activated charcoal is pulmonary aspiration. As such, in patients with mental status alterations or seizure, it should only be given once the airway has been secured and nasogastric tube placement confirmed [41] (Grade III recommendation).

Gastric emptying procedures are not indicated, and induction of emesis is absolutely contraindicated given the high risk of aspiration in the event of seizure. Some authorities recommend whole bowel irrigation for large ingestions of modified-release pharmaceuticals, based primarily on volunteer studies involving subtoxic ingestions [42]. Whole bowel irrigation is potentially useful only in patients with large ingestions of modified-release bupropion whose airway is mechanically protected and who display no evidence of ileus, perforation, or mechanical obstruction (Grade III recommendation).

Seizure Management

Case series suggest that benzodiazepines are effective in the management of bupropion-induced seizures [16–18] and are indicated as first-line therapy (Grade III recommendation). Phenytoin is unlikely to terminate toxicant-induced seizures (see ► Chap. 20, “Toxicant-

Induced Seizures”). A murine model found that phenytoin, carbamazepine, and lamotrigine all failed to block the convulsant effects of bupropion [43]. Barbiturates (phenobarbital, pentobarbital, and thiopentone) are superior to phenytoin as second-line therapy in animal models [44]. The roles of propofol or levetiracetam in bupropion overdose are unclear, although propofol’s GABA agonist effects may allow synergy with benzodiazepines and barbiturates in refractory cases [44]. For seizures refractory to benzodiazepines or in patients with recurrent seizures, barbiturates or propofol are indicated as second-line therapy (Grade III recommendation). There is no justification for prophylactic anticonvulsant therapy in patients with bupropion poisoning.

Cardiovascular Support

Conduction Abnormalities

Despite the electrocardiographic features of bupropion toxicity, sodium bicarbonate is unlikely to attenuate bupropion-induced QRS widening. In the absence of another indication, its use is not indicated (Grade III recommendation). The clinical significance of QT prolongation due to bupropion is unknown and there is no specific treatment in this scenario other than addressing other factors that may be contributing to QT prolongation. There is no evidence to support prophylactic magnesium unless deficient.

Cardiovascular Instability

In patients with significant cardiovascular instability (including cardiogenic shock and arrest), case reports describe the successful use of lipid emulsion [21]. We recommend lipid emulsion therapy be administered in the setting of significant cardiovascular instability (Grade III evidence), ideally after consultation with a medical toxicologist. Three case reports (one involving an infant [45] and two involving teens [46]) describe the successful use of extra-corporeal membrane oxygenation following massive bupropion

overdoses presenting with refractory cardiogenic shock and seizures. These therapies should be considered as adjuncts to standard advanced cardiovascular life support (ACLS) care (Grade III recommendation).

Treatment Recommendations:

Supportive Care

- Monitor for a minimum of 24 h in cases of oral ingestion. Prolonged monitoring is not required when injected or crushed and insufflated.

GI Decontamination

- Activated charcoal is potentially of benefit for patients presenting within 2 h of ingestion provided their airway is mechanically protected (longer for patients with very large ingestions)
- Whole bowel irrigation is possibly of benefit for patients with large ingestions of modified-release formulations with a mechanically protected airway. Contraindications to WBI include ileus, perforation, or mechanical obstruction.
- Gastric lavage is not recommended.

Seizures

- Benzodiazepines are first-line therapy for seizures.
- Barbiturates or propofol are second-line therapy for refractory seizures.
- Phenytoin is not recommended for treatment of bupropion-induced seizures.

Cardiac

- Sodium bicarbonate is unlikely to be effective if QRS widening from bupropion is noted and is not recommended in the absence of other indications.
- In the setting of cardiogenic shock or cardiac arrest refractory to standard ACLS, lipid emulsion therapy is recommended as adjunct treatment.
- In the setting of cardiogenic shock or cardiac arrest refractory to above therapies, extra-corporeal membrane oxygenation is recommended as adjunct treatment.

Key Points

- Bupropion abuse and overdose are increasingly common.
- Routes of abuse include oral, nasal insufflation, and intravenous injection.
- Seizures are the hallmark of neurotoxicity, and presentation can be delayed up to 24 h post-ingestion of modified-release formulations.
- Sinus tachycardia is the most common cardiac manifestation of bupropion overdose.
- QRS widening and QT interval can also be seen. Despite ECG pattern suggesting sodium channel blockade, sodium bicarbonate therapy is unlikely to be effective for the treatment of widened QRS due to bupropion toxicity. No cases of Torsades de Pointes have been reported to date.
- Benzodiazepines are first-line agents for treatment of seizures. Barbiturates or propofol would be appropriate second-line agents.
- Evidence for lipid emulsion and ECMO is extremely limited, but a trial is warranted in patients with severe, refractory cardiovascular toxicity.

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Mark K. Su

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The use of the cyclic antidepressants (CAs) in the treatment of major depression has decreased as newer and safer antidepressants have become available. Cyclic Antidepressants historically have been primarily used to treat major depression but are still prescribed for other psychiatric and medical conditions, such as chronic pain syndromes (e.g., fibromyalgia), peripheral neuropathy, nocturnal enuresis, migraine headache, selected drug withdrawal syndromes, and obsessive-compulsive, attention-deficit, panic and phobia, anxiety, and eating disorders [1, 2]. The CAs are associated with a low therapeutic index, potential severe cardiotoxicity in overdose, and a high frequency of adverse effects secondary to their nonspecific pharmacologic actions. Although CA use is less than it once was, the CAs remain on the 2014 American Association of Poison Control Centers' list of Top 25 Categories of Substances associated with fatalities [1, 3].

Currently available CAs are listed in Table 1. The three most commonly reported CAs involved in reported drug exposures in the United States are amitriptyline, doxepin, and nortriptyline [3, 4]. Outside of the United States, other CAs (e.g., dothiepin and clomipramine) may be seen more commonly in overdose [5–8]. Two other CAs, maprotiline and amoxapine, have minor structural differences compared with traditional CAs but have similar toxicity in overdose.

Toxicity from CAs most commonly occurs following an acute intentional overdose. However, there are multiple ways by which CAs may

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Table 1 Cyclic antidepressants

Generic name	Trade name ^a	Available in USA	Active metabolite
Amitriptyline	Elavil	Yes	Nortriptyline
Amoxapine	Asendin	Yes	Hydroxyamoxapine
Clomipramine	Anafranil	Yes	Desmethylclomipramine
Desipramine	Norpramin, Pertofrane	Yes	None
Dothiepin	Prothiaden	No	Nesmethyldothiepin
Doxepin	Adapin, Sinequan	Yes	Desmethyldoxepin
Imipramine	Tofranil	Yes	Desipramine
Lofepramine	Tymelyt	No	Desipramine
Maprotiline	Ludiomil	Yes	Desmethylnaprotiline
Nortriptyline	Pamelor, Aventyl	Yes	None
Opipramol	Insidon	No	None
Protriptyline	Vivactil	Yes	None
Trimipramine	Surmontil	Yes	Desmethytrimipramine

^aTrade names may vary between countries. The ones given are examples

Table 2 Mechanisms for cyclic antidepressant drug toxicity at therapeutic doses

Combination medications containing other active ingredients (e.g., antipsychotics)
Development of serotonin toxicity
Elevated plasma concentrations of CAs due to genetically based slow hepatic metabolism
Exacerbation of preexisting cardiovascular or central nervous system (CNS) disease
Pharmacokinetic drug interactions with medications that inhibit hepatic metabolism
Pharmacodynamic drug interactions with medications sharing similar pharmacologic actions
Unacclimated (i.e., CA-naïve) individuals started on high initial doses

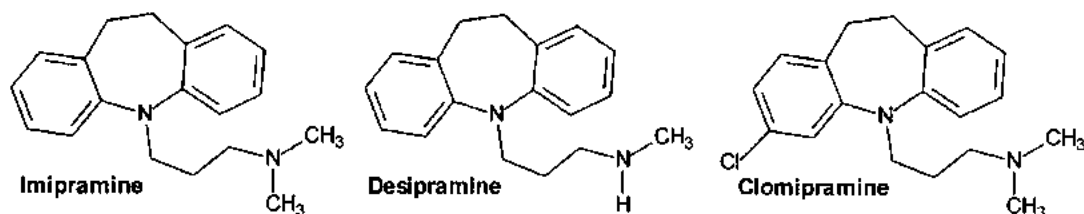
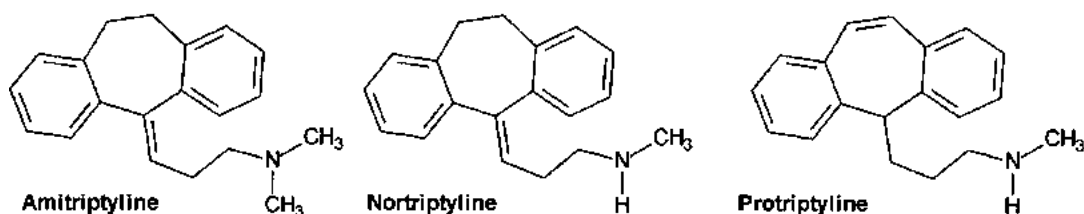
CA cyclic antidepressant

produce mild-to-moderate clinical toxicity when administered in therapeutic doses (Table 2). First, the average therapeutic dose of CAs is highly variable. In general, low doses are used initially, followed by gradual increases until the desired therapeutic response is achieved. This approach allows patients to become acclimated to the potential adverse effects. Patients started at higher initial doses are more likely to develop such adverse effects. Second, toxicity can result when CAs are combined with other medications having similar pharmacologic actions (e.g., antihistamines, antipsychotics) [9]. Third, a subset of the population consists of poor metabolizers of CAs due to CYP2D6 polymorphism, and these individuals

develop higher plasma CA concentrations at any given dose [10, 11]. Fourth, many drugs have the potential to inhibit the metabolism of CAs, resulting in elevated CA plasma concentrations [10]. Fifth, some CAs are available as mixed-drug formulations combined with either benzodiazepines or antipsychotic agents and have the potential for combined drug toxicity. Sixth, patients with certain medical conditions, such as underlying cardiac problems or seizure disorder, are more susceptible to CA toxicity at therapeutic doses [10]. Finally, CAs have the potential to produce serotonin toxicity, especially when taken concomitantly with other serotonergic medications (see ► Chap. 24, “Serotonin Syndrome”).

Biochemistry and Clinical Pharmacology

The CAs have a distinct chemical structure comprising three aromatic rings: a central seven-member ring, two outer benzene rings, and an aminopropyl side chain connected to the central ring (Fig. 1) [1]. There are only minor structural differences among the CAs, usually on the central aromatic ring or aminopropyl side chain. Amoxapine is unique in that it has an aromatic substituent. Maprotiline has an ethylene bridge across a six-member center ring, giving it a tetracyclic chemical structure. Other chemicals

Dibenzazepines**Dibenzocycloheptenes****Fig. 1** Chemical structures of some cyclic antidepressants**Table 3** Agents that may cause a false-positive cyclic antidepressant qualitative drug screen

Carbamazepine
Cyclobenzaprine
Cyproheptadine
Dimenhydrinate
Diphenhydramine
Phenothiazines
Quetiapine

that share the same basic tricyclic chemical structure as the CAs produce similar toxicity in overdose and may trigger a false-positive CA plasma or urine drug screen (Table 3) [12–15].

Pharmacokinetics

All CAs share similar pharmacokinetic properties [10]. They are highly lipophilic and easily cross the blood–brain barrier. Peak plasma levels occur between 2 and 6 h after ingestion at therapeutic doses. Gastrointestinal absorption may be prolonged because of their antimuscarinic effect on gut motility. Bioavailability is only 30–70% because of extensive first-pass hepatic metabolism. They are highly protein bound to α_1 -acid-glycoprotein. Their apparent volume of distribution is extremely large (range 10 to

50 L/kg). Tissue CA levels are commonly 10–100 times greater than plasma levels [10]. Only 1–2% of the total body burden of CAs is found in the blood [16]. These pharmacokinetic properties explain why attempts at removing CAs by hemodialysis, hemoperfusion, peritoneal dialysis, or forced diuresis are ineffective [16].

Pharmacokinetics of Cyclic Antidepressants

Volume of distribution: large

Gastrointestinal absorption: rapid

Bioavailability: 30–70%

Peak blood levels: 2–6 h after ingestion

Protein binding: highly protein bound

Half-life: ranges from 24 to 48 h

Method of elimination: eliminated by hepatic metabolism using CYP-450 system

Active metabolites: some CAs have active metabolites

The CAs are eliminated almost entirely by hepatic oxidation, which consists of *N*-demethylation of the amine side-chain groups and hydroxylation of ring structures (Fig. 2). The removal of a methyl group from the tertiary amine side chain usually produces an active metabolite designated by the *desmethyl*- (or *nor*-) prefix. These active metabolites often have different pharmacologic activities compared with the parent compounds.

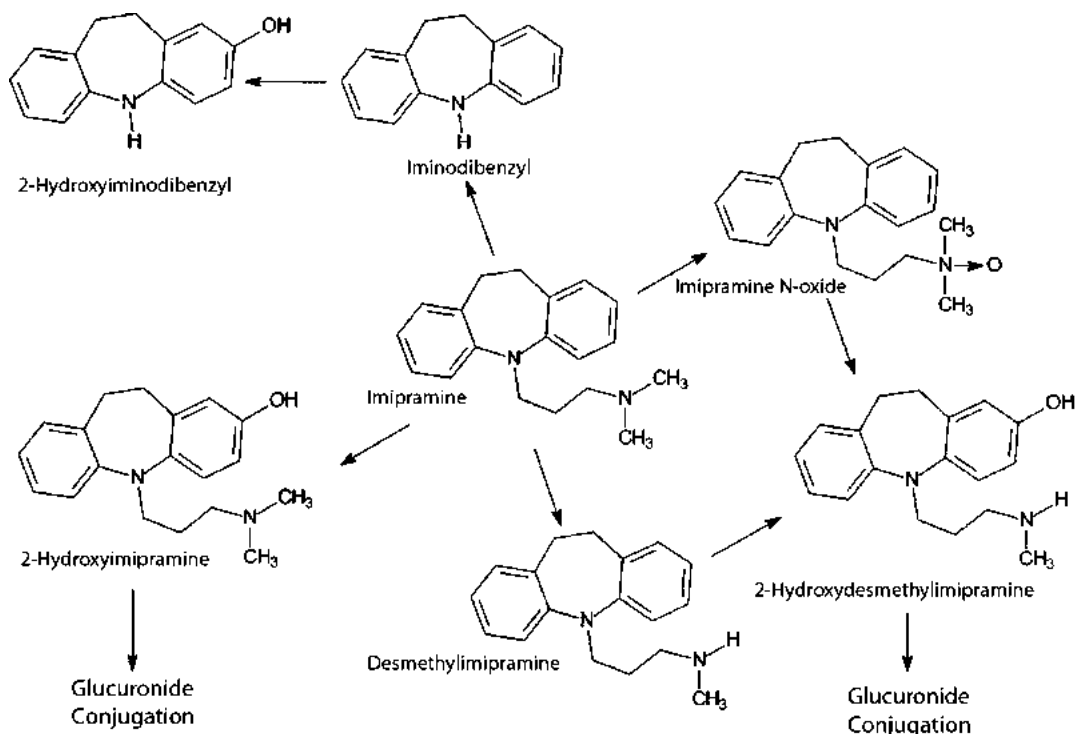


Fig. 2 Structural depiction of the metabolic pathways of imipramine. These metabolic transformations are also typical of other cyclic antidepressants

Amoxapine and maprotiline have active metabolites. Although secondary amines, such as desipramine, nortriptyline, and protriptyline, are effective antidepressants, their metabolites are generally inactive. Clinical toxicity from tertiary CAs usually lasts longer than toxicity from the secondary CAs alone because of the production of active metabolites. Some CAs undergo enterohepatic circulation before their eventual oxidation, conjugation, and renal elimination, but this does not contribute significantly to their toxicity. The average elimination half-life of CAs is approximately 24 h (range 6–36 h) at therapeutic doses, which can increase to 72 h after overdose. As previously noted, inhibition of CA metabolism by other drugs that use the same hepatic enzymes can prolong the half-life of CAs; this carries the risk of elevating CA plasma concentrations and producing clinical CA toxicity at therapeutic doses.

Pathophysiology

The CAs are nonselective agents that exhibit a multitude of pharmacologic effects (Table 4). There are subtle and potentially clinically significant pharmacologic differences among the CAs at therapeutic plasma concentrations. These differences become less important, however, at the higher plasma levels typically associated with overdose. Only a few of the pharmacologic actions of the CAs are believed to have a direct therapeutic effect, among them inhibition of monoamine reuptake (norepinephrine, serotonin [5-hydroxytryptamine (HT)]) and antagonism of postsynaptic serotonin receptors (5-HT₂) [7, 16]. The remaining pharmacologic actions essentially have no therapeutic benefit but contribute significantly to CA-related adverse effects and overdose toxicity. Most of the clinical findings seen in CA

Table 4 Pharmacologic actions of cyclic antidepressants^a

Antagonism of histamine receptors
Antagonism of muscarinic receptors
Antagonism of α -adrenergic receptors
Antagonism of norepinephrine or serotonin reuptake
Antagonism of sodium channel conduction (influx)
Antagonism of potassium channel conduction (efflux)
Antagonism of GABA _A receptors

GABA_A γ -aminobutyric acid

^aListed in descending order of potency

overdose can be explained by the following pharmacologic actions.

Antihistaminic Effects

The CAs are potent inhibitors of peripheral and central postsynaptic histamine receptors [7]. Doxepin is a particularly potent antihistamine, but its nonspecific pharmacologic activity makes it impractical to use for treatment of seasonal allergies or other allergic conditions. Antagonism of central histamine receptors primarily leads to sedation and may contribute significantly to the development of coma and seizures frequently seen in CA overdose.

Anticholinergic (Antimuscarinic) Effects

CAs frequently produce anticholinergic effects [7]. They are competitive inhibitors of acetylcholine at central and peripheral muscarinic receptors. Antimuscarinic is therefore a more precise term because CAs are not antagonists at nicotinic receptors. Central antimuscarinic signs and symptoms vary from agitation to delirium, confusion, amnesia, hallucinations, slurred speech, ataxia, sedation, and coma. Peripheral antimuscarinic manifestations are primarily comprised of dilated pupils, blurred vision, tachycardia, hyperthermia, hypertension, decreased oral and bronchial secretions, dry skin, ileus, urinary retention, increased muscle tone, and tremor. Antimuscarinic signs and

symptoms are exacerbated when CAs are combined with other medications that possess antimuscarinic activity. Examples of such medications include antihistamines, antipsychotics, antiparkinsonian drugs, antispasmodics, and some muscle relaxants.

Physostigmine is an inhibitor of acetylcholinesterase and can reverse antimuscarinic toxicity. Historically, physostigmine was used to reverse CA-induced antimuscarinic effects, but its use was thought to be associated with life-threatening complications [17]. Although antimuscarinic clinical manifestations are a common occurrence in CA overdose, they are not directly responsible for CA-related major toxicity or deaths. Antimuscarinic effects are an important clinical marker of CA toxicity, but they do not require specific therapy other than supportive care. Physostigmine is not indicated in the current management of CA overdose [18].

Antagonism of α -Adrenergic Receptors

Inhibition of postsynaptic central and peripheral α -adrenergic receptors, but not β -adrenergic receptors, is characteristic of most CAs [7]. CAs have a much greater affinity for α_1 -adrenergic than α_2 -adrenergic receptors [7]. Inhibition of α_1 -receptors results in CNS sedation, orthostatic hypotension, reflex tachycardia, and pupillary constriction. This action frequently offsets antimuscarinic-induced pupillary dilation. Patients with CA toxicity can present with constricted, dilated, or midpoint-sized pupils.

Inhibition of Amine Reuptake

Inhibition of monoamine reuptake is believed to be the most important mechanism by which CAs are efficacious in the treatment of depression. CAs are potent inhibitors of norepinephrine and 5-HT reuptake, but they have little affinity for inhibition of dopamine reuptake [7]. Inhibition of neurotransmitter reuptake leads to an increase in synaptic concentrations and subsequent augmentation of the neurotransmitter response. Inhibition of

norepinephrine reuptake is thought to produce the early sympathomimetic effects occasionally seen in some CA overdoses and may contribute to the development of cardiac dysrhythmias [16]. Serotonin toxicity results from increased 5-HT brainstem activity and has been produced by CAs that are particularly potent 5-HT reuptake inhibitors, such as clomipramine and amitriptyline [1]. In general, CAs must be combined with other serotonergic agents to produce serotonin toxicity. Myoclonus and hyperreflexia are signs of increased serotonin.

Sodium Channel Blockade

Cyclic antidepressant-induced cardiotoxicity is the most important factor contributing to patient mortality [6]. Life-threatening cardiotoxicity results from CA-induced inhibition of sodium influx through voltage-gated sodium channels. Inhibition of fast sodium channels in His-Purkinje cells leads to delayed depolarization and conduction abnormalities. Impaired sodium entry into myocardial tissue leads to decreased contractility. Sodium channel blockade, often referred to as a *membrane-stabilizing, quinidine-like, or local anesthetic effect*, results in a prolongation of phase 0 of the action potential. These effects become more pronounced with rapid heart rates, hyponatremia, and acidosis [19]. Sodium channel blockade is expressed on the electrocardiogram (ECG) as prolongation of PR and QRS intervals and right-axis deviation (RAD) of the terminal 40 msec [19]. The RAD is most pronounced in the terminal 40 msec of limb leads, as shown on the ECG by a terminal R wave in lead aVR and an S wave in lead I (see Figs. 21–15, 21–16, and 21–17). Rapid influx of sodium is necessary for the release of intracellular calcium stores and subsequent myocardial contractility. Some of the negative chronotropic effects of sodium channel blockade can be attenuated by sinus tachycardia secondary to antimuscarinic activity [19]. Local changes in electrical conduction can predispose to ventricular dysrhythmias by establishing reentry loops. Severe sodium channel blockade culminates in depressed

myocardial contractility, various types of heart block, hypotension, cardiac ectopy, and widening and RAD of the terminal 40 msec of the QRS complex.

Sodium channel blockade can be overcome in part by serum alkalinization (pH 7.45 to 7.55) and increasing the serum sodium concentration. In humans, intravenous sodium bicarbonate (NaHCO_3) is thought by some to be more effective than either hyperventilation (serum alkalinization) or intravenous sodium chloride in treating CA cardiotoxicity [20], but this has not been clearly established. One theoretical explanation for the postulated greater effectiveness of NaHCO_3 is that it produces both plasma alkalinization and increased serum sodium concentration [20]. The mechanism by which serum alkalinization partially reverses sodium channel blockade is unknown but currently is believed to be unrelated to enhancement of plasma CA serum protein binding (α_1 -acid glycoprotein), although it may involve reduced CA binding to the sodium channel [21]. Serum alkalinization is likely to result in a decrease in the overall inhibition of sodium ion influx. Animal data suggest that hypertonic saline (7.5% sodium chloride) may be as efficacious as NaHCO_3 in reversing CA cardiotoxicity [21]. Whether this finding also would be applicable to humans is currently unknown. Hypertonic saline is believed to act primarily by increasing the extracellular sodium concentration gradient, favoring the inward movement of sodium ions.

Potassium Channel Antagonism

Cyclic antidepressants block myocardial potassium channels and inhibit potassium efflux during repolarization [19]. This effect is seen on the ECG as QT interval prolongation, which is more pronounced at slower heart rates [21]. The extent of QT prolongation that is related to the inhibition of potassium efflux is hard to determine because the sodium channel effect is responsible for the broadening of the QRS complex, which by itself prolongs the QT interval. Many CA overdose patients develop sinus tachycardia, which is partially protective against QT interval prolongation.

Torsades de pointes (see ► Chap. 22, “Toxicant-Induced Torsade de Pointes”) is a potential life-threatening complication of severe inhibition of potassium efflux and delayed repolarization that is seen more commonly with therapeutic doses than with CA overdoses [22]. It is possible that the antimuscarinic-induced sinus tachycardia causes a relative narrowing of the QT interval and protection against torsades de pointes [19].

γ-Aminobutyric Acid A Receptor Antagonism

Generalized seizures occur in approximately 10% of CA overdoses [23]. Possible mechanisms for these seizures include CA-induced GABA_A receptor antagonism, neuronal sodium channel blockade, central anticholinergic activity, effects on biogenic amines, and antihistamine effect. As described below, benzodiazepines and barbiturates are potent GABA_A agonists and are considered the anticonvulsants of choice in treating CA-induced seizures [23]. Propofol is a short-acting intravenous anesthetic with anticonvulsant activity that may be utilized for patients with refractory seizures [24].

Clinical Presentation

Therapeutic doses of CAs are variable and are determined by many factors. In general, typical doses range from 1 to 5 mg/kg/day. Although some patients tolerate higher doses without adverse effects, doses greater than this have the potential to produce clinical toxicity. Life-threatening toxicity usually occurs with ingestions of greater than 10 mg/kg in adults [25]. Some patients are at greater risk for CA-related toxicity, including patients who have coingested cardiotoxic or CNS-depressive medications, geriatric patients, pediatric patients, and patients with heart disease. Cyclic Antidepressant-related toxicity is commonly associated with ingestions of greater than 1 g [25]. Most CA overdose fatalities occur within the initial hours after ingestion, often before the

patient reaches the hospital [26]. Fatalities are unusual for patients who are alive at the time of arrival to the hospital and receive appropriate care [27]. The mortality rate for hospitalized CA overdose patients is approximately 2% [27, 28]. The amount of CA ingested in most overdose cases is unknown. The diagnosis of CA toxicity should be suspected from a history of CA ingestion, clinical presentation consistent with CA toxicity, characteristic ECG abnormalities, or positive plasma CA drug screen.

Qualitative urine or plasma CA drug screens have high sensitivity but low specificity due to false positives (e.g., phenothiazines, carbamazepine). This aspect limits their utility in confirming the presence of CAs, but their low cost and rapid turnaround time also are occasionally beneficial. However, positive qualitative screens do not differentiate between therapeutic and toxic levels. Also, false-positive results are reported with medications that structurally resemble CAs (see Table 3) [12–16].

In contrast, quantitative determinations of plasma CA concentrations are specific for individual CAs and possess low false-positive rates. However, these tests are costly, time-consuming, and rarely clinically useful in the acute overdose setting [29, 30]. Quantitative assays are most useful for differentiating between therapeutic and toxic levels during long-term drug therapy (e.g., compliance, metabolism) [29, 30]. Furthermore, the results of quantitative assays are rarely available at the time of patient evaluation and have a negligible impact on patient care.

Some studies have shown that patients with a combined plasma concentration of parent CA and metabolite of greater than 1000 ng/mL are at greater risk for developing seizures and cardiotoxicity [29, 30]. The severity of clinical toxicity does not always correlate, however, with the extent of plasma CA concentration. Patients can develop severe toxicity at plasma concentrations less than 1000 ng/mL [29, 30]. Conversely, patients with plasma CA concentrations much greater than 1000 ng/mL may not develop seizures or ventricular dysrhythmias [29]. Serious toxicity rarely develops at therapeutic concentrations (<300 ng/mL). For

patients with plasma concentrations in this range, other causes should be considered to explain the patient's condition. As always, the primary focus should be on treating the patient, not the drug concentrations.

A unique characteristic of CAs is their ability to undergo significant postmortem drug redistribution [31, 32]. Plasma concentrations can increase by 10-fold to 50-fold after death as tissue binding sites release CAs, with resultant back diffusion into the blood as a time-dependent process. Theoretically, the accuracy of postmortem CA levels as a reflection of immediate antemortem levels is related inversely to the time interval between death and subsequent specimen collection. Elevated CA concentrations that are obtained after death may be assigned inappropriately as the cause of death, when they simply reflect therapeutic body burdens that have undergone redistribution. Unless this possibility is recognized, it may raise false concerns about the care provided to the patient during his or her hospitalization or a misclassification of the cause of death to drug toxicity or overdose.

Clinical Manifestations of Acute Overdose

Signs and symptoms typically develop within the first few hours after ingestion [33]. The clinical presentation of CA toxicity varies from mild antimuscarinic symptoms to coma and severe cardiotoxicity. Another consideration is that CA ingestions often involve coingestion of other drugs which can produce additional toxicity. Patients who do not manifest significant toxicity (Table 5) by 6 h postingestion are considered at low risk for life-threatening complications. The most frequently reported effects are CNS sedation and sinus tachycardia. Along with other antimuscarinic effects, these effects serve as clinical markers of CA toxicity, but alone they are rarely responsible for fatalities. Antimuscarinic effects are not uniformly present in CA toxicity [25]. The antimuscarinic syndrome is classically associated with diminished bowel sounds and ileus. Gut function is fairly resistant to this effect,

Table 5 Major toxicity criteria following CA overdose

Altered mental status
Cardiac dysrhythmias or conduction defects
Hypotension
Respiratory depression
Right-axis deviation of the terminal 40 msec of QRS in limb leads
Seizures
Widened QRS complex >100 msec

however, and active bowel sounds can be present even in seriously ill patients. The presence of normal bowel sounds does not exclude the possibility of antimuscarinic syndrome.

Mild-to-moderate CA toxicity may present as drowsiness, confusion, slurred speech, ataxia, dry mucous membranes and axillae, sinus tachycardia, urinary retention, myoclonus, and hyperreflexia. Central nervous system depression is often associated with respiratory depression leading to hypoxia or aspiration or both. Many CA overdose patients require endotracheal intubation to manage their respiratory depression and loss of airway protection. Mild hypertension is observed occasionally and rarely requires treatment. Nontolerant individuals (e.g., young children) frequently develop coma and respiratory depression after relatively small overdoses without obvious peripheral antimuscarinic effects and without QRS widening [34]. Overflow urinary incontinence may be mistaken for normal micturition in pediatric (diaper-dependent) patients.

Serious toxicity almost always is seen within 6 h of major CA ingestion and consists of coma, cardiac conduction delays, wide-complex supraventricular tachycardia, hypotension, respiratory depression, premature ventricular beats, ventricular tachycardia, and seizures [4, 25, 28, 33, 34]. Secondary complications from serious toxicity include aspiration pneumonia, anoxic encephalopathy, hyperthermia, and rhabdomyolysis [25]. The acute respiratory distress syndrome is a well-recognized complication of CA overdose [35]. Seizures usually are generalized and brief and occur in roughly 10% of patients [23]. The risk of seizures increases as the QRS complex exceeds 100 msec. The exception to this rule is seen in amoxapine and maprotiline overdoses,

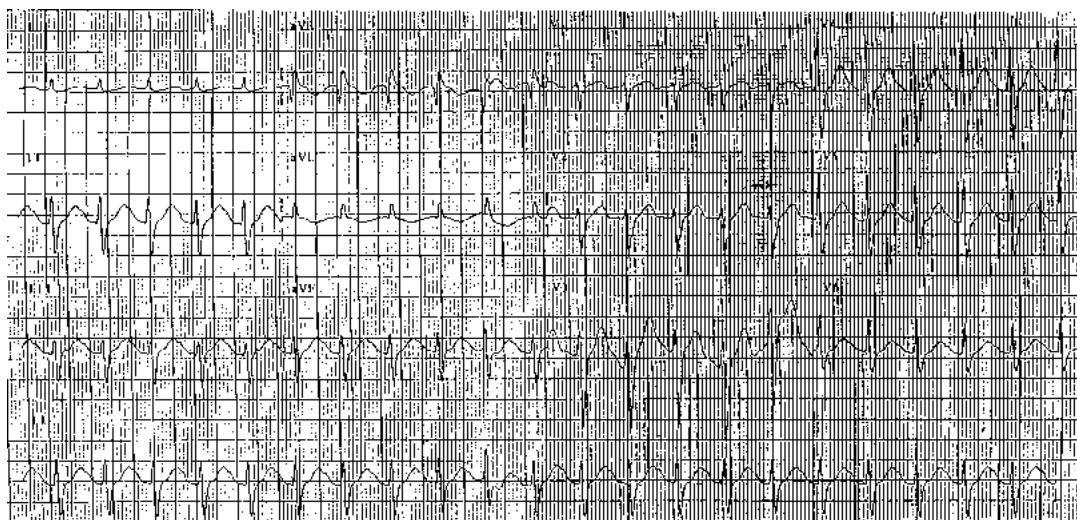


Fig. 3 Electrocardiogram (ECG) from a 39-year-old man after a tricyclic antidepressant overdose. The ECG shows signs of impaired conduction in the His-Purkinje system: QRS widening greater than 100 msec and rightward

deviation of the terminal 40-msec frontal plane QRS vector (aVR). In the presence of tricyclic antidepressant overdose, these ECG findings suggest significant cardiotoxicity

which have been reported to cause status epilepticus [6]. Amoxapine-induced seizures commonly occur without corresponding QRS widening [6].

Electrocardiogram abnormalities are almost always seen with significant CA toxicity and are extremely useful in identifying patients at increased risk for seizures and ventricular dysrhythmias [36, 37]. A QRS duration of greater than 100 msec and 160 msec following overdose is associated with approximately 33% chance of developing seizures and 50% chance of ventricular dysrhythmias, respectively [37]. The “classic” CA ECG, shown in Figs. 3, 4, and 5, consists of sinus tachycardia; RAD of the terminal 40 msec (best seen as a terminal R wave in lead aVR); and prolongation of the PR, QRS, and QT intervals (Table 6). This classic ECG pattern is seen frequently in moderate-to-severe CA toxicity [36], but the absence of these findings does not eliminate the possibility of CA toxicity during the first 6 h after ingestion [29, 30]. Moderate prolongation of the QT interval is noted frequently even at therapeutic CA doses. Nonspecific ST-segment and T-wave abnormalities are observed commonly in CA overdose. High-degree atrioventricular blocks are less commonly reported [36]. These reports

probably reflect the ECG similarities between CA effects and right bundle-branch block [38].

Life-threatening complications can occur in the absence of significant ECG abnormalities [30]. These complications are far more likely, however, in the presence of a QRS interval greater than 100 msec or RAD of the terminal 40 msec greater than 120° [29, 30, 36]. Wide-complex tachydysrhythmias are more likely if QRS prolongation exceeds 160 msec. Widening of the QRS complex and positive deflection of the terminal QRS complex in lead aVR are similar in identifying patients at risk for serious CA toxicity [36]. They usually occur together but may occur in the absence of each other. The development of RAD of the terminal 40 msec or QRS widening seems to be less predictive of CA-induced cardiotoxicity in young children [36]. Pediatric ECGs tend to have a wider range of acceptable variant features including a natural rightward axis, and this complicates the ECG identification of CA toxicity in children [36].

Electrocardiographic abnormalities, if they are to occur, universally develop within 6 h of ingestion and typically resolve over 24–48 h [39]. A subset of the normal population may have a QRS duration of more than 100 msec or terminal RAD

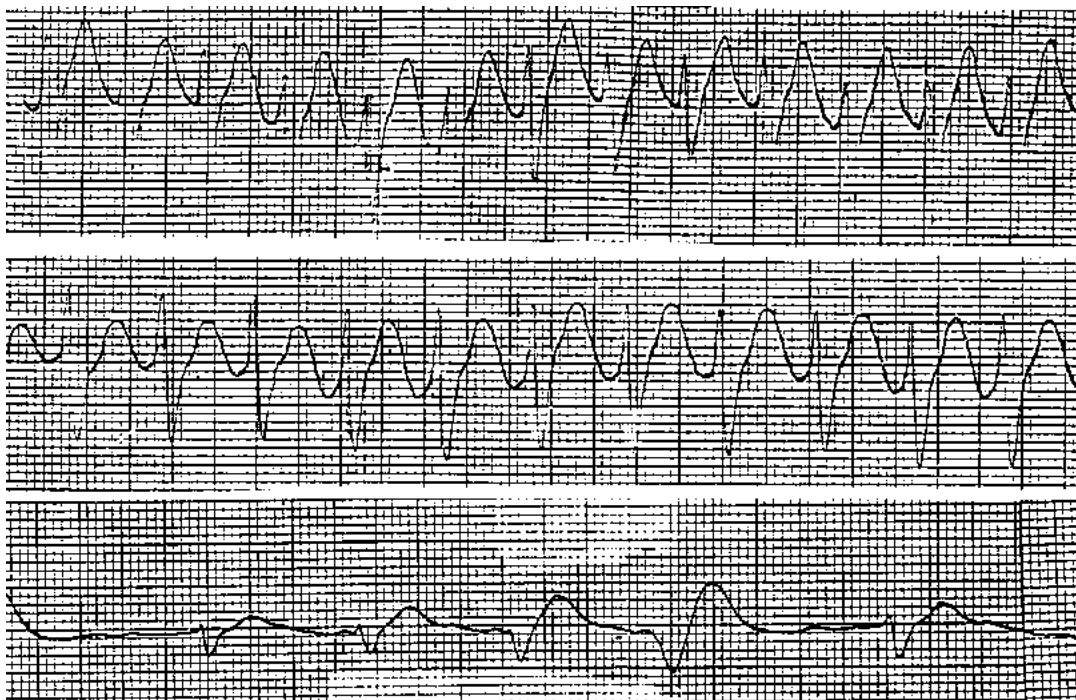


Fig. 4 Electrocardiogram (ECG) from a 39-year-old man after a tricyclic antidepressant overdose (Fig. 3) was the presenting ECG. ECG changes associated with progressively impaired conduction in the setting of an untreated tricyclic antidepressant overdose are shown. QRS width was 120 msec in the *upper* strip, which was recorded after the patient had his first seizure. The *middle* strip reveals a

QRS of 160 msec and was recorded 134 min later, immediately after the second seizure. The *lower* strip was recorded 60 min later, after the fourth seizure, in the radiology suite where the patient was undergoing a cranial computed tomography scan. Subsequently the patient experienced a cardiac arrest, and efforts at resuscitation were unsuccessful

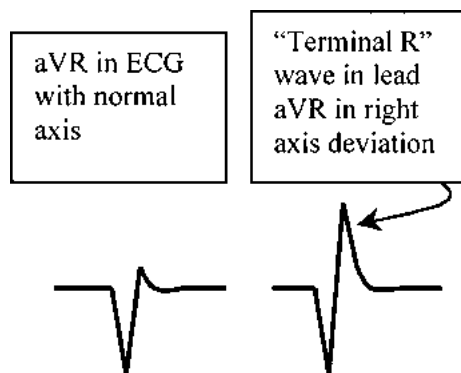


Fig. 5 A positive deflection greater than 3 mm of the terminal portion of lead aVR (R'), frequently called a *terminal R*, is a significant predictor of seizures or arrhythmias in tricyclic antidepressant poisoning. Similar intraventricular conduction delay suggests presence of a fast sodium channel blocker in a poisoned patient

without exposure to sodium channel-blocking drugs; this includes individuals with a right bundle-branch block. These ECG abnormalities in isolation are not specific for CA toxicity. Many patients receiving CA therapy do not have prior ECGs available for comparison. Any observed ECG abnormalities initially should be assumed attributable to CA exposure until proven otherwise.

Diagnosis

Cyclic antidepressant toxicity should be suspected in all patients following overdose with clinical toxicity or characteristic ECG abnormalities or both (see Table 6). The differential diagnosis of CA toxicity encompasses drugs that can

Table 6 Classic electrocardiographic abnormalities in cyclic antidepressant toxicity

Sinus tachycardia
Prolonged PR interval
Prolonged QT interval
Widened QRS complex >100 msec
Right-axis deviation (positive deflection) of terminal QRS complex in lead aVR >3 mm

mimic any one of the three criteria used in making the diagnosis. A urine toxicology screen or serum drug concentration may be useful in confirming the diagnosis but is generally unnecessary and false negatives may occur in early presenters who have not had significant excretion of CA. The best screening diagnostic test for CA toxicity is the ECG because most CA-poisoned patients manifest major toxicity within 2 h of ingestion or not at all. The combination of characteristic ECG changes and typical manifestations of toxicity is a sensitive and a specific approach to the diagnosis of poisoning by these agents [38].

Treatment

All patients should be evaluated immediately for alteration of consciousness, hemodynamic instability, and respiratory impairment. Every patient requires prompt placement of an intravenous line, continuous cardiac monitoring, and a 12-lead ECG. Serial ECGs may be required in patients manifesting any signs of toxicity. Suggested laboratory studies include determinations of serum electrolytes, creatinine, and glucose concentrations. A quantitative serum acetaminophen level is indicated in all intentional overdose patients. Patients with antimuscarinic signs (i.e., abdominal distension and inability to void) may require a urinary catheter to treat urinary retention. Patients who are initially asymptomatic may deteriorate rapidly and should be monitored closely for several hours (Grade II-2 – III recommendations) [22, 23].

Gastrointestinal Decontamination. Although the best method of gastrointestinal decontamination in CA ingestions is unknown, a few generalizations are supported by available evidence [40]. Activated charcoal has been shown to bind

CAs effectively and reduce their absorption [41]. Most patients who have ingested a CA within the previous few hours should receive 1 g/kg of activated charcoal [42] (Grade III recommendation); however, the airway should be adequately protected before activated charcoal administration. Patients who have ingested an overdose of CAs may have sudden deterioration in their mental status and may aspirate if their airway is not protected. Activated charcoal has not been shown to improve outcome after CA overdose. If activated charcoal is given, it should be administered as a single dose.

Serum Alkalinization and Sodium Bicarbonate Therapy. As described earlier, theoretical rationale and empirical data support serum alkalinization and the administration of sodium for the treatment of CA toxicity with widened QRS complexes. This treatment can be achieved either by ventilator-driven hyperventilation with intravenous saline and by the administration of bolus 1 molar (8.4%) NaHCO_3 . QRS widening greater than 100 msec warrants bolus NaHCO_3 therapy and admission to a monitored hospital bed [32]. Patients with a decreased level of consciousness should be treated with mechanical ventilation and induced respiratory alkalosis, with the aim of keeping the serum pH between 7.5 and 7.5. Any hemodynamic deterioration, seizures, or sudden further widening of the QRS complex can be treated with bicarbonate boluses. If multiple repeated boluses of sodium bicarbonate are administered, serum sodium and pH should be monitored.

Indications for ventilator-driven serum alkalinization/ saline or NaHCO_3 therapy include QRS complex duration greater than 100 msec and ventricular dysrhythmias (Table 7) (Grade II-3 – III recommendations) [16, 18, 20]. Intravenous NaHCO_3 and an increase in serum pH have been shown to improve conduction, increase contractility, and suppress ventricular ectopy (Grade II-3 recommendation) [20]. Because of the potential for cardiogenic pulmonary edema and acute lung injury in CA-toxic patients, it is important to reduce the rate of fluid administration when the patient is stabilized. Potential complications of intravenous NaHCO_3 therapy include

Table 7 Indications for serum alkalization in cyclic antidepressant toxicity^a

Terminal right-axis deviation (positive deflection) in lead aVR >3 mm
Ventricular dysrhythmias
Widened QRS complex >100 msec

^aWith induced hyperventilation or sodium bicarbonate administration. See text for details

hypokalemia, hypercapnia, hypotension, prolongation of the QTc interval, and intracellular acidosis [43]. Serum potassium concentrations should be measured frequently, and potassium supplementation should be administered to maintain the serum potassium concentration above 4.0 mEq/L. Induced hyperventilation is performed by inducing a respiratory alkalosis with the targeted end point being a pH range similar to that described earlier.

Intravenous Fat Emulsion. Intravenous fat emulsion (IFE) as an antidote for the treatment of poisoned patients appears to be gaining popularity recently [44]. Possible mechanisms of action of IFE include the creation of an intravascular “lipid sink” to sequester drug, improvement in fatty acid utilization to serve as an alternative fuel source, a direct cardiostimulant effect to improve hemodynamic status, and modulation of ion channels [44]. There are some animal and human data to support the beneficial effect of IFE to improve hemodynamic status and survival in the setting of CA toxicity [45–48]. However, due to the historic efficacy of sodium bicarbonate, additional study is needed before IFE can be recommended as antidotal therapy for CA toxicity at this time.

Altered Level of Consciousness

In general, patients with an altered level of consciousness should be assessed for hypoglycemia and intravenous dextrose should be administered if glucose is determined to be low. Intravenous thiamine and oxygen can be routinely given to almost all patients with a depressed mental status and if concern for chronic alcohol abuse. Naloxone may be given if there are signs of the opioid toxidrome. Antagonism of postsynaptic

muscarinic, histaminic, and α -adrenergic receptors may contribute to the development of altered mentation in CA overdoses. It is possible that other direct CNS effects unrelated to these mechanisms may occur. Coma from CA toxicity typically occurs rapidly. Unresponsive patients may have unrecognized head or neck trauma. Flumazenil should not be given to patients suspected of CA overdose because this may precipitate generalized seizures (Grade III recommendation) [42]. Agitation may be seen in previously comatose patients as they awaken. Agitation is best controlled with reassurance, decreased environmental stimulation, and benzodiazepines. As mentioned previously, physostigmine plays no role in the management of CA poisoned patients.

Seizures

Most seizures occur within the first 2 h after CA ingestion. Typically, these seizures are generalized and brief and commonly do not require anticonvulsant therapy [23]. Multiple seizures are reported in less than 10% of CA overdoses [18, 23]. Focal seizures are atypical and require further neurologic evaluation. Seizures are more common with maprotiline and amoxapine ingestions and require aggressive management because status epilepticus is associated more frequently with these two particular antidepressants [24]. Benzodiazepines (e.g., diazepam, lorazepam) are the anticonvulsants of choice for ongoing seizure activity (Grade III recommendation) [23]. Barbiturates (e.g., phenobarbital) are indicated in the treatment of recurrent seizures or seizures resistant to benzodiazepine therapy (Grade III recommendation). The initial intravenous dose of phenobarbital is 15 mg/kg given in 5-mg/kg increments, but this can be increased safely in patients with continued seizure activity who are not hemodynamically compromised. Because of the potential for inducing hypotension, the initial phenobarbital loading dose should be given in 5-mg/kg increments. Propofol also may be employed as second-line or third-line anticonvulsant therapy, but there is limited

clinical experience with this approach. If not already employed for CA-induced respiratory failure, endotracheal intubation and respiratory support are required when benzodiazepines are combined with barbiturates or propofol or when high doses of either of the latter are used (Grade III recommendation) [24].

If seizures continue despite adequate dosing with benzodiazepines, phenobarbital, and possibly propofol, the next step would be to paralyze the patient with a neuromuscular blocking agent (Grade III recommendation). This paralysis stops the physical manifestations of the seizure and its secondary effects, which include metabolic acidosis, hyperthermia, rhabdomyolysis, and renal failure. It does not stop brain seizure activity, however. After induction of muscle paralysis, these patients require electroencephalographic monitoring and further anticonvulsant therapy. (Toxicant-induced seizures are discussed in detail in ► Chap. 20, “Toxicant-Induced Seizures”.)

Hypotension

Hypotension can be treated initially with isotonic crystalloid in increments of 10 mL/kg. In the setting of impaired cardiac contractility, pulmonary edema may develop if excessive fluids or NaHCO_3 is administered (Grade III recommendation). Vasopressors should be used when hypotension is unresponsive to fluid therapy (Grade III recommendation). Norepinephrine is believed to be the vasopressor of choice in the setting of CA-induced α -adrenergic blockade, but dopamine and epinephrine also have been shown to be effective (Grade II-2 – III recommendations) [39, 49, 50]. Severe CA-induced hypotension represents a potentially reversible cause of cardiovascular collapse. Mechanical support of the circulation with cardiopulmonary bypass, venoarterial extracorporeal membrane oxygenation, overdrive pacing, or aortic balloon pump assistance may be warranted in patients with refractory hypotension, although no studies adequately document their effectiveness (Grade III recommendation) [51, 52].

Dysrhythmias

Cyclic Antidepressants frequently alter cardiac rate, conduction, and contractility. Otherwise asymptomatic patients with sinus tachycardia, isolated PR and QT prolongation, or first-degree atrioventricular block do not require specific pharmacologic therapy. Conduction blocks greater than first-degree blocks can progress rapidly to complete heart block secondary to impaired infranodal conduction. Patients with isolated QRS duration greater than 100 msec may benefit from treatment with serum alkalization and NaHCO_3 therapy replacement, although this is controversial (Grade III recommendation) [20]. This recommendation is made despite the absence of randomized, controlled human trials showing NaHCO_3 therapy-related benefits in otherwise asymptomatic patients with QRS prolongation [20]. Nonetheless, the early use of serum alkalization with NaHCO_3 or induced hyperventilation in the setting of sodium channel blockade has become a common practice for treating QRS widening (Grade II-3 recommendation) [16].

Ventricular dysrhythmias should be treated immediately with molar NaHCO_3 bolus administration (Grade III recommendation) [16]. Lidocaine is the second agent of choice in treating ventricular dysrhythmias (Grade III recommendation) [16] although excessive lidocaine administration is capable of producing seizures. Synchronized cardioversion is appropriate in patients with unstable dysrhythmias. Torsades de pointes should be treated initially with at least 2 g of intravenous magnesium sulfate. Efforts should be made to rule out other causes of torsades de pointes. Overdrive pacing may be attempted to prevent recurrence of this dysrhythmia. Intravenous isoproterenol may be beneficial in treating recurrent torsades de pointes when overdrive pacing is not available. Treatment of torsades de pointes is discussed in ► Chap. 22, “Toxicant-Induced Torsade de Pointes.” The medications in Table 8 should be considered contraindicated in the treatment of torsades de pointes–induced dysrhythmias.

Table 8 Medications contraindicated in severe cyclic antidepressant overdose

Class Ia antidysrhythmics
Class Ic antidysrhythmics
Class III antidysrhythmics
β -Blockers
Calcium channel blockers
Flumazenil

Disposition

Patients who remain asymptomatic for at least 6 h after ingestion do not require hospital admission for toxicological reasons. They still may require hospital admission because of coexisting medical or psychiatric conditions. Psychiatric evaluation is warranted for intentional drug ingestions. All symptomatic patients require hospital admission to a monitored bed. Patients showing signs of moderate-to-severe toxicity should be admitted to an intensive care unit.

Indications for Emergency Department or ICU Admission in Cyclic Antidepressant Poisoning

All patients with evidence of moderate-to-severe CA toxicity require ICU admission.

Patients with mild toxicity can be admitted to a monitored bed.

Criteria for Emergency Department or ICU Discharge in Cyclic Antidepressant Poisoning

No clinical manifestation of toxicity after at least 6 h of observation, including normal vital signs

Normal or baseline electrocardiogram after 6 h of observation

Psychiatric evaluation completed in cases of intentional overdose

Nontoxic serum acetaminophen concentration (intentional overdoses)

Neurologic and pulmonary stability

Absence of antimuscarinic signs

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Lithium salts, particularly lithium carbonate, are widely used to treat bipolar disorders. Although most literature cites the seminal article published in 1949 by the Australian psychiatrist Cade [1] as the initial study promulgating the efficacy of lithium salts in the treatment of mania, many earlier publications recognized its potential utility in the treatment of mood disorders, however. The Cade article, showing an attenuation of mania, followed his observation of a sedating effect of lithium on pigs. In a book by Hammond [2] published in 1871, lithium was recommended for the treatment of mania and depression. Similarly a publication by Lange in 1897, as described by Hanson and Amdisen [3], is reported to have promoted lithium's efficacy of the treatment of depression.

After the publication of the Cade article [1], lithium's use in the treatment of mood disorders became commonplace. Further studies on the use of lithium for bipolar disease were conducted in Europe, resulting in earlier widespread use of these salts there than in the United States [4]. The use of lithium salts in the United States lagged behind Europe because of many reports in the American literature in which the use of lithium as a salt substitute resulted in several deaths.

Along with the widespread use of lithium salts as a therapeutic agent, case reports were published describing significant toxic manifestations from this therapy associated with elevated serum lithium concentrations. El-Mallakh [5] described case reports of lithium toxicity dating back to 1948. In 1978, Hanson and Amdisen [3] described 100 case reports of lithium intoxication from the published literature dating back to 1949. There is little question that unmonitored lithium therapy, particularly in a susceptible patient, may result in toxicity.

Biochemistry and Clinical Pharmacology

Chemistry

Along with oxygen, lithium is the most chemically simple of all therapeutic agents, yet both have complex physiologic effects that are still

not fully understood. Lithium, from the Greek *lithos* meaning "stone," is in group 1A of the periodic table, situated immediately above sodium, providing an explanation for the similarity in behavior of these two ions. Lithium's atomic number of 3 means that it contains three electrons with a single unpaired one in its outermost shell. This outermost electron is ionized easily, creating the Li^+ ion. Lithium has an atomic weight of 6.9, and is therefore a light metal.

Because of the chemical similarities between lithium and sodium, lithium chloride has a salty taste. Starting in the late 1940s, lithium chloride was available in the United States as a salt substitute (West Sal). Ingestion of lithium chloride led to virtually immediate adverse effects [6, 7], some fatal, resulting in the regulatory actions taken in regard to lithium salts by the US Food and Drug Administration [8, 9].

Pharmacokinetics

Pharmacokinetics of Lithium

Volume of distribution: 0.7–1.4 L/kg

Therapeutic plasma concentration: 0.3–1.6 mmol/L

Protein binding: negligible

Plasma elimination half-life: 12–27 h*

Mode of elimination: renal

Method to enhance elimination: hemodialysis

*The half-lives given are for volunteers. Many factors, primarily therapeutic use (as opposed to overdose in a lithium-naïve patient), advanced age, and any decrease in renal clearance, may increase half-life.

Peak plasma lithium concentrations occur 30 min to 4 h after a dose, although this can be prolonged further in delayed-release preparations [4, 5, 10]. Liquid preparations are absorbed most rapidly. For standard lithium preparations, absorption is usually complete within 8 h [10]. When lithium is used therapeutically, target plasma concentrations vary from 0.3 to 1.6 mmol/L, depending on the indication. Lithium circulates as free Li^+ ion in

plasma without significant protein binding. Plasma elimination half-life in volunteers ranges from 12 to 27 h [11–13]. The apparent plasma elimination half-life is longer in patients with long-term lithium treatment, likely related redistribution Li^+ ions from tissue stores into plasma. This same phenomenon probably explains the slow excretion of lithium after its therapeutic use has been discontinued [14]. The half-lives in patients with lithium toxicity range from 12.9 to 50.1 h in different published series [15–17]. Although red blood cell (RBC) lithium concentrations may correlate with brain tissue lithium concentrations better than plasma lithium concentrations, quantification of RBC lithium does not offer clinical advantage over the combination of serum/plasma measurements and clinical exam [18].

Lithium elimination can be reduced dramatically in the elderly, most likely due to age-related reduction in creatinine clearance, and this population should be considered to be at particular risk for toxicity during therapeutic use. Lithium's serum half-life with therapeutic use has been reported to be 36 h in elderly patients [19, 20]. Similarly, any patient, regardless of age, with subnormal creatinine clearance or who are taking medications that decrease glomerular filtration, such as angiotensin-converting enzyme inhibitors and high-dose nonsteroidal anti-inflammatory drugs, should be considered to have at least a relative contraindication to lithium therapy.

When absorbed, lithium distributes to multiple tissues, with the most consequences in the brain, kidney, and thyroid [21, 22]. Tissue concentrations of lithium may continue to increase for hours after plasma concentrations have peaked, with its distribution through the blood–brain barrier into the brain being slower than into other organs [23]. This slow distribution phase probably accounts for the delayed onset of action and the delayed resolution of lithium-induced central nervous system manifestations after toxic exposure. Its volume of distribution is reported variously to be between 0.7 and 1.4 L/kg [24–26]. Lithium is found in the cerebrospinal fluid (CSF), although only at approximately 40% of plasma concentrations [27] because of its active

transport out of the CSF [28]. Lithium concentrations in both white- and gray-matter brain tissue approximate those in CSF [27].

Virtually all of an ingested lithium dose is excreted renally, with only trace amounts found in sweat, saliva, or breast milk. When filtered through the glomerulus, lithium and sodium are reabsorbed in the proximal tubule. Approximately 80% of the filtered lithium undergoes active reabsorption against an electrical and a chemical gradient in this segment of the nephron [4, 14, 29, 30]. Lithium is reabsorbed further in the loop of Henle [4]. In contrast to sodium, lithium is not reabsorbed in the distal tubule [31]. Lithium has a reported renal clearance of 13–56 mL/min [11, 12, 17, 29], and its fractional clearance (lithium clearance/creatinine clearance) has been reported to be 0.17–0.29 [12, 29, 32]. The renal clearance and fractional excretion of lithium decrease during hemodialysis [3]. In volunteer studies, lithium clearance can be increased by the administration of sodium chloride or bicarbonate, acetazolamide, urea, or aminophylline [29]. Neither water loading nor loop diuretics affect lithium clearance [29]. The small amount of lithium that is not eliminated renally is excreted in the feces and perspiration. Lithium exhibits a high clearance by conventional hemodialysis (100–150 mL/min) [3, 33]. Hemodialysis effectively removes only plasma lithium, and there is often a posthemodialysis “rebound” increase in serum lithium concentration as lithium diffuses down its concentration gradient from tissues into the plasma [3, 17, 34]. As expected, CSF lithium concentrations decrease during this redistribution phase [35, 36].

Pathophysiology

Central Nervous System Effects

The mechanism of lithium's mood-stabilizing effect is unknown and a matter of considerable debate. Lithium causes a variety of effects on neurons, although the exact contribution, if any, of these neuropharmacologic actions to its therapeutic effects is uncertain.

Lithium can enter the neuron via the fast sodium channel and stimulate an action potential. Unlike sodium, lithium is a poor substrate for the $\text{Na}^+\text{-K}^+$ pump, and no lithium-related electrochemical gradient across the cell membrane can be maintained. In theory, this causes intraneuronal lithium loading. How this loading might relate to the mood-stabilizing effects of lithium is unclear, however.

Lithium affects many enzymes and other proteins involved in neuronal and nonneuronal function and may modulate neurotransmission and central nervous system excitability. Neurons have many regulatory guanosine triphosphate-binding proteins, and lithium is known to inhibit their activities [37].

Research focusing on the molecular mechanism underlying the therapeutic effect of lithium has revealed that it induces changes in the activities of cellular signal transduction systems, especially the phosphatidylinositol and cyclic adenosine monophosphate (cAMP) second messenger systems. Extracellular signal-related kinase pathways may mediate lithium's antimanic effects [38]. Lithium also may modulate phosphatases that have been implicated in the cause of bipolar disease [39]. Lithium also modulates the precursor uptake, synthesis, storage, catabolism, and release of serotonin, interacts directly with serotonin receptors, and modulates serotonin-receptor interactions [40].

Cardiac Effects

Increase in myocardial lithium may lower intracellular potassium concentrations, causing T-wave flattening and ST-segment abnormalities [41, 42]. Sinus and arteriovenous node dysfunction, intraventricular conduction delays, and fatal bradycardias have also been reported [43, 44].

Thyroid Effects

Li^+ ion concentrates in the thyroid gland, achieving concentrations four to five times those occurring simultaneously in the plasma. Normally the thyroidal response to thyroid-stimulating hormone is mediated by cAMP. The formation and

the action of the latter may be inhibited by lithium, however. Additionally, in rodent models, lithium has been shown to reduce organification of iodine and colloid formation [45–47]. Lithium therapy is associated with an approximately sixfold risk of clinical hypothyroidism, compared with placebo, despite an increase in mean thyroid-stimulating hormone concentrations [48]. Parathyroid hormone and serum calcium concentrations are also increased, though generally not to clinically significant levels [48].

Renal Effects

Acute or chronic exposure to lithium can cause a loss in renal urine-concentrating ability. In 1970, the unresponsiveness of the kidney to antidiuretic hormone (ADH) was reported in patients being treated with lithium [49]. On average, renal concentrating ability is reduced by 15% of normal maximum (-158 mOsm/kg) in patients on chronic lithium therapy [48]. Normally, ADH acts by stimulating renal adenylyl cyclase to produce cAMP. Lithium inhibits this reaction [50]. ADH regulates the renal water channel (aquaporin), and lithium treatment causes a downregulation of this channel [46]. The end result of this loss of renal concentration ability is diabetes insipidus, characterized by excessive free water loss and resulting hypernatremia. Free water loss continues in the face of intravascular volume depletion until the fall in glomerular filtration leads to acute renal failure. Although the hypothalamus responds to the presence of hypernatremia and hypovolemia by increasing ADH excretion, the kidney cannot respond adequately to this homeostatic mechanism [51]. Because of its nonresponsiveness to ADH, this effect is called *nephrogenic diabetes insipidus* (NDI). Lithium also may cause an alkaline urine and renal tubular acidosis [4].

Clinical Presentation

Lithium intoxication is characterized primarily by peripheral neuromuscular signs and, in more severe cases, central nervous system (CNS)

dysfunction. Renal manifestations of lithium toxicity, such as NDI, may occur with or without CNS signs. Lithium may have adverse effects on the thyroid gland and cardiac conduction system therapeutically and during periods of toxicity. Acute lithium toxicity is often associated with gastrointestinal symptoms. A modification of the grading scheme for lithium intoxication, promulgated by Hansen and Amdisen [3, 15, 52], is presented in Table 1.

Lithium intoxication is classically divided into *acute*, *chronic*, or *acute-on-chronic* presentations [53].

By definition, a patient with *acute lithium poisoning* is lithium naive and takes an overdose. Patients with acute lithium poisoning begin the episode of illness with negligible lithium concentrations in the brain, heart, and kidneys. Therefore, particularly in the early hours of the poisoning event, they tend to have few signs and symptoms of toxicity despite serum lithium concentrations far in excess of the “therapeutic” range.

In contrast, a patient with *chronic lithium poisoning* is prescribed lithium therapeutically, and typically some event decreases renal lithium

elimination. In the classic analysis of 123 cases of lithium intoxication by Hansen and Amdisen [3], aside from the obvious acute overdose, intravascular volume depletion in association with negative water balance was found to be the major predisposing factor for lithium intoxication. Volume loss from decreased intake, excessive perspiration, gastrointestinal fluid loss, or diuretics can predispose to lithium toxicity [54–57]. Similarly, drugs that decrease renal glomerular blood flow, most notably angiotensin-converting enzyme inhibitors, may cause lithium toxicity. Although nonsteroidal anti-inflammatory drugs decrease glomerular filtration rate, their propensity to induce lithium toxicity seems to be minimal [10]. Lithium-induced NDI and polyuria [10] can contribute to a vicious cycle of intravascular volume depletion and worsening toxicity. Because thiazide diuretics selectively act to decrease sodium (and increase lithium) reabsorption in the proximal tubule, they are most prone to cause lithium toxicity [58]. Patients with chronic lithium poisoning typically present with CNS manifestations, and serum lithium concentrations may be within or near the “therapeutic” range.

Acute-on-chronic lithium poisoning occurs when a patient on chronic lithium therapy takes an acute overdose. Although these patients begin the episode of illness with some tissue lithium burden, clinically these patients present similarly to those with acute lithium poisoning.

Neurologic Effects

For reasons described earlier, there is overall a poor correlation between serum lithium concentration and clinical presentation. Patients with lithium intoxication present with a clinical picture predominantly characterized by tremor, lower extremity hyperreflexia, ankle clonus, motor hyperactivity, increased tone and rigidity, drowsiness, apathy, sluggishness, ataxia, fasciculations, and stupor, in approximately that order of decreasing frequency [3, 53].

Most patients with lithium toxicity have abnormal electroencephalograms (EEGs) [3, 59]. Some

Table 1 Grading system for lithium intoxication [3]

Grade	Features
0	Asymptomatic
1	Any of the following
	Nausea
	Vomiting
	Tremor
	Hyperreflexia
	Agitation
	Muscle weakness
	Ataxia
	Drowsiness
2	Any of the following
	Stupor
	Rigidity
	Hypotension
3	Any of the following
	Coma
	Seizures
	Myoclonia
	Cardiovascular instability

Data from Refs. [3, 26, 49]

authors have suggested that EEG changes correlate better with lithium toxicity than do serum concentrations [60]. This has not been studied systematically, and it is unclear whether EEG provides any useful information beyond that available from a bedside physical and neurologic exam. EEG changes are typically polymorphic, with rhythmic slowing of theta and delta waves of moderate-to-high voltage. These can be continuous or paroxysmal and diffuse or focal. Epileptiform changes may occur and can even mimic status epilepticus [60]. In the series by Hansen and Amdisen [3], 83% of patients had EEGs on admission, all of which were severely abnormal, mostly with 2–5 Hz spikes and sharp waves. All of these EEGs showed improvement over time as the lithium toxicity resolved, and most of them normalized.

Although in most patients lithium-induced neurotoxicity is transient, there have been many reports of permanent neurologic sequelae in patients with lithium intoxication [3, 10, 60–65]. This phenomenon is referred to as the “syndrome of irreversible lithium-effectuated neurotoxicity (SILENT)” [66]. Patients are typically described as having parkinsonian findings, including tremor, bradykinesia, slowed cognitive processing, and dementia. Interpretation of these reports is limited, however, by the frequent lack of baseline information and other possible confounding factors, such as neuroleptic drug use, preexisting diagnoses, alcoholism, or brain damage due to other factors. To date no large studies have reported long-term follow-up of patients with SILENT, and the prognosis for recovery is therefore unknown.

Renal Effects

Many lithium-induced renal abnormalities have been described with both therapeutic use and intoxication. Various reports have described decreases in creatinine clearance [67, 68], oliguria [4, 67, 68] or polyuria [4, 53, 65–69], renal tubular acidosis [4, 53, 65–69], decreased urinary concentrating ability [4, 54, 66–70], and nephrotic syndrome [4, 5, 68]. Acute renal failure after lithium

intoxication is unusual, occurring in 7% of patients in one series [53]. As previously noted, renal failure can be both a cause and consequence of lithium poisoning.

Diabetes insipidus and hypernatremia have been reported to occur in 20% of patients during therapeutic use or episodes of lithium intoxication [53, 70, 71]. Many more patients have polyuria, polydipsia, decreased urinary concentrating ability, and increased thirst [72]. This diabetes insipidus is not usually responsive to vasopressin and is nephrogenic in origin.

Thyroid Effects

Hypothyroidism, even to the point of myxedema, occasionally is related to lithium therapy [73, 74]. Goiter has been described, as thyroid-stimulating hormone production is increased. The incidence of hypothyroidism associated with lithium therapy has been reported to be 1–20% [74–76]. Risk factors for developing lithium-induced hypothyroidism include female gender, a family history of thyroid disease, and age older than 60 [76]. Because hypothyroidism and depression can appear clinically similar, it is possible for the former to be overlooked. Because of the inhibitory effect of lithium on the thyroid, hyperthyroidism can be suppressed by lithium therapy [77]. An illustrative case report described a patient with lithium toxicity and no prior diagnosis of hyperthyroidism who developed thyroid storm after hemodialysis [77].

Cardiac Effects

Many electrocardiogram changes have been associated with therapeutic lithium use and toxicity, including nonspecific ST-T-wave changes, bradycardia, conduction blocks, and junctional rhythms [46, 78]. The most common effects seen with therapeutic use are T-wave flattening or inversion and depressed ST segments in the lateral leads (Fig. 1) [46, 78].

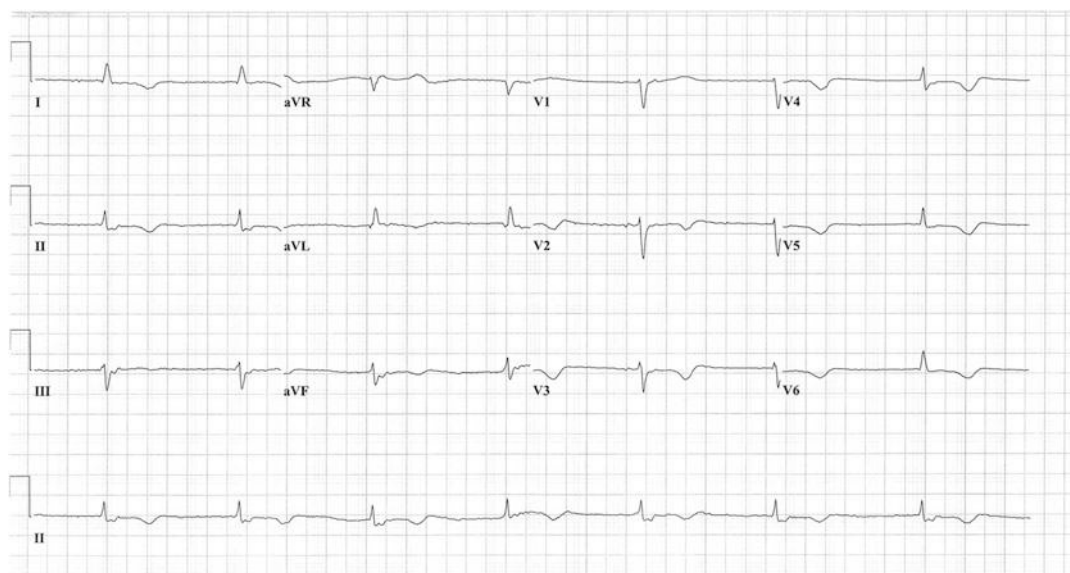


Fig. 1 ECG of a 53-year-old woman with chronic lithium toxicity (level 2.4 mEq/L) and acute delirium. She presented with junctional bradycardia and underwent emergent hemodialysis on day 1 and had spontaneous

conversion to normal sinus rhythm on hospital day 4. Note the diffuse T-wave inversion (*Courtesy of J. Ward Donovan, MD, Pinnacle Health Toxicology Center, Harrisburg, PA*)

Diagnosis

The diagnosis of lithium toxicity usually is made on the basis of the clinical history, determination of serum or plasma lithium concentration, and clinical suspicion. In the absence of a history of lithium ingestion, patients who present with the various clinical features described in the preceding section, such as altered mental status, tremor, lower extremity hyperreflexia and ankle clonus, and diabetes insipidus, should be suspected of having lithium toxicity. If a patient has a history of psychiatric disorder or access to lithium in the environment, this should heighten the suspicion.

Lithium typically is assayed in the plasma using emission photometry, atomic absorption spectroscopy, or a Li^+ ion-specific electrode. In most instances, serum or plasma lithium concentrations are measured, and most clinical experience is with these analyses. Some authors have suggested that a better correlate of tissue lithium concentrations is provided by measurement of red blood cell lithium concentrations; however, there

is little clinical experience with the interpretation of these latter values. Inadvertant collection of blood samples in a tube containing lithium heparin anticoagulant (green top) can cause false elevation of serum lithium concentrations [79]. Because lithium is an unmeasured cation, lithium poisoning has been described to cause a narrow or even negative anion gap [80]. Because the normal anion gap is approximately 12 mmol/L and even cases of acute lithium poisoning rarely feature serum concentrations exceeding 5 mmol/L, this is probably a rare and insensitive finding.

The serum lithium concentration must be interpreted in the context of whether the patient may have had an acute overdose, has been on long-term lithium therapy, or both. Once the diagnosis of lithium poisoning has been confirmed, serial measurements of serum lithium concentrations will help guide management.

Renal failure can be both a cause and consequence of lithium poisoning, and renal function should be assessed in all cases of suspected lithium poisoning. Because of the risk of NDI, serum sodium should be measured, and patients should

be watched for polyuria. If polyuria is present, measurement of serum and urine electrolytes and serial serum sodium measurements are necessary to evaluate and safely manage NDI.

Given the propensity of lithium to induce hypothyroidism, measurements of free thyroxine and thyroid-stimulating hormone are appropriate.

Acute Toxicity

Patients with acute lithium toxicity generally presents with markedly elevated plasma or serum lithium concentrations and a relative paucity of clinical signs, particularly if presentation is early after overdose. This represents the phase during which lithium is primarily in the plasma and has not distributed yet into tissues. If plasma lithium concentration remains elevated for a prolonged time, however, it may distribute into various tissue compartments, and clinical manifestations may become evident thereafter. Because lithium exerts its neurologic effects while resident in the brain, and because distribution of lithium into and out of the brain is slow, the development and resolution of these clinical manifestations lag behind the initial rise and subsequent fall in plasma concentrations.

Chronic Toxicity

The diagnosis of chronic lithium toxicity can be much more challenging than the diagnosis of acute lithium overdose. These patients may have significant tissue lithium stores yet have modest plasma lithium concentrations [3, 53, 81]. Neurologic findings and NDI may persist even after serum and tissue lithium concentrations have fallen to low or undetectable levels.

Treatment

As with all poisonings, the treatment of lithium intoxication may require aggressive management of the patient's airway and ventilation and circulatory support, depending on clinical severity.

Patients who are lithium intoxicated may be hypermetabolic, may be diaphoretic, may have decreased fluid intake or frank emesis, and are likely to be intravascularly volume depleted. Because lithium clearance depends on glomerular filtration rate, fluid resuscitation to reestablish normal intravascular volume and restore normal urine flow is paramount. Because lithium clearance increases with sodium loading [29], resuscitation with isotonic saline to the point of normal intravascular volume clinically with attainment or maintenance of eunatremia may enhance lithium's renal clearance (grade III recommendation). Once this has been achieved, urine output should be closely monitored. If NDI develops, targeted fluid replacement with half-normal saline or even 5% dextrose in water (D5W) may be needed to replace free water losses and maintain eunatremia and euvolemia.

Patients who have severe lithium toxicity may have many secondary complications, including seizures, acute renal failure, severe rhabdomyolysis, and adult respiratory distress syndrome. These complications should be treated by standard supportive measures, with no specific treatment indicated as a result of their occurrence in the context of lithium toxicity.

Gastrointestinal Decontamination

Gastrointestinal decontamination is likely of limited benefit to patients with lithium poisoning, with the possible exception of patients with acute or acute-on-chronic lithium poisoning and impaired renal function.

Activated Charcoal

Lithium does not bind to activated charcoal, and activated charcoal administration has no established or theoretical role in the management of lithium poisoning [82].

Gastric Lavage/Whole-Bowel Irrigation

Gastric lavage has not been shown to alter the outcome or clinical course of patients who have overdosed on lithium and is unlikely to be beneficial. Although whole-bowel irrigation has been

shown to reduce lithium absorption in a randomized crossover study using healthy volunteers, this study used a dose of polyethylene glycol/electrolyte lavage solution (2 L/h for 5 h) that is difficult to safely achieve in clinical practice [83]. Although anecdotal reports suggest that whole-bowel irrigation may decrease absorption, there are no controlled data relating to the effect, if any, of whole-bowel irrigation on either outcome or clinical course of patients who have lithium toxicity. Because whole-bowel irrigation is relatively free of adverse effects, it is reasonable to employ this technique in patients who have successively increasing serum lithium concentrations or who have ingested large amounts of a delayed release preparation (grade III recommendation). Whole-bowel irrigation should only be done, however, in patients whose airways are protected naturally or by virtue of intubation and who have intact bowel function. It is unlikely that whole-bowel irrigation will be beneficial unless the polyethylene glycol solution is given rates that could only be achieved via a naso- or orogastric tube. Although there are no validated protocols for using whole-bowel irrigation, we recommend administration at a rate of at least one liter per hour in individuals greater than 6 years of age and 500 mls per hour if between 9 months and 6 years old. We do not recommend this technique for infants under 9 months.

Indications for ICU Admission in Lithium Poisoning

Significant manifestations of toxicity (e.g., altered mental status, rigidity, hyperreflexia)
Nephrogenic diabetes insipidus (NDI) requiring close monitoring of urine output and serum sodium
Cardiovascular instability
Significant toxicity in which extracorporeal removal (hemodialysis or continuous renal replacement therapy) is planned
Supratherapeutic and rising serum lithium concentrations, in settings in which frequent reassessment and decision-making cannot be achieved in a less intense setting

Sodium Polystyrene Sulfonate

The cation-exchange resin sodium polystyrene sulfonate (SPS, Kayexalate®) binds lithium in vitro [84, 85]. Many animal studies, reviewed in detail by Scharman [86], have shown that SPS administration can reduce measured serum lithium concentrations after either single or multiple doses of the latter. This reduction has been shown to occur when SPS is given after a significant delay following oral administration [87] and even when the lithium was administered intravenously [88]. These two studies show that SPS in the gastrointestinal tract has the capability of decreasing the absorption of lithium and enhancing its clearance. These animal studies used larger doses of SPS (2.5–5 g/kg) than typically are used to treat hyperkalemia in humans (0.5 to g/kg) [86, 89]. It is unlikely that these larger doses can be administered without a significant risk of causing hypokalemia.

Two human volunteer studies showed that doses of SPS of less than 1 g/kg can reduce the absorption of small amounts of lithium [81, 82]. A case report of a patient with lithium overdose described treatment with 150 g of SPS over a 24-h period without significant adverse effects. The authors of this report cited the patient's elimination half-life of lithium of 12 h as evidence of SPS's efficacy [83].

The optimal dose of SPS is unknown. It seems that a single dose of 1 g/kg may reduce lithium concentrations without significantly affecting either serum sodium or potassium concentrations [82] (grade III recommendation). Whether this dosing would result in meaningful clinical improvement and the safety and utility of repeated SPS dosing is unclear. If SPS is administered, cardiac monitoring, frequent measurement of serum sodium and potassium, and replacement of potassium are mandatory. Based on the above, we do not recommend the use of SPS in the routine management of lithium intoxication. In very large overdoses, or in patients with very high serum lithium concentrations in whom hemodialysis cannot be performed, SPS maybe a useful adjunctive therapy. There are no data indicating that SPS treatment alters the outcome of lithium-toxic patients.

Enhancement of Elimination

A fundamental goal in the treatment of lithium toxicity is the enhancement of its elimination. Generally, studies aimed at evaluating the utility of this approach have focused on clearance of lithium from the vascular compartment. This clearance usually is accomplished easily and quickly, particularly in patients with normal renal function. Physiologically, it is most important, however, to remove the lithium from target tissue compartments, particularly the brain. Because this removal cannot be done directly, the indirect approach of clearing the plasma of lithium and creating a concentration gradient that leads to diffusion of lithium from tissues to plasma is employed.

Renal elimination of lithium effectively constitutes the exclusive means by which it is naturally cleared from the body. Because renal lithium clearance is a direct function of glomerular filtration rate, it is important to reestablish and then maintain normal intravascular volume and renal perfusion. Normal saline treatment has been shown to enhance lithium and creatinine clearance in a group of lithium-intoxicated patients [3, 53, 90] (grade II-3 recommendation). Hospitalized psychiatric patients with bipolar disorder who are opposed to their lithium therapy have been known to reduce their lithium concentrations by consumption of large amounts of table salt. Whether normal saline is efficacious because of the competitive effect of the sodium ion on proximal tubular cation uptake or simply by virtue of its utility in reconstituting glomerular filtration is unknown. As noted earlier, overzealous treatment with normal saline can result in hypernatremia in patients with clinical or subclinical NDI. There does not seem to be any role for diuretic administration, including osmotic or loop diuretics [3, 29, 53]. Thiazide diuretic administration may increase serum lithium concentrations and may precipitate toxicity [91–94].

Extracorporeal Techniques

Hemodialysis

Lithium is well cleared by hemodialysis, with reported clearances of 63–170 mL/min [3, 17,

34, 95]; this compares favorably with an endogenous clearance of 13–56 mL/min [95]. Similarly, half-lives of lithium range from 2.3 to 12.9 h on hemodialysis [15, 17, 95]. Most of these studies were done with older-generation dialysis membranes. High-flux hemodialysis membranes are likely to enhance lithium elimination markedly [96–98]. In one report, lithium half-life during hemodialysis with a high-flux system was 1.4–1.9 h [96]. It is possible that acetate hemodialysis is more efficient than hemodialysis performed with bicarbonate-containing dialysate for the removal of intracellular lithium [97]. It has been hypothesized that acetate, being a weak acid, moves into the cell along with protons via the Na^+/H^+ transporter, with resultant net lithium efflux rather than sodium efflux [97].

Continuous Hemodialysis, Hemofiltration, Hemodiafiltration, and Related Techniques

Clearances reported with continuous extracorporeal removal techniques tend to be less than clearances achievable with hemodialysis. Continuous techniques have the advantage of being simpler than hemodialysis, however, and often can be used when the latter is unavailable or the patient is too unstable hemodynamically to undergo effective hemodialysis. Lithium clearances with continuous arterial-venous hemodiafiltration have been reported to be 20–56 mL/min [99, 100]. Clearances with continuous venovenous hemofiltration and/or hemodiafiltration have been reported to range from 27 to 83 mL/min [100–103]. Clearances with continuous venovenous hemodialysis have been reported to be 15–23 mL/min [100, 104]. None of the continuous techniques provide clearances that approach those attainable with hemodialysis. In a patient who cannot tolerate hemodialysis because of hemodynamic instability, however, or if these facilities are unavailable, continuous arterial-venous hemodiafiltration or continuous venovenous hemodiafiltration seems to be preferable to continuous venovenous hemodialysis.

Peritoneal Dialysis

Peritoneal dialysis has been reported anecdotally for the enhancement of lithium clearance

[3, 105, 106]. It is typically done with 2 L/h fluid volume exchanges; however, the clearances reported were only 9–15 mL/min. As a result, peritoneal dialysis has no recognized role in the management of lithium poisoning.

Indications for Extracorporeal Removal

Two recent systematic reviews have examined the question of which patients, if any, benefit from extracorporeal lithium removal. The authors of a Cochrane Collaboration review concluded that, “although the use of hemodialysis to enhance the elimination of lithium in lithium poisoning appears logical, there is no evidence from randomized controlled trials to support nor refute the use of hemodialysis in the management of patients with lithium poisoning” [107].

In contrast, a systematic review conducted by the Extracorporeal Treatments in Poisoning (EXTRIP) workgroup recommended the use of hemodialysis for lithium-poisoned patients with specific clinical features [108]. Acknowledging the very low quality of evidence, the EXTRIP authors based their recommendations primarily on pharmacokinetic considerations using a structured consensus-building process.

EXTRIP Workgroup Recommended Indications for Extracorporeal Drug Removal in Lithium Poisoning

Indications for Extracorporeal Drug Removal (ECDR)

Severe lithium poisoning (decreased level of consciousness, confusion, seizures, or life-threatening dysrhythmias)

Serum lithium concentrations >5.0 mEq/L

Serum lithium concentrations >4.0 mEq/L with impaired kidney function

Expected time to obtain a serum lithium concentration <1.0 mEq/L with optimal management is >36 h

Technique for ECDR:

Intermittent hemodialysis is the preferred modality

Continuous renal replacement therapy is an acceptable alternative if intermittent hemodialysis is not available

Criteria for Cessation of ECDR

Serum or plasma lithium concentrations remain <1.0 mEq/L after post-dialysis redistribution.

Clinical improvement is evident.

If serum lithium concentrations are not available, after a minimum of 6 h of ECDR.

Source: [108].

Similarly, the authors of most previously published case series, review articles, and textbook chapters generally recommend hemodialysis therapy for patients with lithium poisoning, but the specific indications for extracorporeal therapy are inconsistent. Like the EXTRIP review, most authors base their recommendations on serum lithium concentration, renal function, and clinical status [3, 8, 26, 90, 95, 109–114]. One indication that is consistently supported is compromised renal function because this would impair the elimination of lithium in the absence of an extracorporeal removal intervention. In addition, if hemodialysis does confer any improvement in outcome, it is likely that patients with Hansen and Amdisen grade III toxicity (see Table 1) would be the population most likely to benefit, while grade 0 patients with intact renal function are unlikely to achieve any improvement in prognosis. For patients with grade I or grade II toxicity and intact renal function, most authors recommend rehydration, serial clinical examinations, and serial lithium concentration measurements, with hemodialysis reserved for those patients with worsening clinical toxicity and rising or minimally decreasing serum lithium concentrations. A recent study showed substantial variation in recommended treatment when standardized lithium poisoning cases were presented to a group of medical toxicologists [115].

As noted by both the Cochrane and EXTRIP authors, hemodialysis has not been shown, under any circumstances, to alter patient outcome after lithium intoxication. A study conducted in a poison control center examined outcomes in 205 patients with lithium poisoning for whom hemodialysis was recommended over a 1-year

period [15]. Dialysis was actually performed in nine cases, and there was no apparent difference in outcomes between dialyzed and nondialyzed patients. However, this study is highly susceptible to confounding by indication and may have been underpowered to detect an important treatment difference. In essentially all published case series, the majority of acutely lithium-poisoned patients never develop SILENT, and most chronic lithium intoxication patients who develop SILENT have the condition present on presentation [3, 44, 107, 116]. Furthermore, one systematic review noted a greater incidence of persistent neurologic sequelae and deterioration during hospitalization in patients managed with hemodialysis than those who were not dialyzed [117]. Because this study could not control for confounding by indication, it is unclear whether hemodialysis is harmful to some patients or if patients with more serious illness received the treatment.

A rebound in plasma lithium concentration is seen frequently after the termination of hemodialysis [17, 95]. This rebound undoubtedly represents diffusion of lithium ions from peripheral tissues to the plasma and serum. Steady decreases on CSF lithium concentrations despite a posthemodialysis rebound in serum lithium concentration has been clearly demonstrated in a human case report [36]. Serum lithium concentrations may also increase due to continued gastrointestinal absorption. Although most authors recommend repeat hemodialysis sessions until a post-rebound concentration (measured 6 or more hours after the last hemodialysis session) is less than 1 mmol/L, this appears to be an arbitrary recommendation without basis in clinical observation [108]. Alternately, implementation of continuous veno-venous hemodiafiltration following acute hemodialysis has been shown to attenuate the rebound in serum lithium concentrations [118].

Other Therapies

Because theophylline, like aminophylline (the intravenous form of theophylline), has been reported to increase renal clearance, these agents have been investigated as potential adjunctive treatments for lithium toxicity [29]. This potential

has been studied only in volunteers, however, in whom the effect of theophylline on lithium clearance has been highly variable.

A single uncontrolled case report describes the attempt to enhance glomerular filtration with low dose of dopamine (2 µg/kg/min) to enhance lithium excretion [119].

As noted earlier, there are data in a rodent model of lithium toxicity suggesting that SPS may be effective in enhancing the clearance of already absorbed Li^+ ion. As described above, whether there is any clinical utility to this approach is unknown.

Treatment of Nephrogenic Diabetes Insipidus

NDI may be an overt clinical consequence of lithium therapy or may be subclinical and only manifested with the institution of normal saline therapy in an attempt to treat lithium toxicity. The fundamental deficit in NDI is loss of free water, as the kidney continues to produce a large volume of dilute urine despite high serum sodium levels and osmolality. Treatment, therefore, primarily should involve administration of intravenous hypotonic fluids, such as half-normal saline or 5% dextrose in water or enteral administration of water. Antidiuretic hormone therapy is typically ineffective. The reconstitution of intracellular and extracellular fluid volume using these fluids should be done cautiously. Although the fluid deficits can be large, the administration of half-normal saline too rapidly may result in relative overexpansion of the extracellular compartment. The administration of 5% dextrose too rapidly may exacerbate hyperglycemia in a patient with glucose intolerance and on the basis of concomitant osmotic diuresis may aggravate the fluid volume loss. In either instance, we recommend that the fluid volume deficit should be corrected gradually, with frequent monitoring of serum sodium levels.

Criteria for ICU Discharge in Lithium Poisoning

Falling or nondetectable serum lithium concentrations

Resolving clinical signs of toxicity

The goal of therapy is to gradually correct fluid volume deficits comprising the sum of the intracellular and extracellular volume losses. Normal intracellular fluid (ICF) volume is approximately 0.4 L/kg. A reliable estimate of the patient's actual ICF may be obtained using the following equation:

$$\text{ICF} = \frac{(\text{normal ICF} \times [2 \times \text{normal serum Na}^+]) \times \text{weight}}{2 \times \text{measured Na}^+}$$

In this equation, normal ICF is 0.4 L/kg, and normal serum sodium is 140 mmol/L. In a 70-kg patient, the normal ICF would be 0.4 L/kg \times 70 kg or 28 L. If with lithium-induced NDI, the serum Na^+ is 150 mmol/L; the actual ICF would be approximately 26 L, representing a 2-L ICF deficit. The calculation of the extracellular fluid (ECF) volume cannot be done simply based on the measured serum Na^+ but rather must be estimated on clinical grounds. The normal ECF is approximately 0.2 L/kg or 14 L/70 kg. It reasonably can be assumed that hyponatremic patients with NDI and relatively normal physical examinations have an approximately 10% decrease in ECF, although if signs of volume depletion are present, this can be 20%. If ECF volume decreases to 30% of normal, the patient is in frank circulatory shock. The total fluid volume deficit in need of replacement is the sum of the calculated ICF and estimated ECF deficits. An alternative, and in some cases simpler, approach to estimating the total free water deficit (FWD) is to use the following formula and make empirical adjustments in replacement therapy:

$$\text{FWD} = \frac{(\text{measured serum } [\text{Na}^+] - 140) \times 0.66 \text{ wt (kg)}}{140}$$

Adjunctive therapy with hydrochlorthiazide and/or amiloride may reduce the duration and severity of lithium-induced nephrogenic diabetes insipidus. In this setting, HCTZ has a paradoxical antidiuretic effect by increasing aquaporin-2 receptor abundance and affects the expression of major renal sodium transporters, among other mechanisms [120–122]. However, as thiazide diuretic administration may reduce lithium

elimination, this approach is best avoided in patients with measurable serum lithium concentrations [58, 91–94]. Similarly, amiloride has been reported to significantly reduce urine volume and increase urine osmolality in patients with lithium-induced NDI [123].

Special Populations

Pregnant Patients

Concern for the teratogenic potential of lithium has arisen from the demonstration, in several animal experiments, of adverse fetal outcomes occurring in treated pregnant dams [124, 125]. These abnormalities occurred, however, only when animals were given overt maternally toxic amounts of lithium, were markedly dissimilar in various species, and did not occur in lithium-treated primates [126].

In response to the possible teratogenic risk of lithium, a registry of treated patients was initiated in Denmark in 1969 [127]. Similar registries were formed in other countries, leading ultimately to the International Register of Lithium Babies [124, 127, 128]. Based on the results of these registries, concern about potential adverse effects, particularly Ebstein's anomaly, surfaced. These registry data are uncontrolled, however, and prone to ascertainment bias. In contrast, there have been eight epidemiologic studies of offspring outcome among women treated with lithium during pregnancy: two cohort trials broadly dealing with teratogenicity and six case-control studies [124]. Collectively the data from these studies indicate that the initial concern for fetal risk raised by registry data was not verified. Risk has not been ruled out completely, however, and it may be prudent to avoid lithium therapy, particularly during the first trimester of pregnancy, if the goals of treatment can be achieved by other means. In patients in whom lithium treatment is strongly indicated, it has been suggested that pregnancy be monitored by fetal echocardiography and ultrasound evaluation during the mid-second trimester [124]. Consistent with the demonstration that lithium crosses the placenta, a case has been

published suggesting transient neonatal lithium toxicity after birth from a lithium-toxic mother [129].

Because of the high glomerular filtration rate in pregnancy, renal lithium clearance is high. Given the rapid postpartum decline and normalization of glomerular filtration rate, it is important to reduce the maternal lithium dose and monitor plasma concentrations closely after parturition.

Although some lithium is excreted in breast milk, breastfeeding infants of treated mothers tend to have low-circulating lithium concentrations [125, 130]. As would be expected with older individuals, however, should the infant become volume depleted, serum lithium concentrations might rise.

Other Patients

Because lithium clearance depends completely on renal excretion, patients with decreased renal function are at particular risk for lithium toxicity. The presence of renal insufficiency should be considered at least a relative contraindication for treatment. Even in the absence of frank overt elevations in serum creatinine, normal decline in renal function with age suggests that the elderly are particularly vulnerable to lithium toxicity.

Common Errors in Lithium Poisoning

Thinking that diuresis beyond adequate urine production enhances lithium excretion

Failure to recognize significant lithium toxicity in the presence of normal or minimally elevated plasma concentrations

Key Points in Lithium Poisoning

1. Any factor that causes a decrease in lithium's renal clearance may predispose to toxicity.
2. Lithium toxicity is caused by its concentration in tissues (e.g., brain, kidney, thyroid),

and plasma lithium concentrations may not reflect accurately the degree of intoxication.

3. Lithium is cleared renally. Its clearance may be enhanced further by hemodialysis.
4. Nephrogenic diabetes insipidus is a potential complication of its therapeutic use and toxic exposure.

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Monoamine oxidase (MAO) inhibitors were serendipitously discovered in the 1950s when tuberculosis patients in Swiss sanitariums treated with isoniazid were noted to experience mood-elevating effects. Iproniazid, another antitubercular hydrazine derivative, was discovered to inhibit monoamine oxidase and had even greater psychostimulatory effects than isoniazid [1]. This led to its use as an antidepressant and paved the way for the development of the first effective agents in the treatment of major depression, the nonselective irreversible MAO inhibitors. MAO inhibitors have been in clinical use since the 1960s although their use has been supplanted by newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) that have fewer serious adverse effects and are less hazardous in overdose. Their continued decline in use is confirmed by data from the American Association of Poison Control Centers Toxic Exposure Surveillance System which recorded 3,261 total exposures to MAO inhibitors with 12 fatalities from 2001 to 2013 [2–13]. This is compared to 6,076 total exposures and 58 fatalities for the period from 1989 to 2000 [14–24].

Despite their waning popularity, MAO inhibitors are still listed as third- and fourth-line therapy for treatment-refractory or atypical depression [25, 26]. They also have produced positive responses and are used in other conditions, such as social phobia disorders, panic disorders, posttraumatic stress syndrome, obsessive-compulsive disorder,

Table 1 Monoamine oxidase inhibitors

Generic name	Trade name in United States ^a	Available in United States	Inhibits MAO-A	Inhibits MAO-B	Irreversible	Reversible
Brofaromine			X			X
Cimoxatone			X			X
Isocarboxazid	Marplan	X	X	X	X	
Moclobemide	Aurorix, Manerix		X			X
Phenelzine	Nardil	X	X	X	X	
Rasagiline	Azilect	X		X	X	
Selegiline	Eldepryl, Emsam	X		X	X	
Toloxatone			X			X
Tranylcypromine	Parnate	X	X	X	X	

^aUnited State tradenames are given as examples. Although the genric names of these agents are universal, their trade names differ between countries

bulimia, and narcolepsy [27]. As a result, populations at risk for suicidal ingestions or intentional overdose may continue to have accessibility to MAO inhibitors. Their complex pharmacology coupled with unfavorable adverse effect profile and the potential for food (e.g., tyramine reaction) and drug (e.g., serotonin syndrome) interactions, along with a low therapeutic index and potential for fatality when taken in overdose, means clinicians must remain knowledgeable and prepared to manage severe manifestations of MAO inhibitor toxicity and the anticipated complications.

This chapter focuses on the traditional nonselective and irreversible MAO inhibitors due to their increased likelihood to produce severe toxicity. However, major advances in developing less toxic MAO inhibitors, which are reversible and selective in their MAO activity (Table 1), have occurred. These agents will be discussed briefly but their toxicity seems to be less severe than that of irreversible MAO inhibitors and many are not available in the United States. The MAO inhibitors currently available in the United States including phenelzine (Nardil), tranylcypromine (Parnate), isocarboxazid (Marplan), selegiline (Eldepryl, Emsam), rasagiline (Azilect). Selegiline (Eldepryl), and rasagiline (Azilect) are selective MAO B inhibitors that are used as an adjunct in the treatment of Parkinson's disease [28]. At higher doses, selegiline resembles the activity of traditional MAO inhibitor antidepressants. It is currently available in a transdermal

formulation and indicated for use in the treatment of depression [28]. In the United States, MAO inhibitors are not approved for use in children younger than 16 years of age and use should be avoided during pregnancy.

Monoamine Oxidase Inhibitors Available in the United States

Isocarboxazid (Marplan) – used as an antidepressant

Phenelzine (Nardil) – used as an antidepressant

Rasagiline (Azilect) – used to treat Parkinson's disease

Selegiline (Eldepryl, Emsam) – used as an antidepressant and to treat Parkinson's disease

Tranylcypromine (Parnate) – used as an antidepressant

Some drugs have been discovered to have MAO inhibitor activity as an unrelated pharmacological action. Examples include methylene blue, the antidote for methemoglobinemia; linezolid and tedizolid, oxazolidinone antibiotics; procarbazine (Matulane), a chemotherapeutic agent; and zonisamide (Zonegran), an anticonvulsant that has selective MAO B inhibition [29]. Agents that are known to have MAO inhibitor activity but have been withdrawn from the market in the United Sates, and several other countries, include furazolidone (Furoxone), a synthetic nitrofuran with antimicrobial and

antiprotozoan activity, and pargyline (Eutonyl), whose use was discontinued in the 1990s. The latter was an antihypertensive agent whose primary mechanism of action was MAO inhibition. Clorgyline is an irreversible MAO A inhibitor withdrawn from the market in many countries but still is used for experimental purposes.

Herbal products, such as the popular over-the-counter treatment for depression St. John's wort (*Hypericum perforatum*), has been reported to have slight MAO inhibitor activity [30]. However, St. John's wort functions more like a nonselective neurotransmitter reuptake inhibitor than like an MAO inhibitor [30]. Most patients taking St. John's wort do not consider it a drug and often omit herbal products when being asked about their medications. Harmaline alkaloids found in the plant *Peganum harmala* inhibit MAO activity. There are reports of harmaline being abused with the drugs of abuse 5-methoxy-*N,N*-diisopropyltryptamine and 5-methoxy-*N,N*-dimethyltryptamine to enhance their hallucinogenic effects [31–35].

Biochemistry, Pathophysiology, and Clinical Pharmacology

MAO is an intracellular enzyme bound to the outer mitochondrial membrane. It can be found in most human cells with the exception of erythrocytes, which lack mitochondria. MAO removes amine groups from endogenous and exogenous biogenic amines. This oxidative deamination process is the primary mechanism by which endogenous biogenic amines, such as norepinephrine, dopamine, and 5-hydroxytryptamine (serotonin) [36], become inactivated. An equally important function of MAO is the reduction in systemic bioavailability of absorbed dietary biogenic amines, such as tyramine, via hepatic and intestinal metabolism. Inhibition of MAO leads to the accumulation of neurotransmitters in central and peripheral presynaptic nerve terminals and allows for increased systemic availability of dietary amines [36]. MAO does not metabolize circulating catecholamines, whether they are secreted endogenously (e.g., adrenal gland, sympathetic

nerve terminals) or administered intravenously (e.g., epinephrine). This metabolism is accomplished by catechol *O*-methyltransferase, an extraneuronally located enzyme that is not affected by MAO inhibitors [36].

MAO exists as two separate isoenzymes, designated MAO-A and MAO-B. Evidence of the separate isoenzymes was initially provided by their protein chemistry. Now the two genes encoding human MAO A and MAO B have been identified [37]. Despite nearly 70% structural similarity, subtle differences in their binding cavities result in very different substrate and inhibitor specificities [37]. Each isoenzyme has a unique affinity profile for different neurotransmitters, dietary amines, and MAO inhibitors [31, 32, 36]. These substrate preferences are dose dependent and become less relevant at higher substrate concentrations or MAO inhibitor doses. Norepinephrine and serotonin are metabolized primarily by MAO-A, whereas MAO-A and MAO-B have equal ability to metabolize dopamine and tyramine [31, 32, 36]. MAO-B is the exclusive isoenzyme found in serotonergic neurons [30]. This paradox may be explained by simple conservation of energy, in which the MAO-B isoenzyme has a lower affinity for 5-HT and allows for more 5-HT to become recycled. It also allows for increased metabolism of nonserotonin bioamines, keeping the neuron free of false neurotransmitters.

The human brain contains more MAO-B than MAO-A, with MAO-B predominance increasing with advancing age and in some neurodegenerative diseases. Dopaminergic neurons appear to lack MAO-B activity and have limited MAO-A activity [31, 36]. Significant MAO-B activity has been detected in surrounding astrocytes and glial cells. Dopamine inactivation may depend on astrocyte and glial cell metabolism [31, 36]. MAO-A constitutes approximately 75% of the MAO activity in the intestine, whereas approximately equal proportions of both isoenzymes are found in the liver. When only one isoenzyme is inhibited, such as in the presence of moclobemide, which selectively inhibits MAO-A, this dual representation of both isoenzymes in the intestines and liver affords greater protection against the hypertensive reaction to

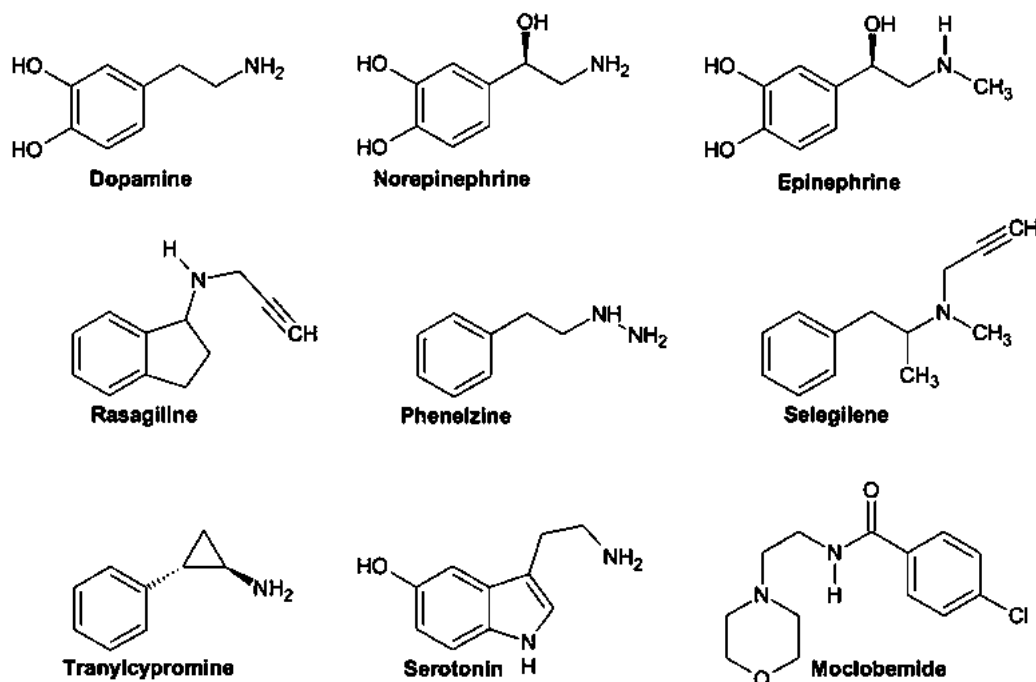


Fig. 1 Chemical structures of monoamine oxidase inhibitors and pertinent neurotransmitters

tyramine-containing foods. Similarities in chemical structure between MAO inhibitors and endogenous amines, such as norepinephrine, serotonin, and dopamine, make them eligible as potential substrates for MAO and cause inhibition of amine metabolism (Fig. 1) [32]. The antidepressant activity of phenelzine, tranylcypromine, and isocarboxazid is attributed to their ability to increase norepinephrine and serotonin neurotransmission by increasing presynaptic concentrations of serotonin and norepinephrine [31]. The actual mechanism by which they exert their therapeutic action is unproven but more likely is related to delayed postsynaptic receptor modifications (e.g., downregulation). Other potential mechanisms of action include indirect release of neurotransmitters and inhibition of neurotransmitter reuptake. MAO inhibitors also inhibit other enzyme systems (e.g., pyridoxal phosphokinase, diamine oxidase), but this is of uncertain clinical significance.

Phenelzine, like isoniazid, can cause pyridoxal phosphate deficiency which may contribute to its neurotoxicity [38]. Selegiline has limited effects on norepinephrine and serotonin metabolism at

therapeutic doses (typically 10 mg/day). At doses greater than 30 mg/day, however, selegiline is capable of increasing presynaptic norepinephrine and serotonin concentrations and has the potential to produce similar drug-related toxicity to that of nonselective MAO inhibitors, such as phenelzine and tranylcypromine [28]. Selegiline's therapeutic benefit in Parkinson's disease is thought to be related to increasing striatal dopamine neurotransmission and protection against neuronal damage from oxidative stress [28]. Oxygen is another substrate for the MAO enzymes, which results in the generation of H_2O_2 at the outer surface of the mitochondrial membrane. This is thought to increase oxidative stress and be deleterious to the cell, which is why MAO inhibitors are being evaluated and pursued as potential neuroprotective agents. However, further research is needed to fully understand the role of H_2O_2 as a cell signal and disease-modifying target [37].

All of the currently available MAO inhibitors in the United States are irreversible and nonselective (MAO-A, MAO-B) in their enzyme

inhibition with the exception of selegiline and rasagiline. The latter are irreversible MAO-B selective inhibitors. Irreversible MAO inhibitors form covalent bonds with MAO enzymes rendering them permanently inactive [31]. When an irreversible MAO inhibitor has been discontinued, it takes approximately 2 weeks before new enzyme synthesis returns MAO activity to 50% of normal [30, 31]. This is the basis for the recommendation of waiting 2 weeks after the discontinuation of an irreversible MAO inhibitor before starting any new antidepressant or proserotonergic agent. MAO inhibitors do not affect enzyme production. Reversible MAO inhibitors (RIMAs) do not form irreversible covalent bonds with MAO. New enzyme synthesis is not necessary to restore MAO, and MAO activity gradually returns to normal over a period of hours as the drug-enzyme complex spontaneously dissociates [39]. Examples of reversible MAO inhibitors include moclobemide, toloxatone, brofaromine, and cimoxatone which are only available internationally.

Pharmacokinetics

Although MAO inhibitors have been used since the 1960s, there is a scarcity of information regarding their pharmacokinetics [36, 39]. In general, they are absorbed rapidly and completely from the gastrointestinal tract but undergo significant first-pass hepatic metabolism, limiting their bioavailability. Their dependence on hepatic metabolism predisposes MAO inhibitors to potential drug interactions with other drugs requiring hepatic oxidation. Peak drug levels usually occur 1–4 h after ingestion. Their volumes of distribution are relatively small (1–3 L/kg) compared with other antidepressants. Their degree of plasma protein binding is unknown, and their elimination half-life averages 2–3 h [40].

Selegiline has many active metabolites, such as desmethylselegiline, *l*-methamphetamine, and *l*-amphetamine. Phenelzine metabolism results in multiple active metabolites, such as B-phenylethylamine, which also serves as a substrate for MAO-B [40]. Tranylcypromine

metabolism has not been fully elucidated. It was suspected to result in generation of amphetamine as a metabolite, but this is not supported by recent literature [41–43].

Clinical toxicity usually is delayed until well after most of the MAO inhibitor already has been metabolized. Blood MAO inhibitor concentrations do not correlate with clinical toxicity. The pharmacokinetic profile of most MAO inhibitors suggests that attempts at extracorporeal removal (e.g., hemodialysis) or administering repeat-dose activated charcoal would be unsuccessful in significantly reducing MAO inhibitor plasma concentrations.

Biphasic postmortem changes have been reported with tranylcypromine and moclobemide in fatal overdose cases [44, 45]. Initially, MAO inhibitor blood levels increase in a similar, but less dramatic, fashion as other antidepressants. After 24 h, drug concentrations show a rapid decline, however, suggesting bacterial degradation.

Pharmacokinetics of Nonselective Irreversible Monoamine Oxidase Inhibitors

Volume of distribution: 1–3 L/kg

Absorption rate: rapidly absorbed in 1–2 h

Bioavailability: 50%

Peak levels: 2–4 h after ingestion

Protein binding: 50%

Metabolism: hepatic metabolism (P-450 system and acetylation)

Plasma half-life: 2–4 h

Active metabolites: no significant active metabolites

Clinical Presentation of Acute Overdose

There are two significant concerns regarding acute MAO inhibitor overdose. First, the lethal dose in relation to the therapeutic dose is smaller than with other antidepressants. Second, the clinical manifestations of toxicity typically are delayed well beyond the usual observation period of other antidepressants [46, 47]. These two

characteristics distinguish MAO inhibitors from the other antidepressants, which have a much higher therapeutic index and usually develop toxicity within 6 h after ingestion.

The usual therapeutic dose for most MAO inhibitors ranges from 0.25 to 1.0 mg/kg. Mild-to-moderate toxicity typically is seen with ingestions of less than 2 mg/kg. Severe toxicity often results from ingestions of 2–3 mg/kg. The potentially lethal dose of irreversible MAO inhibitors is reported to be 4–6 mg/kg [46]. Deaths have been reported in adults with 170 mg of tranylcypromine and 375 mg of phenelzine. Selegiline overdoses can produce similar toxicity as the traditional MAO inhibitor antidepressants as selective MAO inhibition is lost when therapeutic dosing is exceeded. The average therapeutic dose of tranylcypromine is 20–40 mg/day, with a maximum daily dose of 60 mg/day. Phenelzine's therapeutic dose is 45–75 mg/day, with a maximum of 90 mg/day. Isocarboxazid has a therapeutic dose range of 10–30 mg/day. Sheenan et al. reported dosing equivalents as 45 mg of phenelzine equal to 20 mg of tranylcypromine equal to 40 mg of isocarboxazid [48].

An important clinical aspect of MAO inhibitor overdoses is that symptoms characteristically are delayed 6–12 h after ingestion but can be delayed 24 h [46, 47]. The delayed onset of toxicity is believed to be secondary to the gradual accumulation of norepinephrine and serotonin in the brain and peripheral sympathetic neurons which leads to excessive sympathetic receptor stimulation resulting in a hyperadrenergic state. Patients on long-term MAO inhibitor therapy may show earlier signs of toxicity owing to preexisting enzyme inhibition. In severe cases, the hyperadrenergic state can be followed rapidly by hypotension and central nervous system depression, a sympatholytic-like stage thought to reflect catecholamine depletion [46]. Toxicity usually persists 1–4 days after ingestion [46].

The signs and symptoms of MAO inhibitor toxicity are often nonspecific. Even in its most severe form, it can resemble numerous other conditions (see discussion of differential diagnosis

later). Information regarding MAO inhibitor overdoses primarily comes from limited case series [40, 49, 50] and isolated case reports [42, 51–57]. These reports have tremendous variation in presentation, treatment, and outcome. There is no “typical” presentation to MAO inhibitor toxicity, and there is not an orderly progression of symptoms. After an initial latent period, the rapid development of life-threatening symptoms in all patients with MAO inhibitor overdose should be anticipated. The initial symptoms of MAO inhibitor overdose include headache, agitation, irritability, tremor, nausea, and palpitations. The earliest signs of MAO inhibitor toxicity include sinus tachycardia, hyperreflexia, drowsiness, hyperactivity, mydriasis, fasciculations, hyperventilation, nystagmus, and generalized flushing [46].

In cases of moderate toxicity, opisthotonos, muscle rigidity, diaphoresis, hypertension, chest pain, diarrhea, hallucinations, combativeness, confusion, marked hyperthermia, and trismus may become evident [46]. A peculiar ocular finding has been observed with some cases of MAO inhibitor toxicity and is described as “Ping-Pong” gaze, in which the eyes move conjugately from one extreme lateral position to the other in a rhythmic fashion. The movement is smooth and without pause in cycles lasting 3–4 s [52, 57]. The mechanism of this gaze disorder is unknown. In all reported cases, it resolved gradually with patient improvement.

Severe toxicity is manifest by bradycardia, cardiac arrest, hypoxia, hypotension, papilledema, seizures, coma, and worsening hyperthermia. Hypotension is an ominous finding that commonly remains resistant to therapeutic attempts at correction [46, 52]. Fetal demise, cerebral edema, pulmonary edema, and intracranial hemorrhage all have been reported in association with MAO inhibitor overdoses [46, 52]. The most common electrocardiographic abnormality seen in MAO inhibitor toxicity is sinus tachycardia, but T-wave abnormalities also are common [46]. Deaths usually are secondary to multiple organ failure.

Overall, the newer reversible and selective MAO inhibitors seem to be less toxic in overdose than traditional MAO inhibitors. Most of these cases of newer MAO inhibitor overdose involve moclobemide [58–60], although one large case series involved toloxatone [61]. The toxicity of both of these antidepressants is similar in overdose and probably can be generalized to other selective and reversible MAO inhibitors. Most adult patients with ingestions of less than 2,000 mg are expected to remain asymptomatic or develop only minimal symptoms after a single drug overdose [62]. However, toxicity can become severe, when combined with other antidepressants or in large overdoses. Cases of severe serotonin syndrome and death following combination of moclobemide with either SSRIs or SNRIs have been described [62–65]. And death following intentional overdose of moclobemide has been reported [66]. The clinical manifestations of toxicity are similar to those described previously with irreversible agents and can be just as severe, although, the toxicity from reversible MAO inhibitors resolves sooner than with the irreversible agents, and the mortality rate is believed to be less.

MAO inhibitors can produce hypertension by several mechanisms. It may result from spontaneous hypertensive crisis, tyramine reactions

(see later), drug interactions, serotonin syndrome, or high-dose toxicity. Determining the cause of the hypertension depends largely on obtaining an accurate history of the preceding events. Spontaneous hypertensive crisis is a rare condition usually occurring in relation to recent MAO inhibitor dosing [67]. Hypertension can result from exposure to indirect-acting sympathomimetics commonly found in over-the-counter cold and sinus medications [68]. Hypertension may be a constellation of serotonin syndrome which most commonly occurs shortly after exposure to other serotonergic agents and can be severe [69]. The clinical presentation of the serotonin syndrome is discussed (see ► Chap. 24, “Serotonin Syndrome”).

Tyramine Reaction

Tyramine is a dietary amine that normally is metabolized by intestinal and hepatic MAO enzymes (Fig. 2), limiting its bioavailability. Nonselective MAO inhibitors interfere with this process, allowing for a greater amount of tyramine to reach the systemic circulation. Tranylcypromine is associated more frequently with tyramine reactions than phenelzine or isocarboxazid [70, 71]. Selegiline is unlikely to produce

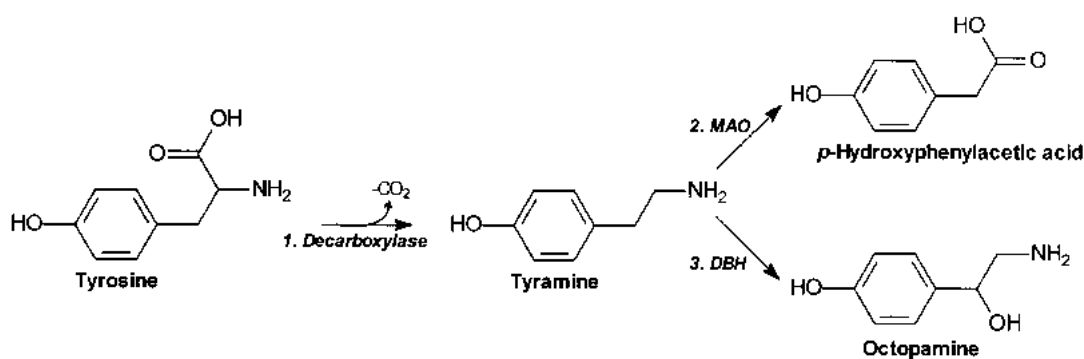


Fig. 2 Synthesis and metabolism of tyramine. Reaction 1: decarboxylation of tyrosine in liver and gastrointestinal tract. Reaction 2: oxidative deamination of tyramine by monoamine oxidase (MAO) in liver, kidney, and other

tissues. Reaction 3: β -oxidation of tyramine by dopamine β -hydroxylase (DBH) located in synaptic vesicles within terminal of sympathetic neurons (From Moore [84])

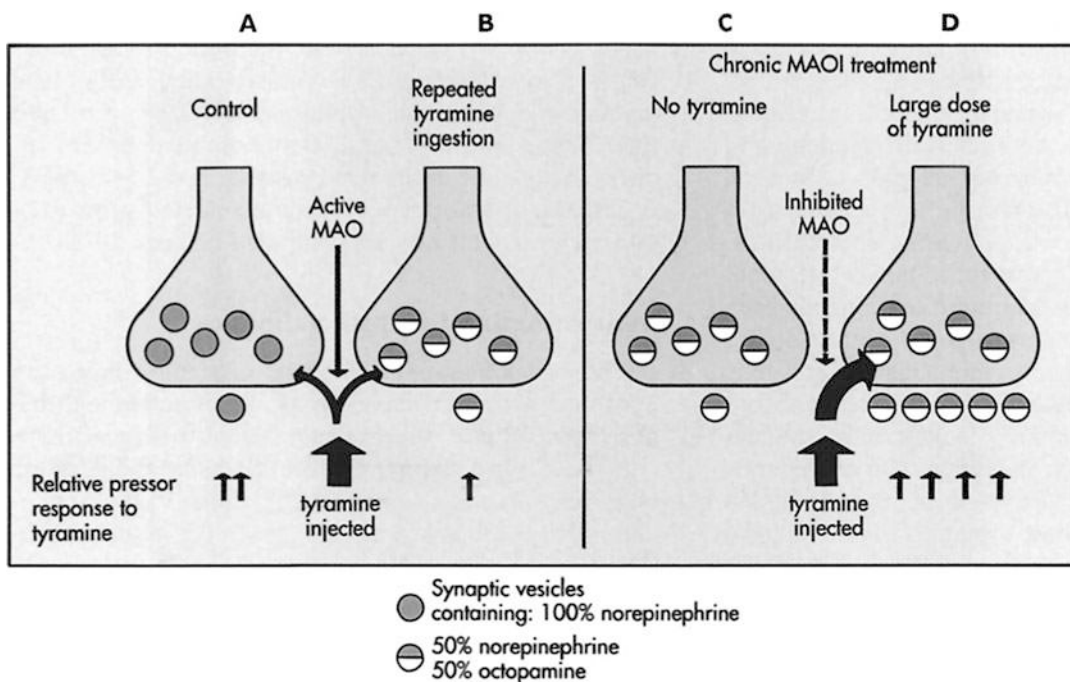


Fig. 3 Acute response to ingestion of tyramine (a); tolerance to repeated ingestions of tyramine (b); long-term treatment with a monoamine oxidase inhibitor (MAOI)

(c); effects of tyramine after long-term MAOI pretreatment (d). The relative increase in blood pressure denoted by the number of arrows (From Moore [84])

a tyramine reaction if taken at therapeutic doses because of its selective inhibition of MAO-B. Tyramine is an indirect sympathomimetic and is structurally similar to amphetamine. As with most indirect sympathomimetics, tyramine enters the presynaptic neuron through amine uptake pumps [70]. When inside the neuron, tyramine is capable of releasing presynaptic stores of norepinephrine and to a lesser degree serotonin and dopamine (Fig. 3) [71]. Tyramine also can displace epinephrine from the adrenal gland.

Tyramine is found in more than 70 foods and beverages. Any one of these sources may trigger a reaction [71]. Tyramine is the basis for the so-called cheese reaction because aged cheese contains a large amount of tyramine. In similar fashion, broad (fava) beans contain large quantities of dopamine, a mixed-acting sympathomimetic compound. Patient compliance to an MAO inhibitor–restrictive diet has been reported to be less than 30% of patients [70]. In addition, approximately 4–8% of compliant patients

experience a tyramine reaction during their therapy [70]. Nonetheless, newer MAO inhibitor treatment guidelines call for avoiding only a few high-risk food groups, such as nonfresh meat or fish, sauerkraut, aged meats and cheeses, Chianti wine, vermouth, pickled herring, concentrated yeast extracts, and broad beans [70, 71].

The tyramine reaction characteristically occurs within 15–90 min after ingesting the dietary amine. The severity of this reaction is highly variable and partially related to the total amount of tyramine ingested [70, 71]. The hallmark symptom of tyramine reactions is a severe occipital or temporal headache [68]. Other associated symptoms include hypertension, palpitations, diaphoresis, mydriasis, neck stiffness, pallor, neuromuscular excitation, and chest pain [68]. Most symptoms gradually resolve over 6 h without specific therapy. Fatalities have been reported, although rarely since 1967, and usually are due to intracranial hemorrhage or myocardial infarction [38]. An electrocardiogram should be

obtained for all patients with tyramine-associated chest pain. Focal neurological findings or a persistent severe headache warrants investigation with a computed tomography scan of the head.

Tyramine Reaction

Diagnosed by rapid onset of headache and hypertension after tyramine ingestion

Can occur with other indirect sympathomimetics (e.g., levodopa)

Phentolamine or nitroprusside are preferred antihypertensive agents

Avoid β -blockers because they may worsen hypertension

Persistent headaches should be evaluated for intracranial hemorrhage

Chest pain should be evaluated for myocardial ischemia

Most tyramine reactions rapidly resolve with appropriate treatment

Asymptomatic patients can be discharged after 4 h of observation

Admit all patients symptomatic for at least 8 h after all signs and symptoms resolve

Diagnosis

MAO inhibitor toxicity is a clinical diagnosis based solely on the history of MAO inhibitor ingestion and hyperadrenergic symptoms. There are no readily available confirmatory tests. Special toxicological testing would be of little value in detecting MAO inhibitors because most of the parent compounds have a short half-life in relation to their duration of action and may not be detectable when symptoms develop. The best use of laboratory tests is to assist in the differential diagnosis of MAO inhibitor toxicity and to identify possible complications of MAO inhibitor overdose, which include hypoxia, rhabdomyolysis, renal failure, hyperkalemia, metabolic acidosis, hemolysis, and disseminated intravascular coagulation. Leukocytosis [55] and thrombocytopenia [42, 52, 72] are seen commonly with MAO inhibitor toxicity.

A positive urine drug screen for methamphetamine or amphetamine may be expected with selegiline ingestions because it is metabolized to the levorotatory *l*-methamphetamine and ultimately *l*-amphetamine and may cross-react with some immunoassays designed to detect the dextrorotatory (*d*-) forms typically encountered in illicit methamphetamine abuse [73, 74]. Chiral analysis can be performed if it is imperative to discriminate between therapeutic selegiline and illicit methamphetamine use [73–75]. There are conflicting reports in the literature suggesting that tranlycypromine is metabolized to amphetamine and therefore may yield a positive result on immunoassays for amphetamine [76]. However, there is a growing body of evidence that supports that the cleavage of the cyclopropyl ring of tranlycypromine to form amphetamine does not occur [41–43, 77]. Consequently, tranlycypromine should not result in a positive amphetamine screen [38, 77].

The differential diagnosis of an unknown MAO inhibitor ingestion is extremely challenging and includes all drugs and medical conditions capable of producing a hyperadrenergic state, altered mental status, hyperthermia, or muscle rigidity (Table 2). MAO inhibitor toxicity also could be associated with a sympatholytic presentation, broadening the differential possibilities further. In reality, without a history of exposure, a conclusive diagnosis of MAO inhibitor poisoning cannot be made because no confirmatory tests are available.

Treatment

All patients with MAO inhibitor overdose require immediate physician evaluation, intravenous access, intensive clinical and cardiac monitoring, and possibly gastric decontamination. There are no known antidotes for MAO inhibitor toxicity. There are no controlled human studies on MAO inhibitor overdose treatment on which to base patient management recommendations. Medical management is based on providing excellent supportive care, avoiding potential drug interactions, and treating medical complications early. Onset of

Table 2 Differential diagnosis of monoamine oxidase inhibitor overdose

	Hyperadrenergic	Hyperthermia	Altered mentation	Muscle rigidity
Amphetamine toxicity	XXX	X	X	X
Antimuscarinic toxicity	X	X	XX	0
Benzodiazepine withdrawal	X	X	XX	0
Cocaine toxicity	XX	X	X	0
Delirium tremens	XX	X	XX	0
Dystonic reaction	0	0	0	XX
Heat stroke	XX	XXX	XXX	X
Hyperthyroidism	X	X	X	0
Hypoglycemia	X	0	XX	0
Malignant hyperthermia	XXX	XXX	XXX	XXX
Meningitis	X	XX	XXX	X
Neuroleptic malignant syndrome	XXX	XXX	XXX	XXX
Phencyclidine toxicity	XX	X	XX	X
Serotonin syndrome	XX	XX	XX	XX
Strychnine toxicity	0	X	0	XXX
Tetanus	X	X	0	XXX
Tyramine reaction	XX	X	X	0

0, not expected to be present; X, expected in the minority of cases; XX, expected to be commonly present; XXX, expected to be present in almost all cases

toxicity is usually gradual and can be delayed, sometimes 24 h after ingestion. The abrupt development of seizures, coma, respiratory insufficiency, and cardiovascular collapse is possible, however. Certain patient groups, such as patients with underlying medical problems, children, and the elderly, may manifest greater toxicity at a given dose of an MAO inhibitor.

Indications for ICU Admission in Monoamine Oxidase Inhibitor Poisoning

1. Admit all patients who ingested >1 mg/kg to an ICU (possible exception reversible MAO inhibitors).
2. Admit all patients with clinical signs of toxicity <24 h since ingestion.
3. Patients with serotonin syndrome, unless mild.

The utility of gastrointestinal decontamination in MAO inhibitor overdose has never been studied. The following recommendations are general guidelines based on the pharmacokinetic profile of MAO inhibitors and human case reports.

Administration of activated charcoal as a single dose of 1 g/kg is reasonable, particularly if it can be given shortly after ingestion, ideally <1–2 h, and there are no other contraindications. The efficacy of treatment with activated charcoal treatment, if any, is expected to decrease as time passes post ingestion. It is important to highlight that there are no studies demonstrating that activated charcoal administration alters the outcome of patients with MAO inhibitor overdoses. Caution must be exercised when giving patients activated charcoal after they have ingested drugs that may cause altered level of consciousness. Multiple-dose activated charcoal administration is not expected to be advantageous. Historically, some medical toxicologists recommend gastric lavage for significant irreversible MAO inhibitor ingestions if it can be performed within 1 h after ingestion because of the high risk of mortality. It is unknown whether this intervention alters the clinical course or outcome in MAO inhibitor overdose. There are no studies to suggest that gastric lavage improves the outcome in poisoned patients and this procedure has been largely abandoned. Because MAO inhibitors are absorbed rapidly,

delayed gastric lavage, or whole-bowel irrigation, is unlikely to be of any clinical benefit and is not recommended. Routine laboratory tests should be performed on all patients, with particular emphasis on identifying complications such as hyperkalemia, metabolic acidosis, and rhabdomyolysis.

Hypertension

Acutely hypertensive patients should be treated with short-acting intravenous antihypertensive agents because of the potential to develop precipitous hypotension. In most cases, an intra-arterial catheter is required for accurate blood pressure monitoring. Traditionally, the antihypertensive agents of choice are α -antagonists or direct-acting vasodilators such as phentolamine or nitroprusside (Level of Evidence [LoE] III). Phentolamine is a nonspecific α -adrenergic receptor antagonist, usually administered as a 2.5–5.0-mg bolus followed by a continuous infusion (1–5 mg/h) titrated until blood pressure elevation is controlled. Phentolamine use commonly is associated with reflex tachycardia. Nitroprusside is given as a continuous infusion with an initial rate of 1 μ g/kg/min, and titrated according to blood pressure response. Prolonged high doses of nitroprusside can predispose to cyanide toxicity (see ► Chap. 40, “Sodium Nitroprusside”) although this is rarely encountered due to the routine addition of thiosulfate to nitroprusside infusions. Nitroglycerin can also be used to control hypertension and may be effective for the relief of cardiac-related chest pain. β -Blockers pose a theoretical risk of increasing the blood pressure through unopposed α -adrenergic receptor-mediated vasoconstriction and should be considered contraindicated (LoE III). Despite its α -receptor blocking ability, labetalol should also be avoided as its β -receptor blockade is much greater than its α -blockade (3:1 oral; 7:1 IV). Because patients with MAO inhibitor toxicity may change rapidly from being hypertensive to being hypotensive, short-acting antihypertensive agents are preferable.

Hypotension

Hypotension carries a poor prognosis in MAO inhibitor overdose [46, 51]. Isotonic intravenous fluid boluses of 10–20 mL/kg are the initial treatment of hypotension. When vasopressors are required, only direct-acting sympathomimetics should be utilized. Norepinephrine is the vasopressor of choice, with epinephrine as the second drug of choice (LoE III). Patients with MAO inhibitor toxicity may have increased sensitivity to vasopressors, and lower starting doses are recommended. (LoE III) It is important to avoid all agents with indirect sympathomimetic actions (e.g., dopamine) and choose from available direct-acting agents instead (Table 3). In general, indirect sympathomimetics can act synergistically with MAO inhibitors to produce an exaggerated hyperadrenergic response, producing excessive rise in blood pressure. Therefore, the use of dopamine should be avoided. Its vasopressor effect may be absent due to neuronal and cytoplasmic depletion of norepinephrine leaving its action at peripheral dopamine and β -adrenergic receptors unopposed resulting in vasodilation and worsening hypotension.

Dysrhythmias

Sinus tachycardia rarely requires specific drug therapy, unless it is producing myocardial ischemia. Lidocaine, or procainamide, are the most likely effective antiarrhythmics in treating MAO inhibitor-induced dysrhythmias [46]. (LoE III) Amiodarone may be a reasonable alternative option but little evidence is available regarding its use in the management of tachydysrhythmias from MAO inhibitor toxicity. Hemodynamically significant bradycardia may develop and can degrade quickly into asystole in the later stages of the overdose [51]. Pharmacological treatment of bradycardia includes atropine, isoproterenol, and dobutamine. Transvenous or transcutaneous pacing may be necessary in severe or refractory bradycardia.

Table 3 Drugs contraindicated with monoamine oxidase inhibitors

Indirect-activity and mixed-activity sympathomimetics	Antidepressants	Miscellaneous drugs
Benzphetamine	Amoxapine	Atomoxetine
Bretylium	Amitriptyline	β -Blockers
Caffeine	Bupropion	Buspirone
Cocaine	Citalopram	Carbamazepine
Dexfenfluramine	Clomipramine	Clonidine
Dextroamphetamine	Desipramine	Cyclobenzaprine
Diethylpropion	Desvenlafaxine	Dextromethorphan
Dopamine	Doxepin	Disulfiram
Ephedrine	Duloxetine	Ergot Alkaloids
Fenfluramine	Escitalopram	Fentanyl
Guanethidine	Fluoxetine	Furazolidone
Isometheptene	Fluvoxamine	Ginseng
Mephentermine	Imipramine	Ketamine
Metaraminol	Maprotiline	Levodopa
Methamphetamine	Milnacipran	Linezolid
3,4-Methylenedioxymethamphetamine (MDMA)	Mirtazapine	Lithium
Methyldopa	Nefazodone	Meperidine
Methylphenidate	Nortriptyline	Methylene blue
Pemoline	Paroxetine	Oral hypoglycemic agents
Phentermine	Sertraline	Phenothiazines
Phencyclidine	St. John's wort	Procarbazine
Phenylpropanolamine	Trazodone	Rizatriptan
Propylhexedrine	Venlafaxine	Sumatriptan
Pseudoephedrine	Vilazodone	Tapentadol
Reserpine	Vortioxetine	Tramadol
Ritodrine		Tryptophan
Theophylline		Zolmitriptan
Tyramine		

Seizures

Benzodiazepines are considered first-line therapy in treating MAO inhibitor-induced seizures [46, 56]. (LoE III) Other GABA-A agonists such as barbiturates (i.e., phenobarbital) or propofol are likely also effective in controlling seizures due to MAO inhibitor toxicity [46, 56]. Clinicians should be aware that all of these agents may cause or worsen hypotension, especially at higher doses. Phenytoin is ineffective in stopping drug-induced seizures and is not recommended in cases of MAO-inhibitor-induced seizure activity (see ► Chap. 20, “Toxicant-Induced Seizures”). General anesthesia

with muscle paralysis may be necessary in cases of status epilepticus to prevent the metabolic acidosis, hyperthermia, and rhabdomyolysis commonly seen with persistent seizure activity. When muscle paralysis is used to control the peripheral manifestations of seizure activity, electroencephalographic monitoring is necessary to assess for the presence of central nervous system seizures. Muscle paralysis is accomplished best using nondepolarizing neuromuscular blocking agents (e.g., vecuronium). (LoE III) Succinylcholine should not be utilized in cases of severe MAO inhibitor toxicity as patients are often hyperthermic with rhabdomyolysis and may be at increased risk of hyperkalemia and

subsequent dysrhythmias. (LoE III) Furthermore, phenelzine lowers pseudocholinesterase activity and may prolong the action of succinylcholine [78].

Hyperthermia

Close and accurate monitoring of core body temperature is indicated in patients with MAO inhibitor toxicity. Rapid and aggressive cooling is required in patients with hyperthermia. First-line therapy includes titration of benzodiazepines, or other GABA-A agonists such as phenobarbital (LoE III), which results in centrally mediated reduction in muscle hyperactivity leading to decreased heat production. This coupled with increasing evaporative and conductive heat loss is essential for the successful treatment of hyperthermia. Increasing heat loss is accomplished best by using ice baths and cool mist spray with fans. Hyperthermia often is resistant to these measures in the setting of persistent muscle rigidity. Consequently, muscle paralysis with nondepolarizing agents should be performed when diffuse rigidity is refractory to benzodiazepine or other GABA-A agonist therapy. Dantrolene use has been reported with apparent success as a muscle relaxant in resistant cases of muscle rigidity [42, 46]. (LoE III) Prior to institution of nondepolarizing neuromuscular blockade, use of dantrolene can be considered in cases in which muscle rigidity is not fully controlled by titration of GABA-A agonists (i.e., benzodiazepines, phenobarbital, or propofol). Antipyretics generally are ineffective in the treatment of drug-induced hyperthermia, and other temperature reduction methods are necessary.

Admission Criteria

All intentional MAO inhibitor overdoses and accidental exposures of greater than 1.0 mg/kg require admission to an ICU. (LoE III) Accidental exposures of less than 1.0 mg/kg still require hospital admission to a monitored bed; however,

these patients are unlikely to develop life-threatening complications. Reversible MAO inhibitors are less toxic than traditional MAO inhibitors, and ingestions of less than 2,000 mg in adults are unlikely to produce significant toxicity. Asymptomatic patients can be admitted to a monitored bed for 24-h observation. Even a single MAO inhibitor tablet may produce life-threatening drug interactions, such as the serotonin syndrome, or other drug interactions under certain circumstances. Asymptomatic patients should be monitored for at least 24 h before medical clearance. Vital sign abnormalities should be recognized early and treated appropriately. Dietary and medication restrictions should be followed meticulously during hospitalization. All patients should be instructed to avoid contraindicated foods and medications for a minimum of 2 weeks. Consultation with a medical toxicologist is recommended. If one is not locally available assistance can be obtained from poison control centers. Patients requiring transfer to hospitals with ICU capabilities should be transferred as soon as possible to avoid the problems anticipated with delayed onset of toxicity. Medical personnel capable of performing advanced cardiac life support and endotracheal intubation should accompany all patients being transferred.

Extracorporeal Removal Techniques

Hemodialysis, hemoperfusion, and peritoneal dialysis have no established role in the treatment of MAO inhibitor poisoning. Hemodialysis should only be used for typical indications such as severe, refractory acidosis, hyperkalemia, or acute renal failure which may be complications of severe MAO inhibitor toxicity.

Tyramine Reaction

In cases of severe hypertension, an α -antagonist or direct-acting vasodilator are the drugs of choice. (LoE III) Phentolamine is typically given

intravenously in 2.5–5 mg doses every 5–15 min until the blood pressure is controlled. The half-life of phentolamine is approximately 20 min, and its duration of action is less than 1 h. Nitroprusside is another rapidly acting direct vasodilator and is administered as a continuous infusion (1–4 µg/kg/min). In cases of moderate hypertension, nifedipine and prazosin have been reported to be effective [46, 68]. (LoE III) β-Adrenergic blocking drugs generally are considered contraindicated because of the risk of unopposed α-receptor stimulation. Hospital admission should be strongly considered for patients whose hypertension does not resolve completely within 6 h after onset. Gastrointestinal decontamination is unlikely to offer any significant benefit because the onset of toxicity is so rapid after tyramine exposure. Tyramine reactions are immediate, without delayed sequelae. Asymptomatic patients require only 6 h of observation.

Criterion for ICU Discharge in Monoamine Oxidase Inhibitor Poisoning

Stable patient who is at least 24 h post ingestion

Drug Interactions

Long-term MAO inhibitor drug therapy predisposes to many potentially significant drug interactions (see Table 3). Documentation of human MAO inhibitor drug interactions often is limited to single case reports or case series. Controlled human studies are impractical owing to the severe and potentially life-threatening nature of these reactions. Animal studies often have limited applicability to human toxicity. Patients taking MAO inhibitors should not receive other prescription or nonprescription medications unless strongly warranted and only after drug compatibility with MAO inhibitors has been confirmed (Table 4).

Drug interactions involving MAO inhibitors can be grouped into three categories – pharmacodynamic, pharmacokinetic, and idiosyncratic. The most common pharmacodynamic reaction

Table 4 Drugs considered safe with monoamine oxidase inhibitors^a

Direct-activity sympathomimetics	Miscellaneous drugs
Albuterol	Acetaminophen
Dobutamine	Aspirin
Epinephrine	Barbiturates
Fenoldopam	Benzodiazepines
Isoproterenol	Calcium channel blockers
Norepinephrine	Cephalosporins
Terbutaline	Corticosteroids
	Inhalational anesthetics
	Lidocaine
	Morphine ^b
	Nitroglycerin
	Nitroprusside
	Nitrous oxide
	Nonsteroidal antiinflammatory drugs
	Penicillin
	Phentolamine
	Procainamide

^aAlways use the lowest effective dose
^bSome commonly available drug interaction resources suggest an interaction between morphine and phenelzine based on weak evidence and without mechanistic explanation [85]

involves drugs with indirect sympathomimetic actions [68, 79], such as amphetamine, methamphetamine, pseudoephedrine, and ephedrine. These drugs have the potential to produce a hyperadrenergic condition similar to the tyramine reaction and can be found in over-the-counter preparations, drugs of abuse, and some prescription products. Pharmacokinetic drug interactions have been noted with MAO inhibitors because they are metabolized through the cytochrome oxidase enzyme system and can inhibit the hepatic metabolism of other drugs. The potentiation of opiate and sedative-hypnotic drugs is an example of this type of enzyme inhibition [68]. Phenelzine is metabolized in part via acetylation; as a result slow acetylators of hydrazines may be at increased risk for adverse drug effects of phenelzine. Phenelzine is also a relatively weak inhibitor of CYP 2C19 and CYP 3A4, but the clinical relevance is unclear [38].

Tranylcypromine is a potent highly selective competitive inhibitor of CYP 2A6 [38]. Tranylcypromine and phenelzine have been shown to increase insulin release and predispose to hypoglycemia, especially in patients taking oral sulfonylurea agents [68, 80, 81]. Insulin dosage also may warrant reduction.

Serotonin syndrome is a potentially life-threatening idiosyncratic reaction. It most commonly occurs when MAO inhibitors are combined with other serotonergic agents [82, 83]. A complete description of serotonin syndrome and a listing of serotonergic medications can be found in ► Chap. 24, “Serotonin Syndrome” [68]. Given the relative high-frequency use of opioids, special mention is warranted regarding agents such as tramadol, tapentadol, meperidine, and dextromethorphan which may produce serotonin syndrome in combination with MAO inhibitors [78]. All pro-serotonergic medications are contraindicated for 2 weeks after discontinuation of an irreversible MAO inhibitor. (LoE III) This recommendation is particularly important to prevent the development of serotonin syndrome.

Equally important is the recognition that certain medications are generally compatible with MAO inhibitors (see Table 4). Aspirin, acetaminophen, ibuprofen, and morphine have been used in combination with MAO inhibitors without complications [68]. It should be noted that some commonly available drug-drug interaction resources suggest there is a potential interaction between morphine and phenelzine. The nature and basis of the interaction is unclear. Some sources indicate potentiation of opioid effects specifically CNS/respiratory depression. While there is an unconvincing case report implicating this combination in the development of serotonin syndrome [85]. No plausible mechanism was identified. Direct-acting sympathomimetic agents, such as norepinephrine, can be used with caution, using lowest possible effective dose. Direct sympathomimetics do not rely on the release of neurotransmitters for their activity and are inactivated by catechol *O*-methyltransferase, which is unaffected by MAO inhibitors [68].

Key Points in Monoamine Oxidase Inhibitor Poisoning

1. Clinical toxicity often is delayed 6–24 h after ingestion.
2. MAO inhibitors are not detected by common drug tests.
3. Drug concentrations are not useful for managing overdose patients.
4. Selective, reversible MAO inhibitors are less toxic than irreversible MAO inhibitors.
5. MAO inhibitors have little effect on the electrocardiogram except for sinus tachycardia.
6. Consider serotonin syndrome in patients taking two or more serotonergic agents.
7. Admit all patients who ingested >1 mg/kg for 24 h of observation.
8. Do not use β -blockers to treat tachycardia or hypertension.
9. Do not use indirect sympathomimetics.
10. Avoid combining serotonergic agents.
11. Do not give meperidine, tramadol, or dextromethorphan to patients taking MAO inhibitors.
12. Extracorporeal removal is an unproven modality in MAO inhibitor overdose.
13. Selegiline is metabolized to methamphetamine.
14. Tranylcypromine does not produce amphetamine in the urine.

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While many drugs have some effect on serotonergic receptors this chapter focuses upon the toxicity seen with medications whose primary antidepressant therapeutic mechanism of action is to modify serotonergic transmission. This includes selective serotonin reuptake inhibitors (SSRI), serotonin noradrenergic reuptake inhibitors (SNRI), and tetracyclic and triazolopyridine antidepressants (Tables 1, 2, 3, and 4).

The release of serotonin into the synapse from presynaptic vesicles follows depolarization and influx of calcium into the cell. Presynaptic serotonin concentrations are maintained by both presynaptic synthesis from precursors such as tyramine and by the reuptake of serotonin from the synapse. Serotonin homeostasis is maintained by metabolism by monoamine oxidase inhibitors. Presynaptic reuptake utilizes biogenic amine reuptake transporters for both serotonin and also noradrenaline [1]. Reuptake inhibitors such as SSRI and SNRI block the amine transporter at similar locations but with some variation of binding substrates and affinity [2].

The impetus for the development of primarily serotonergic drugs came from observations of efficacy of clomipramine compared with other tricyclic antidepressants in some patients. This efficacy was ascribed to relatively greater serotonin reuptake inhibition of clomipramine compared with most other tricyclic antidepressants. This led to more specific receptor targeted drug development leading to the prototypical SSRI fluoxetine. Subsequent development also

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Table 1 Therapeutic pharmacokinetics SSRI [67]

Agent (Chemical class)	Defined daily dose (mg)	Bioavailability %	Protein binding %	Vd L/kg	Tmax (hrs)	Elimination	T1/2 (hrs)	Notes
Fluoxetine ^{a,b} (phenylpropylamine)	20	90%	94	20–45	6–8	Hepatic	1–4 days	Active metabolite norfluoxetine has half-life 7–15 days Inhibit CYP2D6
Fluvoxamine ^c (benzene and substituted derivatives)	100	53%	77	5	5	CYP2D6 CYP1A2	15	Inhibits CYP1A2 and CYP2C19
Paroxetine ^c (phenylpiperidines)	20	50	95	3–12	6	CYP2D6 COMT ^a	20	Inhibit CYP2D6 Some muscarinic receptor blockade
Sertraline (tametralines)	50		98	20	6–8	CYP3A4	26	
Citalopram (phenylbutamines)	20	80	80	14–16	4	CYP2D6 CYP2C19	36	
Escitalopram (phenylbutamines)	10	80	56	12		CYP3A4 CYP2C19	27–32	

^aAlso available in combination with olanzapine

^bAvailable in some countries in a delayed release form (90 mg weekly)

^cAvailable in some countries in an extended release form

encompassed screening for cardiotoxicity and the introduction of compounds with lower likelihood of significant pharmacokinetic interactions [3].

The overall use of serotonergic antidepressants greatly exceeds the population estimates for their major therapeutic indications [4]. As a group their higher safety in overdose and different side effect profile compared with tricyclic antidepressants has contributed to their high volume of use. As a consequence, serotonergic antidepressants are commonly taken in deliberate self-poisoning. The North American National Poison Data System reports frequent hospital presentations but low morbidity and mortality for these agents [5]. These observations and evidence of different relative toxicity within the groups are also supported by fatal toxicity indices (FTI) which are calculated from deaths per million prescriptions. The FTI for venlafaxine 13.2 (CI 9.2 to 18.5) is significantly higher than that of SSRIs and the tetracyclic antidepressants (point estimates ranging from 0.7 to 3.3) [6]. This is consistent with clinical observations of severity [6–9].

Toxicity is most commonly seen following deliberate self-poisoning but may also be seen in the context of significant drug-drug interactions and to a lesser extent drug-disease interaction. In single agent ingestions the overall risk of morbidity and mortality is low, but there is significant variation in the relative risk of toxicity between the four drug classes and within some drug classes. Within this group SNRIs are the most likely to require intensive care admission. Specific clinical assessment and management focuses upon the detection of serotonin toxicity (see ► Chap. 24, “Serotonin Syndrome”), cardiovascular toxicity, and neurological toxicity.

SSRIs

Biochemistry and Clinical Pharmacology

SSRIs are a chemically diverse group of lipid soluble compounds (Table 1). Their principle route of elimination is hepatic, predominantly by

Table 2 Therapeutic pharmacokinetics NSRI

Agent (Chemical class)	Defined daily dose (mg)	Bioavailability (%)	Protein binding %	Vd L/kg	Tmax (hrs)	Elimination	T1/2 (hrs)	Notes
Venlafaxine ^a [45] (phenylpropylamine)	100	42	30%	6.8	5.5 ^a 2 ^b	Hepatic CYP2D6	4	High first pass metabolism, major active metabolite <i>O</i> -demethyl- venlafaxine
Desvenlafaxine ^a (<i>O</i> -demethyl- venlafaxine) [73] (phenylpropylamine)	50	80	30%	5.7	7–8	45% renal unchanged Hepatic glucuronidation UDP-glucuronosyltransferase	9–15	
Duloxetine [74, 75] (naphthalene)	60	50	90	10–14	6	CYP1A2	10–12	

^aExtended release preparations are available. The apparent half-life of extended release is longer, 15 h

^bNormal release

Table 3 Therapeutic pharmacokinetics tetracyclic antidepressants

Agent (Chemical class)	Defined daily dose (mg)	Bioavailability %	Protein binding %	Vd L/kg	Tmax (hrs)	Elimination	T1/2 (hrs)	Notes
Mirtazapine (piperazinoazepine) [54, 67]	30	50	85	5	2	Hepatic CYP2D6 CYP 3A4	20–40	Severe renal impairment reduce clearance by 50%
Mianserin (dibenzazepine) [67, 76]	60	30	90		2.6		10–17	

Table 4 Therapeutic pharmacokinetics phenylpiperazines

Agent (Chemical class)	Defined daily dose (mg)	Bioavailability %	Protein binding %	Vd L/kg	Tmax (hrs)	Elimination	T1/2 (hrs)	Notes
Nefazodone (phenylpiperazines) [67]	400	20	99	0.2–0.9		Hepatic CYP 3A4	2–4	Hydroxynefazodone
Trazodone (phenylpiperazines) [65–67]	300	63–91	95	5–9	1.3–2	Hepatic CYP 3A4	6	Active metabolite m-chlorophenyl- piperazine Produced by CYP 3A4
Vortioxetine (phenylpiperazines) [77, 78]	10	75		35	6	CYP 2D6	57	

cytochrome P450. Fluoxetine and paroxetine cause clinically important inhibition of some cytochrome enzymes (Table 1) [10]. At steady state the half-life is less than 2 days for all the SSRIs with the exception of fluoxetine and its active metabolite norfluoxetine (half-life 7–15 days). In therapeutic doses sertraline and citalopram show linear and fluoxetine, fluvoxamine, and paroxetine nonlinear pharmacokinetics. In overdose it is likely that all would show nonlinear elimination kinetics (Table 1).

Inhibition of presynaptic reuptake of serotonin increases synaptic serotonin and agonism at the 5HT_{1a} receptor which is thought to mediate much of the antidepressant effects of SSRIs. Serotonin reuptake inhibition by SSRIs is significantly higher than inhibition of dopamine or norepinephrine reuptake. There are no other reported clinically significant direct effects on other

neuroreceptors [10]. Paroxetine has some muscarinic receptor antagonism which is significantly less than that seen with clomipramine and of doubtful clinical significance [11].

Pathophysiology of Toxic Effects

The serotonin syndrome is the most commonly seen toxicity of SSRIs and relates directly to the extent of inhibition of serotonin reuptake. The major variation in toxicity within the class is seen with citalopram and escitalopram. Inhibition of repolarization of myocardial cells by blocking potassium efflux channel's coded for by the HERG gene causing QT prolongation and an increased risk of Torsades de Pointes is reported for SSRIs but the risk is highest for citalopram and escitalopram [12–14].

Clinical Presentation and Life-Threatening Complications

Overall the risk of death or significant morbidity from single SSRI ingestions is low. The most frequent specific clinical findings are signs of serotonin syndrome. All patients should be assessed for QT prolongation; the risk is significantly higher for ingestions of citalopram and escitalopram. Within intensive care units patients with SSRI ingestions are most commonly seen in the context of multiple drug ingestion.

Serotonin Syndrome

Clinically, the serotonin syndrome comprises a cluster of clinical effects producing a spectrum of severity. While the syndrome is common it is unusual to see significant toxicity that requires treatment in intensive care. The syndrome is attributed to serotonin agonism at the 5HT_{2a} receptor. The severity of SSRI-induced serotonin syndromes is dose related and reflects the synaptic serotonin concentration. Ingestion of two or more additive or synergistic serotonergic agents has a higher risk of severe toxicity than ingestion of a single agent [15]. An example of the effects of such synergism is the co-ingestion of therapeutic doses of a monoamine oxidase inhibitor and a SSRI.

The most common clinical signs are those associated with a mild serotonin syndrome, specifically brisk reflexes and poorly sustained clonus. The risk of toxicity from ingestion of a single SSRI increases with dose but there does not appear to be any within class difference in the risk of serotonin toxicity. Serotonin syndrome was seen in 14% of 469 individuals with self-poisonings with single SSRIs in a prospective single center consecutive case series. No patients developed serotonin syndrome that required ICU admission [14]. Within this cohort a GCS of <9 was seen in 11 patients, 10 of whom had co-ingested sedative medication. Short self-limited generalized seizures were seen in 1.9% of patients, but there was no apparent difference within the class.

Cardiovascular

The potential for significant cardiac toxicity manifests as QT prolongation is dose related, and the

highest risk is for citalopram and escitalopram [14, 16–22]. Torsades de pointes has been reported for both citalopram and escitalopram, but the overall risk is low [23, 24]. QT prolongation and torsades de pointes have been reported with fluoxetine [13].

The low risk of torsade is also supported by observational studies reporting three deaths in 5,251 patients with citalopram overdose [12]. Citalopram is associated with the higher risk of death than other SSRIs [25]. The risk of QT prolongation increases with ingestions of more than 600 mg citalopram and 300 mg of escitalopram but may not be manifest for 12 h [16, 20]. Patients with prolonged QT at admission or with ingestions of more than 600 mg citalopram or 300 mg of escitalopram require continuous ECG monitoring for at least 12 h. In those patients with QT prolongation monitoring should continue until the QT normalizes. Magnesium, potassium, and calcium should be checked and corrected if low (see ► Chap. 22, “Toxicant-Induced Torsade de Pointes”).

The tachycardia commonly seen in serotonin toxicity can complicate the assessment of QT prolongation by overestimating the QTc. Detection of prolonged QT is best assessed using the Fossa nomogram especially in the presence of tachycardia rather than using QTc calculations [26, 27] (Grade II-2 recommendation).

Diagnosis

Diagnostic algorithms for a categorical diagnosis of serotonin syndrome have been developed, validated, and widely used [28] (Fig. 1). However, treatment is normally based upon an assessment of severity of the syndrome, and so patients require repeated physical examinations focusing upon the severity and duration of clonus, presence of fever, and respiratory failure [15] (see ► Chap. 24, “Serotonin Syndrome”).

Treatment

Serotonin Syndrome

Specific treatment in patients with mild to moderate serotonin syndrome is often not required. Most

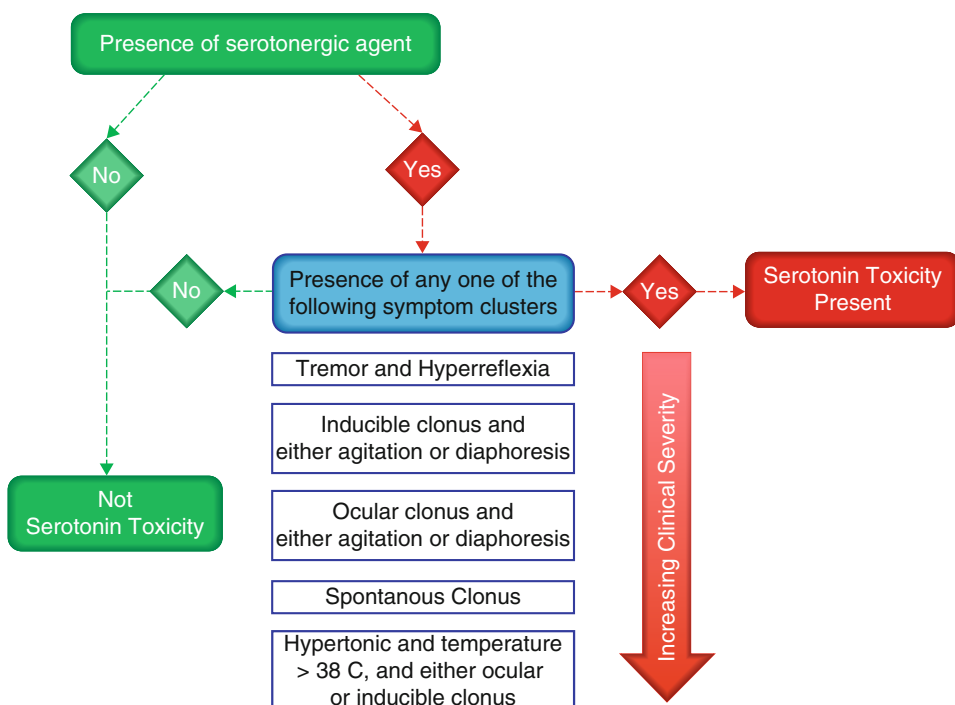


Fig. 1 Hunter criteria for serotonin toxicity (Figure used under a Creative Commons license from wikitoX.org)

patients with agitation, tremor, or unsustained clonus will gain symptomatic relief from benzodiazepines or 5HT_{2a} antagonists such as cyproheptadine titrated against clinical effects. Severe serotonin toxicity manifesting as fever, spontaneous sustained clonus, and hypercapnic respiratory failure is rare in ingestions of single agents but is an indication for ICU admission (see ► Chap. 24, “Serotonin Syndrome”).

Decontamination

Administration of activated charcoal up to 4 h after ingestion reduces the risk of QT prolongation following ingestion of either citalopram or escitalopram [18, 20, 22]. Suggested thresholds for decontamination are more than 600 mg citalopram or 300 mg of escitalopram [16, 20]. While it is likely that decontamination would reduce the rate and severity of serotonin syndrome, it is not warranted in single agent SSRI ingestions. Decontamination should be considered in patients who meet criteria for ICU

admission and in particular if they have taken multiple serotonergic synergistic medications.

QT Prolongation

Correction of hypokalemia, hypocalcemia, and hypomagnesemia is indicated in patients with true prolongation of the QT interval (see ► Chap. 22, “Toxicant-Induced Torsade de Pointes”) [26]. Given the relatively low risk of TdP associated with most of these agents, there is little reason to give magnesium to patients who are not magnesium deficient [29].

NSRIs (SNaRIs)

Biochemistry and Clinical Pharmacology

The bicyclic serotonin and noradrenaline reuptake inhibitor (SNRI or NSRI) antidepressants venlafaxine and desvenlafaxine are

phenylpropylamines that are structurally and pharmacologically related to the nonopioid analgesic tramadol but not to any conventional antidepressant medications. Duloxetine is chemically distinct containing a naphthalene moiety, which consists of two fused benzene rings. NSRIs are potent inhibitors of neuronal serotonin and noradrenaline reuptake and weak inhibitors of dopamine reuptake. They have no notable monoamine oxidase inhibitor activity and minimal affinity for muscarinic, cholinergic, histamine, or α_1 - and α_2 -adrenergic receptors.

The pharmacokinetics of NSRIs in therapeutic use is summarized in Table 2. Both venlafaxine and desvenlafaxine are available in extended release which prolongs the absorption phase producing a later T_{Max} and also increasing the apparent half-life. A study based on 76 self-poisonings with extended release venlafaxine showed the mean half-life in overdose to be 12.9 h [30].

Pathophysiology of Toxic Effects

The most commonly seen toxicity is an extension of the therapeutic effect of blocking amine reuptake. Both synaptic serotonin and noradrenaline concentrations are increased. The combination of signs produced by both synaptic serotonin excess and a noradrenaline excess-induced sympathomimetic syndrome contributes to satisfying the diagnostic criteria for serotonin toxicity [28]. This may explain the higher rates of serotonin toxicity seen in cohort studies that compare NSRI with SSRI [31, 32].

At high doses there is evidence of cardiac sodium channel blocking leading to delayed depolarization. Duloxetine blocks persistent late Na currents preferentially [33]. Animal models suggest venlafaxine cardiotoxicity and QRS widening are due to dose dependent Na⁺ channel blockade in the resting state [34]. Mild systolic hypertension is reported in venlafaxine and desvenlafaxine [9, 35]. Hypotension is reported following large ingestions of venlafaxine and is attributed to reduced myocardial contractility [36]. Venlafaxine and desvenlafaxine have been associated with Takotsubo

cardiomyopathy in both therapeutic doses and in overdose [37, 38].

The mechanism of seizures is not well defined. Hypoglycemia responsive to octreotide has been reported [39].

Clinical Presentation and Life-Threatening Complications

As venlafaxine is the prototypical drug of this class, published experience of effects in overdose is greater than its active metabolite desvenlafaxine or duloxetine. Available data does not suggest significant differences in toxicity within this class [40, 41].

Venlafaxine has higher rates of serotonin toxicity, seizures, and prolongation of the QRS complex than seen in SSRI [32]. Onset of toxicity may be delayed for a significant period of time for extended release preparations [32]. Death from cardiovascular complications is reported [36, 42, 43].

Rhabdomyolysis with creatinine kinase greater than 1,000 was noted in 3.8% of venlafaxine poisoning and appeared in patients with or without seizures [44].

Serotonin Syndrome

Serotonin syndrome occurred in 30% of patients in a consecutive series of venlafaxine poisoning [9, 31]. While a diagnosis of serotonin syndrome is not necessarily an indication for specific treatment, it is dose related and may identify a group of patients at greater risk of seizures and/or cardiovascular toxicity [44].

Central Nervous System Effects

Sedation is seen in large overdoses and probably is due to histamine antagonism [45]. The most common central nervous system (CNS) effects are agitation as part of the spectrum of serotonin toxicity and seizure activity [9]. While the mechanism of seizure activity is unclear there is a clear dose related risk.

A consecutive case series of patients who ingested venlafaxine found an overall incidence of usually self-limited seizures of 5–8.9% [44, 46]. Most seizures occurred within 16 h of ingestion but may potentially occur for up to 24 h. The probability of seizures was dose related (Table 5)

Table 5 Probability of seizures from venlafaxine in adult patient [46]

Venlafaxine dose (mgs)	Median probability of seizures (95% credible interval)
1,000	0.05 (0.03–0.08)
5,000	0.19 (0.09–0.35)
10,000	0.75 (0.30–0.96)

and was reduced by gastrointestinal decontamination with activated charcoal [46].

A poison center study reported seizures occurring in 6.9% of duloxetine ingestions and were only seen at doses greater than 1,800 mg [41].

Cardiovascular

A review of 369 venlafaxine presentations in 273 patients with a median ingested dose of 1,500 mg (range 75 mg to 13,500 mg) showed that only minor cardiovascular effects were observed [47]. Tachycardia was noted in 54% of presentations, 40% had a systolic BP >140 mmHg, 5% had a systolic BP < 90 mmHg. Comparable rates of hemodynamic changes were confirmed in another case series [35]. Prolonged QT intervals were observed in 6% of patients. A QRS duration > 120 ms occurred in 7% of patients, all of whom had ingested over 5 g [47]. Batista reports a consecutive series of 80 patients with venlafaxine ingestions. Four developed acute heart failure, all following ingestions of over 3,000 mg. Three of these four died. Echocardiography showed diffuse left ventricular dysfunction [36]. Other reports of death or acute cardiomyopathy have all been in doses of greater than three grams [36, 43, 48, 49]. However, the specificity and sensitivity of a threshold dose has not been established as significant toxicity has been reported through all dose ranges. Takosubo cardiomyopathy has been associated with overdose and therapeutic doses of venlafaxine and desvenlafaxine, including one patient who developed torsade de pointes [37]. Takosubo cardiomyopathy was associated with QT prolongation and with torsade de pointes, although most patients who have developed this arrhythmia had multiple risk factors. In a case series of 75 desvenlafaxine overdose, 32% showed mild hypertension and 39% sinus tachycardia, no patients had seizures or a QRS duration that exceeded 120 msec [50].

Diagnosis

The clinical assessment and diagnosis of NSRI toxicity is typically made on the basis of the history and clinical setting. Patients should have repeated assessment for serotonin toxicity, and those who develop signs of severe toxicity should be assessed for respiratory failure and rhabdomyolysis. Patients with serotonin toxicity are more likely to develop other significant toxicity in the author’s experience. For patients who develop a QRS duration monitoring is indicated until their ECG returns to normal. In practice, these patients normally have other signs of toxicity. Patients with hypotension that does not respond to intravenous fluid administration should have an echocardiogram to assess myocardial function. There is an association of QT prolongation with Takotsubo cardiomyopathy [50].

Treatment

For most patients who have overdosed on an NSRI their clinical course will be uncomplicated, and they are unlikely to require intensive care admission.

Patients with a reduced level of consciousness who require intubation should receive a single dose of activated charcoal. A single dose of activated charcoal reduced venlafaxine bioavailability by 29% and increased clearance by 35% [46]. Gastrointestinal decontamination with activated charcoal reduces significant clinical toxicity for ingestions of more than 1,000 mg of venlafaxine [46] (Grade II-2 recommendation).

While QRS widening is relatively common after NSRI overdose significant arrhythmias are rare in ingestions of less than 8 g of venlafaxine [47]. As all the compounds in this class are weak bases and ECG changes are consistent with sodium channel blockade, it seems logical to treat significant tachy- or bradyarrhythmias with plasma alkalization as first line therapy (see ► Chap. 39, “Sodium Channel-Blocking Antidysrhythmics”). There are three cases reported where QRS widening responded to sodium bicarbonate [42, 51] (Grade III recommendation).

Seizures associated with NSRI toxicity are generally self-limited but can be recurrent. The preferred agents to treat drug-induced seizures are benzodiazepines or barbiturates [52].

Tetracyclic Antidepressants

Biochemistry and Clinical Pharmacology

Mirtazapine and mianserin are potent presynaptic antagonists of central alpha adrenoreceptors ($\alpha_2 > \alpha_1$), promoting monoamine release (noradrenaline and serotonin), while not blocking their reuptake. Mirtazapine is an antagonist at both 5-HT_{2a} and 5-HT₃ receptors which attenuates potential serotonin toxicity. It has also been suggested effects on increasing serotonergic function are weak and not contributing significantly to mirtazapine's therapeutic effects [53]. Mirtazapine is also a potent antihistamine leading to sedation and has weak antimuscarinic activity [54].

The pharmacokinetics in therapeutic doses are summarized in Table 3. Both have a high first pass metabolism. It is likely that following overdose the first pass metabolism is saturable leading to increased bioavailability.

Pathophysiology of Toxic Effects

Sedation due to histamine antagonism is the major toxic effect.

Clinical Presentation and Life-Threatening Complications

Mirtazapine

Deaths from mirtazapine poisoning appear to be very rare and comparable to SSRI in fatal toxicity index (FTI) [6] and in poison control data [12]. These observations of low toxicity have been supported by clinical and poison center case series to show minimal effects other than tachycardia, mild hypertension, and minor CNS depression [55–58].

Berling et al. reviewed 89 single agent mirtazapine ingestions and showed the lowest GCS was 10, all within 6 h, with no complications or need for ICU admission. There were no cases of seizures, serotonin toxicity, delirium, or QT prolongation reported in case series [55, 57]. The lack of serotonin toxicity may be explained by the 5HT_{2a} antagonism.

Mianserin

Data on mianserin are even more limited than that for mirtazapine but qualitatively similar. The fatal toxicity index is comparable to mirtazapine [6]. A few patients with serious arrhythmias (heart block and ventricular fibrillation) have been reported but other toxic effects are usually minor [59–61]. One hundred consecutive cases of mianserin hydrochloride poisoning were followed-up by a Poisons Information Service. When mianserin was the only drug ingested, effects were mild and neither deep coma nor convulsions were reported [62, 63]. Although mianserin may rarely cause agranulocytosis, this does not appear to be a dose-related effect [64].

Diagnosis

There are no diagnostic features on physical examination or investigation. The major anticipated toxicity is sedation and potential airway compromise. Significant neurological or cardiac toxicity should prompt assessment for other co-ingestions or other etiologies.

Treatment

Treatment is supportive.

Triazolopyridines (Phenylpiperazines)

Biochemistry and Clinical Pharmacology

Nefazodone and trazodone are structurally related. Both drugs are weak inhibitors of presynaptic serotonin reuptake, but the effects of this are modulated by antagonism of postsynaptic

5-HT_{1a}, 5-HT_{1c}, and 5-HT₂ receptors [65]. There is no significant effect on norepinephrine uptake. Both compounds are antagonists of histamine and alpha 1-adrenoceptor receptors but there is no significant affinity with other receptors [65, 66].

Nefazodone hydrochloride sale was discontinued in 2003 in some countries due to the small possibility of hepatic (liver) injury, which could lead to the need for a liver transplant or even death. The incidence of severe liver damage is approximately 1 in 250,000–300,000 patient-years [67].

The pharmacokinetics in therapeutic use is summarized in Table 4.

Pathophysiology of Toxic Effects

The risk of death is low with a fatal toxicity index comparable to sertraline [68]. No deaths were reported in a consecutive multicenter case series of 180 cases of trazodone [69]. The major clinical syndrome is impaired level of consciousness, due to histamine antagonism, and hypotension secondary to vasodilation from alpha 1-adrenoceptor antagonism [70]. QT prolongation is reported and is thought to be due to effects on the I_{Kr} current channel [71].

Clinical Presentation and Life-Threatening Complications

The most common sign of acute trazodone poisoning is CNS depression [70]. However, trazodone rarely produces coma or seizures when it is the only drug ingested [5]. **Trazodone**-induced CNS effects show marked improvement within 6 to 12 h after ingestion and almost always are resolved within 24 h [70].

Orthostatic hypotension is the most frequently reported cardiovascular abnormality noted in trazodone overdose and usually responds to fluid administration [70]. Trazodone is rarely associated with QT prolongation, ventricular arrhythmias, and sudden death [71, 72].

Diagnosis

There are no diagnostic features on physical examination or investigation. Patients should be assessed for QT prolongation.

The major anticipated toxicity is sedation and potential airway compromise. Significant neurological or cardiac toxicity should prompt assessment for other co-ingestions or other causes.

Treatment

Treatment is supportive.

Indications for ICU Admission

Severe serotonin toxicity

Seizures

QRS widening

QT prolongation

Ingestion of > 600 mg citalopram or >300 mg escitalopram

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Part VII

Medications: Anticonvulsant

Frank LoVecchio

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Greater than two million Americans suffer from epilepsy, and 10% of the population has at least one convulsion in their lifetime. Phenytoin has been commercially available in the United States since 1938 and had been a first-step anticonvulsant for all types of epilepsy, with the exception of absence seizures. In conjunction with benzodiazepines, phenytoin is efficacious in the acute treatment of status epilepticus [1] and has been used prophylactically after head injury [2]. Phenytoin was used as a class 1B antidysrhythmic agent, particularly in the setting of digoxin toxicity, but it no longer is considered a first-line agent for that indication.

Significant morbidity or mortality are infrequent after intentional oral phenytoin overdose [3]. Hypersensitivity reactions, falls, rapid intravenous administration, and extravasation of the drug into soft tissues are responsible for most phenytoin-related mortality and morbidity. The latter two adverse effects are related directly to the propylene glycol, an alkaline diluent, available in the injectable form of the drug [4]. This diluent and most of the local and cardiovascular effects have been eliminated with the newer phenytoin prodrug preparation fosphenytoin.

In 2014, the American Association of Poison Control Centers reported 2745 phenytoin and 14 fosphenytoin exposure calls, of which 1 was associated with death and 45 had major adverse outcomes [5]. One death was also reported in the 2013 database [6]. Although poison center data are limited, these data at least suggest that

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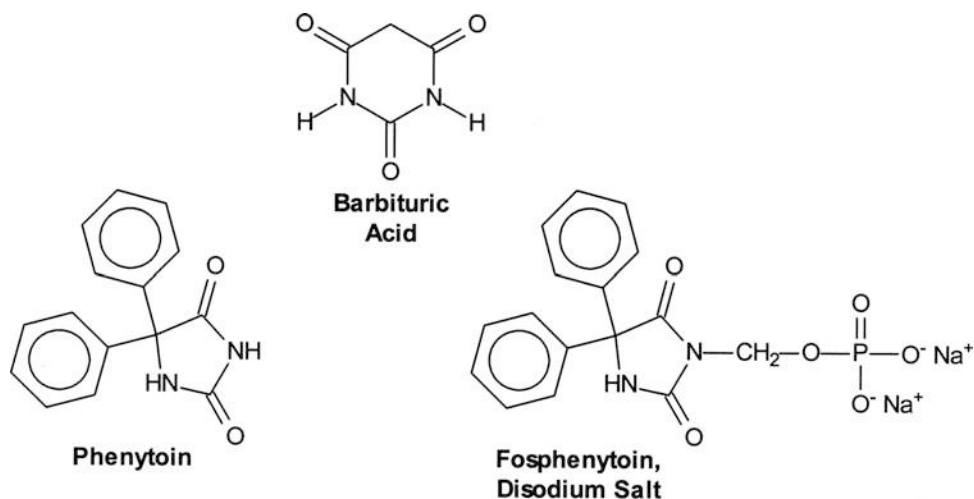


Fig. 1 Chemical structures of anticonvulsant medications

significant morbidity and mortality are rare after acute phenytoin exposure.

Biochemistry and Clinical Pharmacology

Phenytoin, or 5,5-diphenyl-2,4-imidazolidinedione, is similar in chemical structure to the barbiturates but has a five-membered ring (Fig. 1). It is a weak acid with a pK_a of 8.3. To maintain parenteral phenytoin in solution, it is adjusted to a pH of 12.

Pharmacokinetics

Given phenytoin's relatively high pK_a , its solubility is limited at physiologic pH and in gastric acid. Absorption of oral phenytoin is slow and imperfect, particularly after an overdose. Peak serum concentrations occur 3–12 h after a single oral dose. Many factors influence kinetics in overdose (e.g., quantity, coingestions, long-term therapy). Intramuscular phenytoin administration results in local precipitation of the drug with sporadic absorption and is not recommended.

After absorption, phenytoin is distributed with a volume of distribution of 0.6 L/kg, approximating body water. Central nervous system

concentrations equilibrate with concentrations in plasma within 10 min of intravenous infusion and correlate with therapeutic efficacy, whereas myocardial concentrations reach equilibrium with plasma within 30–60 min. Within the central nervous system, concentrations are higher in the brainstem and cerebellum than in the cerebral cortex. [7]

Phenytoin is 90% bound to plasma proteins, principally albumin. The free or unbound form is responsible for the drug's clinical effects. The free phenytoin fraction ordinarily constitutes 10% of the plasma level. The unbound fraction of the drug is greater in patients at extremes of age, pregnant women, patients with renal failure, patients with hypoalbuminemia, patients with hyperbilirubinemia, and individuals taking drugs that compete for phenytoin binding sites (e.g., salicylates, valproate, phenylbutazone, tolbutamide, and sulfisoxazole) [8].

Pharmacokinetics of Phenytoin

Therapeutic range: 10–20 $\mu\text{g/mL}$ (20–40 $\mu\text{mol/L}$)

Free phenytoin concentration: 1–2 $\mu\text{g/mL}$ (2–4 $\mu\text{mol/L}$)

Peak after therapeutic oral dose: 3–12 h

Plasma half-life: 6–60 h

Less than 5% of phenytoin is excreted unchanged in the urine. Most is metabolized by hepatic microsomal enzymes, primarily by cytochrome P450 (CYP) 2C9 and secondarily by CYP2C19. Its major (60–70%) metabolite, the parahydroxyphenyl derivative, is generated by CYP2C9. Inhibitors of CYP2C9 such as amiodarone, fluconazole, fluoxetine, metronidazole, or zafirlukast increase phenytoin serum concentrations. Although CYP2C9 inducers such as phenobarbital and rifampin decrease phenytoin concentrations, inhibitors of CYP2C19 such as cimetidine, felbamate, fluvoxamine, ketoconazole, lansoprazole, omeprazole, paroxetine, and ticlopidine increase phenytoin levels. Finally, inducers of CYP2C19 such as carbamazepine and rifampin may lower serum phenytoin concentrations [9].

Phenytoin is metabolized further by means of glucuronidation, then secreted in the bile, reabsorbed, and subsequently excreted in the urine as the glucuronide conjugate. The metabolism of phenytoin is highly dose dependent at low concentrations. At plasma concentrations less than 10 $\mu\text{g/mL}$ (40 $\mu\text{mol/L}$), its elimination is first order, with a constant percentage of drug being metabolized per unit of time. At higher concentrations, including concentrations in the therapeutic range (10–20 $\mu\text{g/mL}$ [40–80 $\mu\text{mol/L}$]), its metabolism becomes saturated, however, and elimination changes to zero order (i.e., a fixed amount of drug metabolized per unit of time) (Fig. 2). This change in kinetics can markedly prolong the elimination rate of phenytoin, which has an apparent half-life during therapeutic use of 6–24 h. When used therapeutically at the high therapeutic range, a modest increase in the daily dose may result in a disproportionate increase in the plasma concentration and subsequent toxicity. Individual variation occurs with regard to the serum or plasma concentration at which this transformation from first-order to zero-order kinetics occurs. Incremental increases in dose should be limited to the lowest increase possible, and patients should be monitored carefully, particularly when it is necessary to increase phenytoin doses to greater than 300 mg/day (or approximately 5 mg/kg/day) [8].

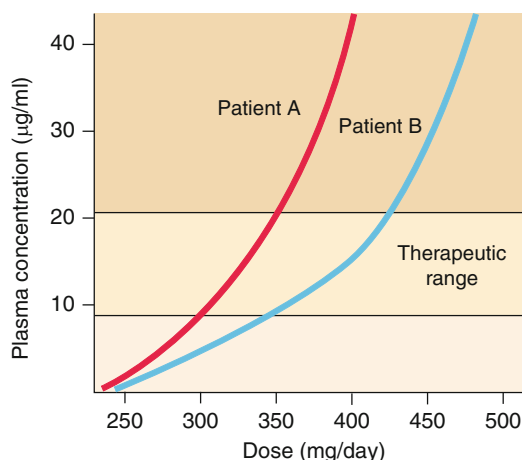


Fig. 2 The relationship between the dose and steady-state plasma concentration of phenytoin is illustrated for two patients. In both patients, there is a linear relationship between the dose and the plasma concentration at low doses. As the dose increases, there is a transition to a nonlinear relationship. This transition occurs at different doses in each patient (From Ref. [10])

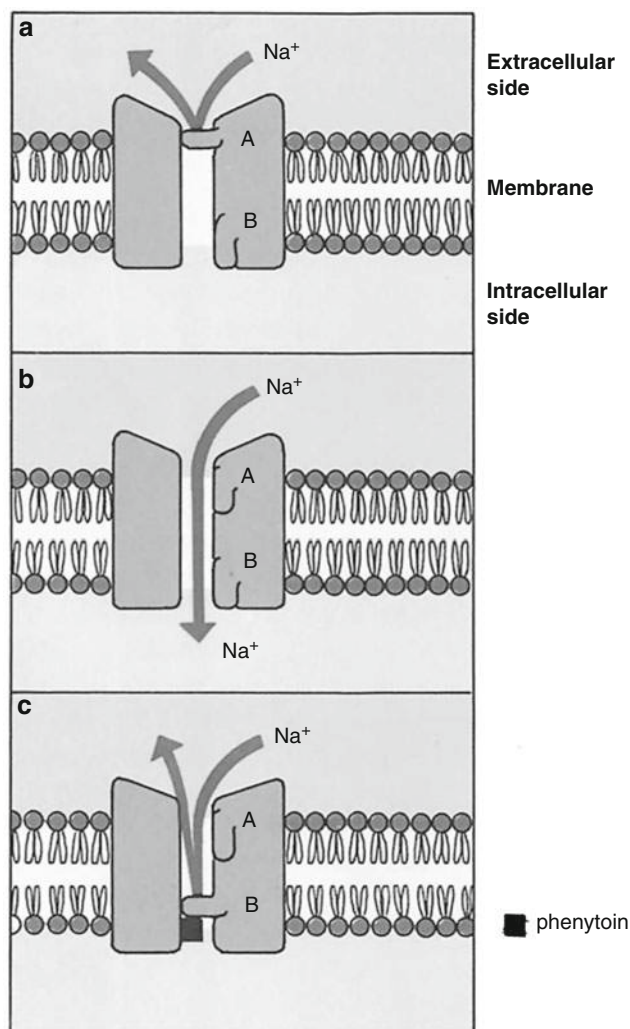
Pathophysiology

The precise mechanism by which phenytoin exerts its anticonvulsant action is unknown. The two presumed mechanisms of phenytoin's anticonvulsant effect are prolongation of neuronal sodium channel inactivation (Fig. 3) and the resulting inhibition of excitatory neurotransmitter release (see ► Chap. 20, "Toxicant-Induced Seizures").

High frequency of neuronal action potential generation is responsible for seizure development. Suppression of this high-frequency firing may occur as a result of voltage-dependent sodium channel inactivation or prolongation of the recovery from inactivation. Phenytoin inhibits sodium channels by reducing their capacity for recovery from inactivation. Phenytoin stabilizes sodium channels in an inactive state and limits the ability of neurons to depolarize at high frequency [9]. Phenytoin does not affect low-frequency neuronal firing. At higher concentrations in vivo, phenytoin delays activation of outward potassium currents in neurons and prolongs the neuronal refractory period [11].

Fig. 3 Action of phenytoin

on sodium channel. (a) Resting state in which sodium channel activation gate (*A*) is closed. (b) Arrival of an action potential causes depolarization and opening of activation gate (*A*), and Na^+ flows into the cell. (c), When depolarization continues, an activation gate (*B*) moves into the channel. Phenytoin prolongs the inactivated state of the sodium channel, presumably by preventing reopening of the inactivation gate (*B*). (From Ref. [10])



Phenytoin also may exert some anticonvulsant effect by acting through adenosine receptors. Adenosine is an endogenous anticonvulsant that suppresses seizure propagation [12, 13] by inhibiting excitatory neurotransmitter (e.g., glutamate) release. Phenytoin may inhibit adenosine reuptake, resulting in a net increase in extracellular synaptic adenosine and enhancement of its effect on neurotransmitter release [13, 14]. Phenytoin has no clinically significant action at γ -aminobutyric acid receptors or known effects on calcium channel conductance.

At toxic levels in the brain, phenytoin suppresses memory and balance by inhibiting the only areas of the brain that exhibit spontaneous neuronal burst

discharge: the hippocampus and the cerebellum. Cerebellar stimulation and alteration in dopaminergic and serotonergic activity may be responsible for the acute dystonias and movement disorders such as opisthotonos and choreoathetosis that infrequently accompany phenytoin toxicity. Seizures after toxic phenytoin ingestion are extremely rare, and their mechanism is not understood [12–15].

Phenytoin also may inhibit myocardial sodium channels; however, cardiac disturbances and negative inotropy attributed to this effect of phenytoin are reported infrequently. Similar to other class 1B antidysrhythmics, such as lidocaine, phenytoin blocks cardiac sodium channels and has a minimal effect on potassium efflux. At therapeutic doses, no

effects are noted on electrocardiogram, and at toxic doses, the effects are typically insignificant [16–18].

Diluent Effects

The acute-onset cardiovascular toxicity seen with intravenously administered phenytoin has been attributed to its diluent. Older parenteral formulations of phenytoin contain 40% propylene glycol and 10% ethanol, adjusted to a pH of 12 with sodium hydroxide. The propylene glycol component seems to be responsible for the reported coma, seizures, circulatory collapse, and ventricular dysrhythmias [14] after rapid intravenous administration of phenytoin. Propylene glycol is a strong myocardial depressant with vasodilatory and vagal effects [16, 17]. In animals, phenytoin partially reverses the toxic effects that occur when propylene glycol is given alone [18]. Noncardiovascular effects of propylene glycol include hyperosmolality, hemolysis, and lactic acidosis [16]. In addition, the ethanol diluent fraction of phenytoin may precipitate a reaction in patients ingesting disulfiram or disulfiram-like medications.

Clinical Presentation

The clinical toxicity of phenytoin varies as a function of dose, duration, route, and rate of administration. The latter two parameters are paramount. The rapid intravenous administration of phenytoin carries the greatest risk of life-threatening toxicity occurring as a result of the propylene glycol diluent. The gravest consequences occurring after intravenous administration of phenytoin are cardiovascular (bradycardia, hypotension, and asystole) [19–21]. Toxicity from acute or chronic oral overdose may be manifested by nystagmus, nausea and vomiting, ataxia, dysarthria, choreoathetosis, opisthotonos, and central nervous system depression or excitation [22]. Deaths associated with oral ingestion of phenytoin are extremely rare and typically involve a coingestion [22, 23]. Major cardiac toxicity after oral overdose has never been reported [22, 23]. Tissue necrosis

and sloughing after extravasation of intravenous phenytoin also have been described [20, 22, 23].

Relationship Between Plasma Concentration and Toxicity

Therapeutic plasma phenytoin concentrations are 10–20 µg/mL (20–40 µmol/L), with a free phenytoin concentration of 1–2 µg/mL (2–4 µmol/L). Some patients require plasma concentrations greater than 20 µg/mL (40 µmol/L) for adequate seizure control [24]. The therapeutic range for phenytoin is narrow, and some patients have a greater predisposition for toxicity than others. Individual variation in toxicity is a function of baseline neurologic status, individual response to the drug, and free drug fraction. Patients with underlying brain disease are predisposed to toxicity and may become toxic at lower plasma concentrations [25]. In general, toxicity correlates with increasing plasma concentration, but this is not a universal tenet. Some patients tolerate concentrations greater than 40 µg/mL (80 µmol/L) [25]. Nystagmus typically appears first at phenytoin concentrations equal to or greater than 20 µg/mL (40 µmol/L) but may occur at lower or higher levels. Almost all patients with phenytoin-induced seizures have concentrations greater than 30 µg/mL (60 µmol/L). Signs of toxicity typically occur at free phenytoin concentrations equal to or greater than 2 µg/mL (4 µmol/L) and are consistently severe at greater than 5 µg/mL (10 µmol/L) [26, 27].

Central Nervous System Toxicity

Central nervous system toxicity after acute or chronic phenytoin overdose is manifested by nystagmus, dysequilibrium, and cerebellar ataxia. Central nervous system depression and cognitive defects (confusion, dizziness, and memory impairment) may occur [24, 25]. Paradoxically, high concentrations of phenytoin have been reported to be associated with seizures [24–27].

When phenytoin concentrations in the brain increase beyond therapeutic values, inhibitory cortical and excitatory cerebellar/vestibular effects

occur. The usual initial sign of toxicity is nystagmus, which is seen first on forced lateral gaze and subsequently becomes spontaneous. A decreased level of consciousness is common with initial sedation, lethargy, ataxic gait, and dysarthria. Progression to confusion, coma, and apnea can occur in massive ingestions [28]. Acute dystonias and movement disorders such as opisthotonos and choreoathetosis have been described [29]. Depressed or hyperactive deep tendon reflexes, clonus, and extensor toe responses also may be elicited [29–31]. Phenytoin-induced seizures are rare, universally preceded by other signs of toxicity, and usually brief and generalized [32, 33]. Some signs of neurologic toxicity may outlast the presence of measurable drug levels by weeks, especially mild peripheral neuropathy or acute, typically reversible cerebellar ataxia [34].

Vertical, bidirectional, or alternating nystagmus may occur with severe intoxication or be absent at levels high enough to cause coma, complete ophthalmoplegia, and loss of corneal reflexes. Absence of nystagmus does not exclude severe phenytoin toxicity. Nystagmus often returns as serum phenytoin concentrations decrease and coma lightens [26, 27, 35].

Cardiovascular Toxicity

Cardiac toxicity after oral phenytoin overdose in an otherwise healthy patient has not been reported and if observed warrants aggressive assessment for other etiologies. Acute cardiovascular toxicity has been limited almost entirely to cases involving intravenous administration at rates greater than 50 mg/min and is manifested by hypotension, decreased peripheral vascular resistance, bradycardia, conduction delays that may progress to complete atrioventricular nodal block, asystole, ventricular tachycardia, or ventricular fibrillation [16, 18].

Electrocardiographic changes reported are increased PR interval, widened QRS interval, and ST-T wave changes. Most of these effects can be attributed to rapid intravenous administration of the preparation containing propylene glycol and typically are avoidable with slower administration (50 µg/min of phenytoin or slower). In six healthy

volunteers taking approximately 1 g of phenytoin in a simulated oral overdose, sinus bradycardia and a shortened PR interval were noted in two patients but did not correlate with peak plasma phenytoin concentration [36].

Vascular and Soft Tissue Injury

Intramuscular injection of phenytoin may result in hematoma, sterile abscess, and myonecrosis [37] at the injection site. Reported complications after extravasation following intravenous infusion have included skin and soft tissue necrosis requiring skin grafting and compartment syndrome, gangrene and amputation. Rhabdomyolysis is a potential complication. A syndrome of delayed bluish discoloration of the affected extremity, followed by erythema, edema, vesicles, bullae, and local tissue ischemia, also has been described [38].

Non-Dose-Related Adverse Effects

Some adverse effects of long-term phenytoin administration are dose dependent and duration dependent, as noted earlier, whereas others seem to be non-dose related (i.e., idiosyncratic), such as gingival hypertrophy [34] and anticonvulsant hypersensitivity syndrome [32]. Hypersensitivity reactions to phenytoin usually occur within the first few months of therapy and include fever, skin rashes, blood dyscrasia, and hepatitis. Phenytoin, phenobarbital, carbamazepine, and perhaps felbamate all are causes of anticonvulsant hypersensitivity syndrome, which is related causally to the generation of toxic arene oxide metabolites in some individuals receiving these drugs. Treatment is generally supportive with removal of the offending agent and avoidance of other anticonvulsants that are metabolized to arene oxide compounds [29].

Diagnosis

Determination of a plasma phenytoin concentration is the most commonly used method of diagnosing dose-dependent toxicity. Use of this metric

is not infallible, however. The idiosyncratic phenytoin hypersensitivity syndrome is not dose dependent and is independent of the magnitude of the plasma concentrations. Patients with decreased plasma albumin concentrations generally have higher levels of free phenytoin (i.e., increased free fraction) and greater biologic effects. These patients may exhibit phenytoin toxicity despite total phenytoin levels in the usual therapeutic range. Patients who manifest toxic signs despite serum phenytoin concentrations in the therapeutic range, particularly if they may be hypoalbuminemic, should have free phenytoin concentrations measured, if available [36].

Toxicity from other anticonvulsants such as carbamazepine or phenobarbital, sedative-hypnotics, ethanol, or phencyclidine and nontoxicologic causes constitute the major differential diagnosis of a patient presenting with altered mental status, ataxia, and nystagmus. Most of these toxicologic diagnoses can be excluded by history and determination of drug concentrations.

Common Errors in the Assessment of Phenytoin Toxicity

Missing the diagnosis of phenytoin toxicity in hypoalbuminemic patients with normal blood phenytoin concentration

Failing to recognize that at toxic levels plasma phenytoin concentrations may decrease slowly owing to saturation of its metabolic enzymes

Not obtaining serial levels in an acutely toxic patient

charcoal administration. The administration of activated charcoal may reduce peak plasma phenytoin concentrations. Because virtually all patients with oral phenytoin toxicity as their sole acute medical diagnosis recover completely, it is unlikely that the administration of activated charcoal would alter their outcome. Whether activated charcoal administration shortens the clinical course of these patients is unknown (Level III). In addition, the presence of activated charcoal may prolong attaining stable therapeutic maintenance concentrations for seizure control.

Indications for ICU Admission in Phenytoin Poisoning

Significant coingestions

Coma

Cardiotoxicity from rapid administration

In human volunteer studies, multiple doses of oral activated charcoal decreases the area under the curve and phenytoin half-life [37, 38]. Multiple-dose activated charcoal is associated with possible aspiration in patients with depressed airway protective reflexes, however, and has never been of proven benefit in overdose patients [37, 38].

Because phenytoin is extensively protein bound, it is not appreciably removed by hemodialysis or hemoperfusion, and these two modalities are not useful in phenytoin toxicity. Seizures should be treated with intravenous benzodiazepines (e.g., diazepam) or barbiturates or both, and their occurrence should prompt a search for other causes, given the low likelihood of their causation by phenytoin.

Cardiovascular toxicity is unexpected after oral phenytoin overdose and should suggest other causes. Prolonged cardiac monitoring after oral ingestion is unnecessary. Hypotension that occurs during intravenous administration of phenytoin usually responds to discontinuation of the infusion and the administration of isotonic crystalloid. Atropine and temporary cardiac pacing may be used for symptomatic bradydysrhythmias.

Patients with serious complications after acute oral ingestion (e.g., seizures, coma, altered mental status, ataxia) should be admitted for further

Treatment

Supportive treatment is the cornerstone of medical management for phenytoin toxicity. Appropriate initial management of acute oral phenytoin overdose includes intravenous access; airway and ventilatory support as clinically warranted; and, if presentation is early (within the first hour) after ingestion, possibly oral or orogastric activated

evaluation and treatment. Others with only mild symptoms may be treated in the emergency department and discharged after their levels have returned to normal, provided that they are not actively suicidal and no coingestions warrant admission. Otherwise stable patients can be discharged even with supratherapeutic plasma phenytoin concentrations, provided that appropriate precautions against falling due to ataxia are taken (e.g., patient minimally ataxic, has caregiver at home, not anticoagulated).

Individuals with continuing signs and symptoms of phenytoin toxicity may need to be admitted or followed in an observation unit. Given the long and erratic absorption phase of phenytoin after oral overdose, the decision to discharge or clear a patient medically for psychiatric evaluation cannot be based on a single physical examination and serum concentration. Patients with signs or symptoms of chronic intoxication should be admitted for observation and discharged when the clinical effects have resolved, or minimized, and consecutive serum levels are decreasing. Phenytoin therapy should be stopped in all cases, and if toxicity continues to resolve, a serum level may be reassessed in 2–3 days to guide resumption of therapy.

Patients with significant or persistent complications after intravenous administration of phenytoin should be admitted and managed by appropriate supportive and diagnostic means. Orthopedic or plastic surgical consultation should be obtained for patients with significant extravasation of intravenous phenytoin or other signs of local vascular or tissue toxicity after infusion.

To prevent complications due to intravenous infusion of phenytoin, it should be administered under close observation, with constant cardiac and blood pressure monitoring. The infused solution should be given slowly (no faster than 50 mg/min if under direct physician observation and intensive cardiovascular monitoring or 25 mg/min under less closely monitored conditions) through a large, well-positioned catheter. Proportionately slower administration (e.g., 0.5–1 mg/kg/min up to adult infusion rates) should be given to pediatric patients.

Criteria for ICU Discharge in Phenytoin Poisoning

Decreasing plasma phenytoin concentrations
Absence of coma

Key Points in the Management of Phenytoin Poisoning

1. Supportive care usually is all that is needed.
2. Serial levels to establish a trend are commonly needed.
3. Rule out coingestions.
4. Give benzodiazepine for seizures, which are rare.

Fosphenytoin

The limiting properties of the parenteral form of phenytoin (incomplete aqueous solubility, toxic nature of the vehicle, and tendency to precipitate in intravenous solutions) have been addressed in the development fosphenytoin, a prodrug of phenytoin (Fig. 1). With a pH of 8, fosphenytoin is less irritating to the tissues than is phenytoin. Fosphenytoin is the disodium phosphate ester of phenytoin and is converted to phenytoin by phosphatases in the blood and various organs, principally liver. The concentration and dose of fosphenytoin are expressed in phenytoin equivalents. The conversion half-life is 10–15 min. Fosphenytoin is tolerated intravenously and intramuscularly, and most patients can be loaded successfully within 30 min without significant side effects [17–19]. Given intravenously, fosphenytoin can cause pruritus and, much less commonly than with intravenous phenytoin, hypotension. Blood pressure and cardiac monitoring are recommended when loading with fosphenytoin intravenously but not intramuscularly. With intravenous infusion pumps set at lower rates of phenytoin administration (e.g., <30 mg/min), however, adverse effects are not reported as commonly, suggesting a

continued role for the traditional form of the drug as a cost-effective alternative to fosphenytoin.

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Table 1 Nonepilepsy-related medical conditions for which carbamazepine is used

Neuropathic pain [4, 5]
Agitation and aggression [6]
Psychosis [7]
Bipolar disorder [5, 8]
Cocaine dependence [9] ^a

^aSeveral reviews have not found strong evidence supporting its use in the treatment of cocaine dependence [10]

Carbamazepine (CBZ) is a carbamylated derivative of iminostilbene and is related structurally to the cyclic antidepressants [1]. It is currently considered the drug of first choice for treatment of focal epilepsy [2, 3] and is also effective in the treatment of partial seizures (simple and complex) with and without secondary generalization, generalized tonic-clonic seizures (grand mal), and combinations of these seizure types [2]. Carbamazepine is also used to treat many other medical conditions (Table 1).

Due to its widespread use, the potential for CBZ poisoning is relatively high. Data from the American Association of Poison Control Centers documented 3964 cases of CBZ overdose in 2013, of which 11% had a moderate and 1.4% a major effect [11]. CBZ has also been reported as a substance of abuse [12, 13].

Biochemistry and Clinical Pharmacology

See Fig. 1.

Pharmacodynamics

The mechanism of action of CBZ is not fully understood. However, it inhibits activity of voltage-gated sodium channels and as a result stabilizes hyperexcited neurons, suppressing propagation of excitatory impulses [1]. It also inhibits presynaptic reuptake of adenosine, thereby enhancing presynaptic inhibitory modulation of excitatory neurotransmitters (e.g.:

glutamate) release. Glutamate activates the *N*-methyl-D-aspartate (NMDA) receptors allowing the influx of Na⁺ and Ca²⁺ into neuronal cells. A decrease in glutamate thus protects against seizures [1, 14].

It is hypothesized that an inhibitory effect on central dopaminergic and noradrenergic neurotransmission is responsible for the antimanic effects of CBZ [2].

Pharmacokinetics

Absorption of CBZ from the gastrointestinal tract is relatively slow yet bioavailability approaches 100% with the conventional tablet formulation. The controlled-release (CR) or extended-release (ER) formulations are absorbed more slowly and less completely than the immediate-release (IR), and bioavailability is about 15% lower for these formulations [1, 2].

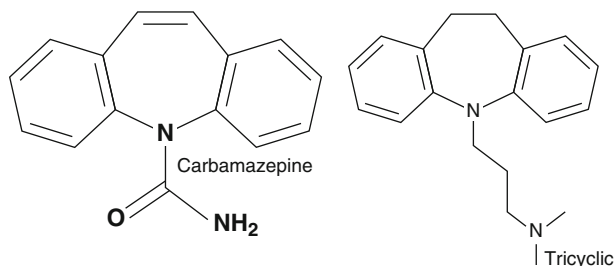
When taken as a single oral therapeutic dose, the IR tablet commonly yields a peak concentration of unchanged CBZ within 4–12 h [1, 15]. When CR tablets are administered singly and repeatedly, peak concentration of the parent compound in plasma is 25% lower than with IR tablets. Liquid formulations are absorbed more rapidly [2].

Steady-state plasma concentration of CBZ is attained within about 3–4 days [15]. Controlled-release tablets result in a more stable plasma concentration and less fluctuation at steady state [2].

The apparent volume of distribution of CBZ is 0.8 to 1.9 L/kg [2]. Plasma protein binding is around 70–80% [15]. The concentration of unchanged drug in saliva and cerebrospinal fluid reflects the non-protein-bound fraction present in plasma and is approximately 20–30% of that in plasma [1, 2]. Carbamazepine is secreted in breast milk, with concentration ranging from 25% to 60% of plasma. Carbamazepine readily crosses the placenta [2, 16].

Carbamazepine is metabolized in the liver via the epoxide-diol pathway. The main metabolite (CBZ-10,11-epoxide [CBZE]) is pharmacologically active. Cytochrome P-450 3A4 is the major

Fig. 1 Carbamazepine is structurally similar to cyclic antidepressants



isoform responsible for this metabolism. A reactive arene oxide compound, distinct from the 10,11-epoxide metabolite, is also formed as a result of phase I oxidative metabolism of CBZ. This is thought to be the metabolite responsible for hypersensitivity reactions and teratogenic effects associated with CBZ administration [17]. Carbamazepine induces its own oxidative metabolism and that of other drugs. Given the gradual onset of this effect on drug clearance over the first few weeks of administration, it is considered the prototypical drug with time-dependent kinetics [2, 15].

The elimination half-life of unchanged CBZ after a single oral dose averages 36 h. After repeated administration, however, this varies from 16 to 24 h, depending on the duration of treatment. After a single 400-mg dose, around 72% is excreted in the urine mainly in the form of epoxide, hydroxylated, and conjugated metabolites. About 28% of a dose is also excreted in the feces [2, 15]. In patients receiving concomitant treatment with other cytochrome P-450 enzyme-inducing drugs, half-life values averaging 9–10 h may occur. Clinically important pharmacokinetic interactions with other drugs that may affect the plasma concentration of CBZ are listed in Table 2 [15, 18, 19].

Toxicokinetics

The clinical manifestations of toxicity develop within 1–3 h of overdose and usually involve the central nervous, cardiovascular, and respiratory systems. These clinical effects may be prolonged or delayed in onset, depending on the form and amount of CBZ ingested. These effects are due to both delayed and prolonged absorption and the production of the active metabolite, CBZ-10,11-

Table 2 Examples of pharmacokinetic drug-drug interactions with carbamazepine

Mechanism	Effect	Drug causes
CYP3A4 inhibition	Reduced clearance/ increased plasma concentration	Propoxyphene, fluconazole, itraconazole, ketoconazole, isoniazid, erythromycin, clarithromycin, cimetidine, verapamil, diltiazem, fluoxetine, fluvoxamine, nefazodone, ritonavir, grapefruit juice
CYP3A4 induction	Increased clearance/ reduced plasma concentration	Phenytoin, phenobarbital, valproate, rifampin

epoxide. Carbamazepine overdose results in slow and erratic absorption, and serum concentration may be persistently high for 2–3 days due to the continued absorption of CBZ from the gut. This results from the slow dissolution of CBZ from the tablet formulation and its anticholinergic effects on gut motility. Peak serum concentration can be delayed up to 96 h postingestion of CR preparations [20]. Elimination half-life in overdose ranges from 10 to 29 h [21].

Carbamazepine's active metabolite CBZE has roughly the same anticonvulsant effect as CBZ and also has neurotoxic effects. The ratio of CBZE to CBZ parent drug is concentration-dependent. When CBZ concentration is in the supratherapeutic range, CBZE concentration is

often greater than 150% of the CBZ parent drug concentration. When the CBZ concentration is within therapeutic range, the epoxide concentration tends to be lower and around 20% of the parent compound. This may explain the wide range of clinical effects seen when trying to correlate toxicity with serum CBZ concentrations [22].

At therapeutic concentrations, CBZ is 80% and CBZE is 50% protein-bound. However, both compounds exhibit concentration-dependent protein binding. At high serum concentrations, the fraction of unbound drug is much higher. The brain concentration of CBZ and CBZE is dependent on the free-drug concentration. As a result, in overdose, the concentration of both CBZ and CBZE in the central nervous system is relatively higher than at therapeutic doses [22].

Toxicodynamics

As well as its therapeutic effects on inactivated presynaptic sodium channels, CBZ is also a powerful antagonist at acetylcholine receptors (both muscarinic and nicotinic), NMDA, and central nervous system adenosine (A1) receptors. Many signs of toxicity are the result of effects on these receptors in overdose [1, 14].

Clinical Presentation of Carbamazepine Overdose and Life-Threatening Complications

Correlation Between Ingested Dose, Serum Drug Concentration, and Toxicity

Toxicity from CBZ overdose is dose-dependent. Ingestion of >20 mg/kg is often associated with an anticholinergic toxidrome and mild neurological symptoms and signs of mydriasis, nystagmus ataxia, and movement disorders. Severe toxicity is commonly seen after doses of more than 50 mg/kg with coma and seizures. Minor ECG changes may also occur commonly but rarely with significant arrhythmias [14, 23].

The degree of toxicity may relate to serum concentration. However, it is unclear whether

CBZ peak serum concentration correlates well with the severity of clinical effects. In a prospective study of 25 adult CBZ exposures, correlation between serious clinical signs and serum CBZ concentrations was poor [22]. However, in pediatric patients, peak serum CBZ concentration correlated well with the depth of coma, presence of convulsions, hypotension, and the requirement for mechanical ventilation [24]. A serum CBZ concentration of >25 mg/L correlates well with the presence of coma [25]. Significant toxicity (coma, seizures, respiratory failure and cardiac conduction defects) correlates with a serum concentration greater than 40 mg/L (170 μ mol/L) [26]. Toxicity may also be the result of high CBZ-epoxide concentration and a low CBZ-to-epoxide ratio [27]. This may occur at therapeutic doses, and the activity of unmeasured metabolite may provide an explanation for the limited correlation observed between serum CBZ concentration and clinical toxicity in some patients [22].

Anticholinergic Toxicity

An anticholinergic (AC) toxidrome is often prominent in the early stages of CBZ poisoning. Patients may show signs of significant delirium and agitation as well as peripheral signs of AC toxicity (tachycardia, ileus, urinary retention). This may precede the onset of coma. Anticholinergic effects on gut motility are also responsible for delayed and prolonged CBZ absorption and fluctuating signs of toxicity in some cases [14, 24].

Central Nervous System Toxicity

The most predominant neurologic signs are drowsiness, ataxia, nystagmus, and dystonia [24].

Coma

Coma with respiratory depression is reported in 21–48% of CBZ poisoning cases [22, 25]. CNS depression results from excess blockade of presynaptic voltage-gated sodium channels and the antagonistic effect on adenosine A1 receptors [14]. Massive ingestion of CBZ is associated

with deep coma, fixed dilated pupils, absent doll's eye reflex, and absent oculovestibular reflex. A full neurological recovery commonly results after several days. In one such case, the reported ingested dose was 5.8 g, and in another, peak serum CBZ concentration was 70 mg/L (295 μ mol/L) [28–30]. Cyclical coma, with waxing and waning of the patient's conscious state, is also reported after large CBZ ingestions. This is the result of fluctuating concentrations of CBZ/CBZE on the CNS and GI tracts. With high CBZ serum concentration, coma results and gut motility stops. As a result, absorption of further CBZ ceases. Already absorbed CBZ is metabolized in the liver, and as the serum concentration falls, conscious state improves and the anticholinergic effects on the gut also reduce. The result is an increase in absorption of CBZ from the intestine with consequent increase in serum concentration and recurrence of coma [14].

Seizures

The frequency of seizures after CBZ overdose increases as the Glasgow Coma Score falls [21]. Carbamazepine may cause seizures following overdose, particularly in patients with underlying seizure disorders [21]. Seizures occurring after overdose are the result of central anticholinergic antagonism of inhibitory presynaptic nicotinic receptors. This interrupts the normal control mechanism for release of neurotransmitters into the synapse. Antagonism of central A1-adenosine receptors, which have a role in decreasing excitatory neurotransmitter release, also plays a role in seizure propagation in overdose [14].

The concentration of the epoxide metabolite may also have a causative role in CBZ-induced seizures [31]. Seizure activity may be facilitated by hyponatremia from the antidiuretic actions of the drug [32]. Status epilepticus, although uncommon, has been described after CBZ overdose [25, 33].

Abnormal Movements

Abnormal movements, including choreoathetosis, dyskinesia, and dystonia, are described in patients taking CBZ therapeutically and in overdose. These may be related to its central anticholinergic effects [34, 35].

Cardiovascular Toxicity

Cardiovascular effects of CBZ poisoning are most likely to be the result of a combination of its anticholinergic and sodium channel blocking effects [14]. Carbamazepine is structurally similar to tricyclic antidepressants. This may influence its effects on myocardial sodium channel conductance. However, significant sodium channel blockade is uncommon following CBZ poisoning [1]. Heart block and bradycardia have been documented following exposure to CBZ, even at therapeutic concentrations [36].

In a retrospective case series of 62 patients with CBZ poisoning, 37% had sinus tachycardia, 24% transient right bundle branch block-like pattern, and 0.3% an atrio-ventricular block, which resolved in 48 h. Sodium channel blockade was not seen on any ECGs in this series [24]. However, isolated cases of QRS widening associated with CBZ poisoning are reported [37, 38].

Hypotension and poor myocardial contractility can result after significant CBZ intoxication. In a pediatric case series, cardiovascular instability resulting from reduced cardiac output and poor myocardial contractility was associated with a mean peak serum CBZ concentration of 50.4 μ g/mL (213 μ mol/L) [24].

Respiratory System Toxicity

Given the profound central nervous system depressant effects of CBZ, hypoventilatory respiratory failure and aspiration pneumonitis are anticipated adverse effects of acute overdose without appropriate and timely airway support. In addition, acute pulmonary edema is a potential complication of aggressive fluid volume replacement in the patient with CBZ-induced myocardial dysfunction [39].

Other Organ System Manifestations

Rhabdomyolysis and acute tubular nephropathy with myoglobinuria may occur after CBZ overdose, particularly in patients presenting after prolonged unconsciousness or generalized seizure activity.

Special Populations

Children

The endogenous elimination of CBZ is more rapid in children. However, incidence of dystonic reactions, choreoathetosis, and seizures may be higher in pediatric patients with overdose [40].

Pregnant Patients

Teratogenicity occurs at a rate of 9.7% with the use of any anticonvulsant medication [41]. Fetal abnormalities induced by aromatic anticonvulsants are most likely due to a fetal deficiency of the epoxide hydrolase enzyme necessary to break down the arene oxide [42]. Carbamazepine as a monotherapy during pregnancy has been associated with the increase risk of fetal malformations especially spina bifida [43].

Adverse Effects of Long-Term Carbamazepine Administration

Anticonvulsant Hypersensitivity Syndrome

Anticonvulsant hypersensitivity syndrome is an uncommon but potentially fatal multisystem disorder that occurs after exposure to CBZ, phenytoin, and phenobarbital [17, 44]. It may be related to the benzene ring structure of these drugs and the oxidative metabolism to a toxic arene oxide metabolite. The first reported case of CBZ sensitivity was described in 1965. The hypersensitivity reaction involves all organ systems, including the lung, liver, kidney, skin, and bone marrow [45].

There may be a pharmacogenetic component to the development of these reactions and an association between HLA allele variations and adverse reactions to some anticonvulsants. HLA-B15:02 is associated with carbamazepine-induced Stevens Johnson syndrome in Asian populations [46].

Sudden Unexplained Death in Epilepsy

The phenomenon of sudden unexplained death in epilepsy (SUDEP) is well described. There are many proposed mechanisms and associated risk factors. Two case-controlled studies have found an association between increased risk of SUDEP and therapeutic CBZ use. SUDEP cases had higher serum CBZ concentrations than those of matched controls. However, patients with recurrent seizures often require higher doses of anticonvulsants [47, 48].

Other Effects

Other adverse effects of CBZ therapy include inappropriate antidiuretic hormone secretion and hepatic and hematologic toxicity. Aplastic anemia has occurred uncommonly in association with CBZ therapy (1 in 200,000 patients treated). However, transient leukopenia, in 10%, and hepatic enzyme elevation, in up to 10%, are more common. These are more likely to occur in the first few months of treatment [2].

Diagnosis

In addition to the investigations required for the general care and management of the poisoned patient, serial quantitative serum analysis of CBZ concentration will assist in risk assessment and guide treatment. The accepted steady-state therapeutic concentration range for CBZ is 4–12 µg/mL (20–50 µmol/L) [1, 2, 15].

Treatment

Resuscitation and Supportive Care

Given the progressive clinical effects of CBZ toxicity, patients should to be closely monitored for clinical deterioration. Significant toxicity may be delayed due to erratic drug absorption, anticholinergic slowing of GI motility, or ingestion of controlled-release formulations [20, 21].

Endotracheal intubation and mechanical ventilation are indicated based upon standard clinical criteria such as in difficult to control agitation in patients exhibiting early anticholinergic toxicity or falling level of consciousness. Fluid volume resuscitation for hypotension should be undertaken with caution in CBZ-poisoning as patients are commonly euvoletic. Aggressive fluid resuscitation may result in pulmonary edema. An echocardiogram may assist in diagnosis of myocardial depression and guide pressor or inotrope use. Significant QRS interval prolongation is uncommon. However, as in the treatment of other sodium channel blocker overdoses, intravenous hypertonic sodium bicarbonate therapy should be administered to produce a systemic alkalemia if significant QRS-prolongation is present. Recurrent CBZ-induced seizures should be treated with γ -aminobutyric acid (GABA)_A agonists such as benzodiazepines (e.g., diazepam, lorazepam) and barbiturates (e.g., phenobarbital). (Grade III recommendation) In the presence of hypotension, cardiac failure or severe arrhythmia related to membrane stabilizing activity that is refractory to standard supportive care, veno-arterial extracorporeal cardiac assist devices could be used if available [49].

Activated Charcoal

A single dose of activated charcoal should be administered to patients ingesting more than 50 mg/kg as this dose is commonly associated with the development of significant toxicity (Grade III recommendation). Patients already exhibiting signs of CNS depression or agitation should be intubated first. Multiple-dose activated charcoal (MDAC) enhances CBZ clearance [34, 50]. Notably, it is unclear whether single or multiple doses of activated charcoal significantly improve clinical outcome [51]. However, in a study of 12 patients, receiving either single or multiple doses of activated charcoal, mean serum CBZ half-life was significantly shorter with MDAC (12 vs. 28 h). Mean duration of coma (20 vs. 29 h), and need for mechanical ventilation (24 vs. 36 h) were also shorter with MDAC administration [50].

Repeated administration of activated charcoal may be associated with significant risk, particularly from slowed motility and ileus from anticholinergic effects on the GI tract. Pulmonary aspiration of charcoal, bowel obstruction or ischemia and fluid, electrolyte, and acid-base abnormalities (when mixed with cathartics) have been reported [52]. Close observation of the abdomen for absence of bowel sounds, developing distension, or increasing nasogastric aspirates should alert the clinician that further charcoal administration is contraindicated.

Whole Bowel Irrigation

Whole-bowel irrigation has not been shown to change outcome in patients poisoned with controlled-release preparations of CBZ [51]. As with repeat-doses of activated charcoal, the development of ileus will contraindicate this therapy and may result in a significant risk of adverse events.

Extracorporeal Removal of Carbamazepine

Modern dialysis filters and machines with high blood flow rates have demonstrated comparable clearance when compared to older literature describing treatment with charcoal hemoperfusion [53, 54]. Extracorporeal CBZ removal is also superior to MDAC in enhancing CBZ elimination [55]. However, there are no studies comparing outcome after extracorporeal removal of CBZ to supportive care alone. Because of its low protein binding, the CBZ-epoxide metabolite is also dialyzable.

Intermittent hemodialysis and hemoperfusion both improve the features of severe CBZ poisoning. (Grade III evidence) Hemodialysis improves heart rate and level of consciousness and reduces convulsions as carbamazepine concentration falls after poisoning [56]. However, continuous renal replacement therapy and peritoneal dialysis are likely to be much less effective. The rate of improvement in clinical effects with these two therapies suggests little added benefit to supportive care alone [55].

Emergent intermittent hemodialysis is indicated in cases with refractory seizures and/or hypotension, or arrhythmias. (Grade III

recommendation) Dialysis may also benefit cases with prolonged coma or with rising or persistently elevated CBZ concentration greater than 60 mg/L (254 micromol/L) despite MDAC treatment.

Oxcarbazepine

Oxcarbazepine is a 10-keto analog of carbamazepine and has a very similar structure. As a result, very similar effects are expected with therapeutic use and in overdose. Oxcarbazepine is indicated in the treatment of partial and generalized tonic clonic seizures for adults and children as a mono or adjunctive therapy [2].

Pharmacodynamics

The pharmacological activity of oxcarbazepine is exerted through its active metabolite 10-monohydroxy derivative (MHD) which blocks voltage-gated sodium channels thereby stabilizing hyperexcited neurons.

Pharmacokinetics

Oxcarbazepine is a pro-drug that is rapidly absorbed and extensively metabolized in the liver to its pharmacologically active metabolite (10-monohydroxy carbamazepine, MHC). The apparent volume of distribution of MHC is around 0.5–1 L/kg and it is 40% plasma protein-bound. Oxcarbazepine has a very short elimination half-life of 1.3–2.3 h, whereas MHD's apparent half-life averages 9 h [2]. Therapeutic serum concentration for the MHC is 3–35 mg/L.

Overdose

There are limited data regarding effects of oxcarbazepine in overdose. In an observational poison center study, the most common clinical effects following overdose were drowsiness (25.3%), vomiting (8.4%), dizziness/vertigo (6.5%), tachycardia (3.2%), and agitation (1.8%). Major toxic effects, reported in 0.9%,

included coma, tachycardia, seizures, respiratory depression, agitation, confusion, and hypertension. However, both hypotension and bradycardia are reported following overdose [57].

There are a number of cases where large ingested doses were reported and only moderate adverse effects were observed. A 13-year-old boy, weighing 60 kg, ingested a reported total of 15,000 mg oxcarbazepine. The only abnormality observed was a GCS of 13, which gradually improved over 12 h. A single dose of activated charcoal was administered on presentation. Two hours after ingestion, his oxcarbazepine and MHC serum concentrations were 7.9 mg/L and 34.6 mg/L, respectively. Oxcarbazepine was quickly metabolized. Eight-hour serum concentration was 0.3 mg/L, becoming undetectable 24 h postingestion. MHD reached a peak of 46.6 mg/L, 8-h postingestion [58]. In another case, a 36-year-old man, weighing 78 kg, ingested a reported oxcarbazepine dose of 30,600 mg. On presentation, 2-h postingestion, vital signs and mental state were normal. Over the following 24 h, he was somnolent but always had a GCS of 15. Two hours postingestion, his serum oxcarbazepine and MHC concentrations were 31.6 and 37.2 mg/L, respectively. Again serum oxcarbazepine concentration fell rapidly to 0.67 mg/L at 24 h. MHD concentration peaked 7-h postingestion at 59 mg/L [59].

Oxcarbazepine is a pro-drug and the formation of the active MHD metabolite may be a rate-limiting process in the development of toxicity. This may contribute to the relatively low toxicity of the drug in patients with large ingested doses. However, the effect of interrupted enterohepatic recirculation/gut dialysis following charcoal administration cannot be excluded [58].

Adverse Effects of Oxcarbazepine in Therapeutic Dosing

Hyponatremia, from inappropriate secretion of antidiuretic hormone (SIADH) or an SIADH-like mechanism, is a common adverse effect of oxcarbazepine therapy. It is reported in up to 29.9% of patients using this agent. Approximately 2.5% of patients on oxcarbazepine may

have serum sodium concentrations of less than 125 mmol/L. However, symptomatic hyponatremia with nausea, headache, lethargy, and weakness is uncommon, but the risk may be greater in older patients. Hyponatremia resolves with fluid restriction and either a decrease in dose or cessation of the drug. Serum sodium monitoring should be performed in patients on long-term oxcarbazepine therapy [60, 61]. Other common reported side effects are dose-related and include drowsiness/somnolence, dizziness/vertigo, nausea/vomiting, diarrhea, and diplopia [62, 63].

Treatment

Resuscitation and Supportive Care

Supportive care management of oxcarbazepine poisoning is similar to carbamazepine poisoning [57].

Activated Charcoal

A single dose of activated charcoal reduced the absorption of oxcarbazepine in healthy volunteers, with repeated doses accelerating the elimination of its active metabolite MDC. This suggests that activated charcoal should be beneficial for gastrointestinal decontamination following oxcarbazepine overdose [64].

Extracorporeal Elimination

Limited data suggest that extracorporeal removal does not enhance oxcarbazepine or MHD elimination. In one study, the removal of MHD by plasmapheresis was only 3–4% of the daily therapeutic oxcarbazepine dose and 5–6% of the MHD body stores [65]. In a case of oxcarbazepine overdose, the clearance of MHD by dialysis was 30–100 times less than total endogenous clearance of the drug [66].

Key Points in the Evaluation and Treatment of Carbamazepine and Oxcarbazepine Poisoning

1. Carbamazepine is used widely in the management of a variety of neurobehavioral disorders, including trigeminal neuralgia, bipolar affective disorder, and epilepsy.

2. The major clinical manifestations of acute toxicity are coma, respiratory failure, seizures, anticholinergic toxicity, tachycardia, and hypotension.
3. Treatment of acute carbamazepine poisoning is largely supportive and may include airway and ventilatory support, intravenous pressor, or hypertonic sodium bicarbonate therapy, and seizure control with benzodiazepines and barbiturates.
4. Drug clearance of CBZ may be enhanced by multi-dose activated charcoal.
5. Extracorporeal treatments such as hemodialysis and hemoperfusion may enhance drug clearance in severe CBZ poisoning with hypotension or seizures refractory to supportive therapies or life-threatening arrhythmias. Intermittent hemodialysis is the preferred modality.
6. Carbamazepine is an established cause of anticonvulsant hypersensitivity syndrome and is associated with birth defects. Its use is contraindicated in the presence of a previous history of anticonvulsant hypersensitivity syndrome. Caution is also advised with regard to its use in pregnancy.
7. Oxcarbazepine is a pro-drug that is rapidly absorbed from the GI tract and requires hepatic metabolism to produce an active metabolite.
8. Poisoning primarily results in CNS depression.
9. Supportive care and respiratory support are the mainstay of therapy.
10. Activated charcoal may enhance oxcarbazepine clearance
11. Extracorporeal elimination does not appear to increase oxcarbazepine or MHD clearance.

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Second Generation Anticonvulsants: Gabapentin, Lamotrigine, Levetiracetam, and Topiramate

54

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The second generation anticonvulsants are generally considered to be the nonbenzodiazepine antiepileptic medications approved by the US Food and Drug Administration (FDA) after 1967 when valproic acid was marketed. There was a surge of newer anticonvulsant pharmaceuticals approved for clinical use, starting with vigabatrin in the late 1980s and continued throughout the 1990s (oxcarbazine, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, fosphenytoin, levetiracetam, and zonisamide). Discontinuation of some of these pharmaceuticals in the USA and other countries has already occurred due to the decisions of the manufacturer, FDA, and other regulatory authorities, secondary to side effects and clinicians choosing more efficacious options. This chapter will not discuss all of the second generation anticonvulsants or the newest anticonvulsant lacosamide. Rather, it will focus specifically on gabapentin, lamotrigine, levetiracetam, and topiramate, because they are very common exposures or involve the greatest risk of toxicity resulting in the need for critical care management.

Gabapentin

In the USA gabapentin is approved therapy for partial seizures in children and adults and postherpetic neuralgia [1]. There are numerous off label uses including: neuropathic pain, mood disorders, posttraumatic stress disorder, bruxism, amyotrophic lateral sclerosis, trigeminal neuralgia, restless leg syndrome, parkinsonism, and reflex sympathetic dystrophy [1, 2]. However, the validity of the positive results found in the trials involving gabapentin in the treatment of neuropathic pain was discovered to be compromised by lack of research ethics [3].

Biochemistry and Clinical Pharmacology

Gabapentin was originally designed to act on postsynaptic gamma aminobutyric acid (GABA) channels, but its mechanism of action is not definitively known [1]. One suggestion for the

mechanism of action of gabapentin involves presynaptic voltage-gated calcium channels specifically possessing the alpha-2-delta-1 subunit [4]. These channels are thought to modulate release of neurotransmitters which participate in epileptogenesis and nociception.

Absorption of gabapentin occurs in the proximal small bowel and is saturable which may limit toxicity [5]. The volume of distribution is 58 ± 6 L, the protein binding is less than 3%, and has an elimination half-life of 5–7 h. Gabapentin does not undergo metabolism and is excreted in the urine as unchanged drug [2].

Pathophysiology of Toxic Effects

The toxic effects of clinically significant gabapentin overdose include lethargy, ataxia, central nervous system (CNS) depression, hypotension, bradycardia, tachycardia, and dizziness [1, 6].

The predominant clinical effect is CNS depression. Because gabapentin is excreted unchanged in the urine, patients with a history of end stage renal disease (ESRD) are particularly susceptible to more severe CNS depression. In a poison center case series, the clinical effects occurred less than 5 h with a median of 2 h and resolved in 24 h [1].

Clinical Presentation and Life-Threatening Complications

Two different poison center case series revealed a variable degree of clinical effects which included no symptoms to CNS depression, hypotension, and mechanical ventilation [1, 7]. It is difficult to determine a dose response from these studies.

The literature reports conflicting clinical effects after gabapentin overdose (Grade III). An old case report of a 49 g ingestion of gabapentin resulted in no serious consequences [8]. In contrast, a 62-year-old female was found dead in her hotel room with an elevated postmortem gabapentin serum concentration [9]. An accurate history, timing, and the dose she ingested are unknown.

A single intentional overdose in a patient with ESRD developed somnolence necessitating intubation [10]. Mental status returned to baseline quickly following hemodialysis. A 30-year-old female with ESRD, developed resting tremor and difficulty naming objects and performing three step commands after chronic cumulative gabapentin overdose [2]. She improved with a decrease in dose and regular HD. She was noted to have multiple comorbidities including lupus, previous stroke, and expressive aphasia that could have confounded the findings.

Diagnosis/Diagnostic Considerations

The diagnosis of gabapentin toxicity is based on history and clinical findings. A serum gabapentin level is not routinely available and should not be used to guide therapy. Diagnostic testing should be performed to assess end organ toxicity and coingestants.

Treatment

Gastrointestinal decontamination is theoretically attractive to prevent absorption of gabapentin, but the options have slowly decreased over time. Whole-bowel irrigation is not indicated for gabapentin overdose. Activated charcoal (AC) may absorb gabapentin, but its use must be strongly cautioned because of sedation and loss of airway reflexes, leading to increased risk of aspiration. The benefit may not outweigh the risk in many cases because of a low level of toxicity or the patient is so critically ill, decontamination will not help or could cause harm (Grade III recommendation.). There are no data indicating that the administration of activated charcoal alters the outcome in these patients. These same considerations apply to other second generation anticonvulsants.

There is no antidote for gabapentin overdose. The management involves supportive care, which includes cardiovascular monitoring, pulse oximetry, end tidal CO₂ monitoring, mechanical ventilation, sedation, and intravenous fluids and vasopressors for hypotension [7]. Elimination

may be enhanced with hemodialysis [10] (Grade III recommendation).

Special Populations

There are no studies specifically designed to investigate the effects in pediatric patients, although one poison center study included nine patients from 11 months to 18 years of age [1]. In three patients in which the dose was known to be 300 mg or less, no effect was seen. If it was unknown or 1,200 mg or greater, drowsiness, dizziness, ataxia, hypotension, and tachycardia were reported. The five hospitalized patients were treated with AC and cathartic, and the longest duration of clinical effects was 5 h or less. As in adults, diagnostics and treatment will be supportive and corrective of physiological abnormalities, until homeostasis is achieved (Grade III recommendation).

Data is limited but gabapentin does not appear to have increased risk to the fetus [11]. Treatment of the mother should be identical to the treatment of the nonpregnant patient. In general, gabapentin overdose is particularly ideal for a minimalist approach that places the mother and fetus at minimal risk (Grade III recommendation). Pregnant patients taking antiepileptics can register with the North American Antiepileptic Drug Pregnancy Registry, which can help inform them of possible malformations in the offspring.

In elderly patients with decreased renal function the therapeutic dose of gabapentin should be decreased. In the overdose patient, decreased renal elimination of gabapentin will increase the duration of clinical effects, but it is impossible to predict the duration of effects (Grade III).

Indications for ICU Admission

- Gabapentin with history of chronic kidney disease or end stage renal disease with a significant overdose
- CNS depression with concern about airway patency and respirations or cardiovascular insufficiency

Key Points

- Gabapentin overdose frequently produces mild symptoms.
- The parent drug is excreted unchanged in the urine.
- Clinically significant CNS depression is typically reserved for large overdoses or patients with end stage renal disease.
- Clinical effects are seen before 5 h and resolve within 24 h.

Criteria for ICU Discharge

- Baseline mental and cardiovascular status

Pharmacokinetics

- Elimination half-life of 5–7 h
- Volume of distribution: 58 \pm 6 L
- Protein binding: < 3%
- Mechanism of clearance: excreted in urine as unchanged drug
- Active metabolites: none, undergoes no metabolism
- Methods to enhance elimination: hemodialysis

Common Errors in Management

- Not exercising an appropriate degree of caution with gabapentin overdose and renal insufficiency

Biochemistry and Clinical Pharmacology

The anticonvulsant mechanism of action of lamotrigine is similar to phenytoin and carbamazepine. It binds to inactive voltage-gated sodium channels, preventing the release of glutamine. Without the excitatory stimulation of glutamine, propagation of the neuronal depolarizations is interrupted, causing seizures to terminate [12, 14]. Another major anticonvulsant mechanism is the inhibition of presynaptic voltage-gated calcium channels [15]. Inhibition of these N and P-O calcium channels prevents the presynaptic release of the excitatory neurotransmitter glutamate, halting seizure activity. Lamotrigine also has weak inhibitory effect on the 5-HT₃ receptor and dihydrofolate reductase [16].

The absorption of lamotrigine is rapid and complete with a bioavailability of 98%. The volume of distribution is 0.9–1.3 L/kg and protein binding is approximately 55%. Peak plasma levels occur at 1–3 h with therapeutic dosing, and hepatic metabolism creates inactive glucuronidated metabolites. The elimination half-life is 24–37 h with 90% of metabolites excreted in the urine [12, 14].

Valproic acid can compete with lamotrigine for glucuronidation, which could inhibit its metabolism, potentially prolonging the elimination half-life and toxic effects [12]. Lamotrigine metabolism is not affected by the typical inducers such as phenobarbital, phenytoin, rifampin, carbamazepine, and St. John's Wort.

Pathophysiology of Toxic Effects

Lamotrigine loses its selectivity toward the neurological sodium channels in overdose and causes blockade of cardiac conduction sodium channels, which can be significant enough to cause complete heart block and death [17]. These are the same channels that can be altered because of genetic mutations seen in Brugada syndrome, Romano-Ward syndrome, sick sinus syndrome, and heart block [13]. Sodium and potassium channelopathies have been linked to idiopathic

Lamotrigine

In the USA, lamotrigine is an anticonvulsant medication approved to treat simple and complex partial seizures; generalized tonic-clonic seizures; particularly absence and atonic seizures; and seizures from Lennox-Gestaut syndrome. Lamotrigine is also approved for treatment of bipolar disorder with depression predominance, because it inhibits the reuptake of serotonin, norepinephrine, and dopamine [12, 13].

epilepsy and could be the cause of sudden cardiac death in epilepsy patients [18].

Despite therapeutic use as an anticonvulsant, lamotrigine overdose has caused seizures in patients with or without epilepsy [15, 19, 20]. One patient also had a widened QRS, so the authors presumed the underlying mechanism of toxicity was sodium channel blockade in the cardiac and nervous systems, similar to tricyclic antidepressants. The mechanism of status epilepticus after lamotrigine overdose proposed by a group of authors is lamotrigine induced downregulation of GABA-A receptors and upregulation of glutamate receptors [15].

Drug-related eosinophilia and systemic symptoms (DRESS) has been reported from therapeutic lamotrigine [21, 22]. This hypersensitivity reaction can cause multiorgan injury or even failure, requiring critical care management. People with anticonvulsant hypersensitivity syndrome (ASH) should also avoid lamotrigine because it may stimulate the same reaction [23]. The US lamotrigine label contains a black box warning for skin rash with concern for progression to Stevens-Johnson syndrome.

Other toxic effects include bone marrow suppression from antifolate activity, hepatic necrosis from overdose or therapeutic dose, pancreatitis, and on a lighter note giggling [21, 22, 24–27].

Clinical Presentation and Life-Threatening Complications

The three large case series of lamotrigine overdose differ in their findings. The older study found the majority of lamotrigine overdose cases to be benign, and only 3% with major outcomes and no fatalities [28]. This poison center study combined accidental pediatric exposures and intentional overdoses (Grade III).

The second study was a retrospective evaluation of bedside consults over 9 years [29]. They had nine patients with a single ingestion of lamotrigine. Of these, 3/9 had seizures, 4/9 had hypertension, 5/9 tachycardia, 2/9 with insignificant QRS widening, and 4/9 QT prolongation. None of these effects were considered life-threatening (Grade III).

The latest case series also looked at one poison centers experience with second generation anticonvulsants and ranked lamotrigine the highest in toxicity [7]. Regardless of the differences, the greatest immediate threats to life are the effects on the central nervous and cardiovascular systems (Grade III).

Multiple reports of altered mental status and status epilepticus requiring intubation follow lamotrigine overdose [14, 30]. Ataxia has also been reported after status epilepticus resolved and in the absence of seizures [31, 32]. Myoclonus and choreiform movements have also been described after overdose [15, 33]. Patients with massive ingestions of lamotrigine may present initially with only encephalopathy [34]. One review of intralipid emulsion therapy reported the successful reversal of agitation, nystagmus and myoclonus [35]. Similarly, ataxia, encephalopathy, and seizures have also been reported in multiple pediatric cases [14, 31, 36] (Grade III).

Case reports also include fatal hepatic necrosis attributed to lamotrigine at therapeutic doses and nonfatal hepatitis that resolved with discontinuation of the drug [21, 24, 37]. DRESS syndrome and pancreatitis have also been described with lamotrigine therapy [22, 27].

Dysrhythmias and cardiovascular collapse are well-documented severe effects from lamotrigine overdose [17, 38–41]. These authors have universally described ECG finding consistent with sodium channel blockade, which include prolonged QRS, R wave > 3 mm in AVR. Prolonged QT is sometimes seen related to additional inhibited conduction through the delayed potassium rectifier channels (Grade III).

Diagnosis

The diagnosis of lamotrigine toxicity is based on history and clinical findings. Serum lamotrigine concentrations >14 mg/L are potentially toxic although there is no clear correlation between serum concentration and drug toxicity [12]. Serum concentrations are almost never available in a timely fashion to assist in clinical decision-making.

Cardiopulmonary monitoring is critical, along with serial ECGs when a rhythm disturbance is suspected. Frequent neurological assessment will often be necessary for seizures, myoclonus, and worsening encephalopathy.

Laboratory testing for organ injury related to cardiovascular instability, DRESS, or anticonvulsant hypersensitivity syndrome (AHS) is necessary. Consultation with a burn surgeon or dermatologist may be necessary to assist in management of the dermatological injury of DRESS or AHS.

Treatment

Gastrointestinal decontamination considerations are similar to gabapentin as outlined above. The treatment of lamotrigine exposure starts with quality supportive care. Benzodiazepines are the mainstay of treatment of seizures and status epilepticus. Intravenous lipid emulsion (ILE) therapy has been used successfully as an antidote to reverse severe cardiovascular toxicity related to lamotrigine overdose [38–41]. All of these patients already received multiple therapies that were not effective, including intravenous boluses of sodium bicarbonate. They all have rapid temporal improvement in hemodynamics, but one died later from anoxic brain injury (Grade III).

Hemodialysis or hemoperfusion may be beneficial in enhancing the elimination of lamotrigine because of the moderate protein binding and volume of distribution. One review did not recommend hemodialysis because only 20% was removed in 6 h [23]. In a case report of a patient with QRS widening which progressed to complete heart block, hemodialysis was started 74 h postingestion, decreasing the elimination half-life initially [17]. Multiple sessions occurred with variable success at enhancing elimination. Ultimately, the patient died from pneumonia and disseminated intravascular coagulation, when family withdrew care (Grade III).

Patients who have DRESS or AHS should have lamotrigine discontinued. Do not use other medications that cause AHS such as phenytoin, phenobarbital, and carbamazepine. Supportive care of

organ injury includes care similar to a burn patient with loss of protective skin (Grade III).

Special Populations

Treatment of pediatric patients is identical to the adult. Benzodiazepines for seizures, intravenous fluids, and vasopressors. Intravenous lipid emulsion therapy may be for serious cardiovascular instability such as wide QRS tachydysrhythmias and hypotension. One review reported successful use of ILE in 13/14 pediatric cases to reverse toxicity of a variety of lipophilic pharmaceuticals [42] (Grade III).

Pregnant patients should be treated in the same manner as the nonpregnant patients. Survival of the mother without hypoperfusion or hypoxia will benefit the fetus. Lamotrigine does cross the placenta during pregnancy (Grade III). There have been conflicting reports of lamotrigine causing orofacial cleft birth defects but a large case-control study failed to find an increase in birth defects with lamotrigine therapy [43].

Elderly patients with decreased glucuronidation will have a prolonged elimination half-life of lamotrigine. Changes in renal function should not affect the elimination of lamotrigine (Grade III).

Indications for ICU Admission with Lamotrigine Toxicity

- Status epilepticus
- Coma
- Dysrhythmias with QRS or QT prolongation
- Hypotension
- Systemic reactions such as Steven-Johnson syndrome

Key Points Regarding Lamotrigine Toxicity

- Neurologic abnormalities are common in lamotrigine overdose.
- Status epilepticus may occur in overdose.

(continued)

- Cardiovascular instability may be refractory to standard therapy and ILE may be considered.
- Fatal hepatic necrosis with lamotrigine have been reported.
- Skin rashes may occur and may progress to Steven-Johnson syndrome or toxic epidermal necrolysis. DRESS and AHS have also been reported with therapeutic lamotrigine.

Criteria for ICU Discharge Following Lamotrigine Toxicity

- Resolution of seizures, myoclonus, agitation, and sedation
- Resolution of dysrhythmias and hypotension
- Stabilization of organ injury in the setting of AHS and DRESS

Pharmacokinetics of Lamotrigine

- Volume of distribution: 0.9–1.3 L/kg
- Protein binding: 55%
- Mechanism of clearance: Glucuronic acid conjugation
- Active metabolites: none
- Peak plasma concentrations 1–3 h
- Therapeutic dosing elimination half-life 24–37 h

Common Errors in Management of Lamotrigine Toxicity

- Lamotrigine can cause seizures despite it being an anticonvulsant.
- Failure to recognize lamotrigine as the cause of DRESS, AHS, hepatic necrosis, and pancreatitis.

Levetiracetam

Levetiracetam was first approved by the FDA in 1999 for adjunctive treatment of partial onset seizures in adults [44]. Since then, it has been

approved as add on therapy for myoclonus and generalized seizures in adults and children and promising efficacy for the treatment of status epilepticus [45–47].

Biochemistry and Clinical Pharmacology

Levetiracetam has an unknown mechanism of action but may involve inhibition of voltage-dependent N-type calcium channels; facilitation of GABA-ergic inhibitory transmission through displacement of negative modulators; reduction of delayed rectifier potassium current; and/or binding to synaptic proteins which modulate neurotransmitter release [45, 47, 48]. The gastrointestinal absorption is rapid and nearly complete (95% bioavailability) [44]. It is highly water soluble having protein binding <10%, with peak plasma concentration 1 h after oral dosing and elimination half-life of 7 h. Twenty-four percent of levetiracetam is hydrolyzed to nonactive metabolites in tissues. Because it is not metabolized in the cytochrome system of the liver, there are no metabolic drug interactions. Elimination half-life can be increased by 40% if renal function is impaired.

Pathophysiology of Toxic Effects

The primary toxic effect of an oral overdose of levetiracetam ranges from no effect to severe central nervous system depression requiring intubation [49–51]. The pathophysiology of the sedation is unclear (Grade III).

Clinical Presentation and Life-Threatening Complications

Case reports include multiple supratherapeutic doses that did not result in clinically significant side effects in two children. These children were dosed with ten times and four times the therapeutic dose for 1 week with no side effects [50] (Grade III).

There is a case report of a 38-year-old woman who intentionally ingested 30 g of levetiracetam

presenting to the emergency department 6 h later obtunded [49]. She was intubated and supported on mechanical ventilation but rapidly improved in 24 h and was extubated, without permanent effects. The authors attributed the prompt clinical improvement to the calculated elimination kinetics of a 5 h elimination half-life compared to 6 h seen in healthy volunteers. In overdose first order kinetics were maintained (Grade III).

In comparison, a case report of a 49-year-old male who intentionally ingested 11 g of levetiracetam along with ethanol arrived in the emergency department six and half hours postingestion asymptomatic [52]. He remained clinically stable throughout his hospital stay for the next 22 h in the medical intensive care unit (Grade III).

A polydrug intentional ingestion of cyclobenzaprine, lacosamide, and levetiracetam causing sodium channel blockade and mechanical ventilation for 24 h has been reported [53]. This patient required intravenous boluses of sodium bicarbonate, electrical cardioversion, advanced cardiac life support, and norepinephrine infusion. The serum levetiracetam concentration was in the therapeutic range. The authors attributed the cardiac effects to the combination of lacosamide and cyclobenzaprine, because they both slow conduction through fast sodium channels.

There are two independent 9 year poison center studies of levetiracetam exposures. The first study of 222 exposures revealed no deaths with one major outcome (0.5%) and three (1.4%) moderate outcomes. The vast majority (90%) having minor, minimal, or no effects [51]. These effects included mild CNS depression, vertigo, or ataxia. The median age was 14 years old and 87% were unintentional.

The second study recorded the effects of multiple newer anticonvulsants including levetiracetam. The authors ranked them all with a toxicity score. Levetiracetam exposures had the lowest toxicity of all newer anticonvulsants [7]. In both studies, the predominance of minimal effects seen in unintentional pediatric exposures, and even intentional exposures, is reassuring that good outcomes are expected in the majority of levetiracetam cases (Grade III).

Diagnosis

Levetiracetam levels may be obtained and therapeutic concentrations are from 10 to 40 mcg/mL. However, monitoring drug levels is likely of limited clinical value except in massive overdoses with significant symptoms (Grade III).

Treatment

Gastric decontamination considerations are similar to gabapentin outlined above (Grade III). There is no antidote for levetiracetam overdose. Supportive care, most notably monitoring for central nervous system depression requiring tracheal intubation and mechanical ventilation until the effects have resolved [49]. Improvement is expected within 24 h from time of ingestion. Therefore, minimizing sedation in the mechanically ventilated patient will expedite extubation and decrease the opportunity for complications. Conversely, the initially asymptomatic patients monitored for 24 h without effect can be considered medically cleared (Grade III).

Enhanced elimination of levetiracetam with hemodialysis is theoretically possible with highly water soluble, low protein binding pharmaceutical [23]. Hemodialysis can clear 50% of levetiracetam from the blood in 4 h. Hemodialysis may be relevant in the massive ingestion or a renal failure patient with profound coma and elevated serum levetiracetam concentration. However, most cases will improve so rapidly, hemodialysis will not be necessary (Grade III).

Special Populations

Unintentional pediatric exposures are expected to cause minimal symptoms [51]. Even intentional ingestions may have only mild central nervous system depression. Frequent neurological monitoring for worsening central nervous depression in the initially symptomatic patient for 24 h will be adequate (Grade III).

Levetiracetam does cross the placenta. There is limited data available for levetiracetam during pregnancy, but thus far it is not associated with any birth defects. In an observational study measuring levetiracetam concentrations in pregnant individuals there was one stillbirth at 36 weeks but it is unknown if this was related to levetiracetam [54]. In another study designed to measure levetiracetam levels in neonates there were no birth defects observed, indicating levetiracetam is safe in pregnancy [55]. The pregnant patient should be assessed and treated in an identical manner as the nonpregnant patient. The benefit of treating the mother outweighs the risk or threat to the fetus (Grade III).

Prolonged sedation may be seen in an elderly patient with impaired renal function. Levetiracetam is predominantly eliminated in the urine. There is no concern for drug interactions with hepatic impairment or polypharmacy (Grade III).

Indications for ICU Admission with Levetiracetam Toxicity

- Significant CNS depression, airway monitoring

Key Points Regarding Levetiracetam Toxicity

- Levetiracetam overdose typically produces mild clinical effects.
- Mechanical ventilation has been reported in one 30 g overdose.
- If the patient is sedated, expect improvement in 24 h.
- Renal failure could prolong elimination and sedation.

Criteria for ICU Discharge After Levetiracetam Toxicity

- Baseline mental status

Pharmacokinetics of Levetiracetam

- Highly water soluble

- Time to peak serum concentration 1 h
- Protein binding: <10%
- Enzymatic hydrolysis to inactive metabolites
- Mechanism of clearance: 66% excreted in urine as unchanged drug
- Elimination half-life 7 h

Common Errors in the Management of Levetiracetam Toxicity

- If a patient has sedation after levetiracetam overdose, they should be admitted to a monitored setting because mechanical ventilation has been necessary in rare massive ingestions.
- Impaired renal elimination may prolong elimination and increase risk for sedation.
- Cardiovascular effects are not expected from levetiracetam.
- A major effect or death from levetiracetam in unintentional pediatric exposures.

Topiramate

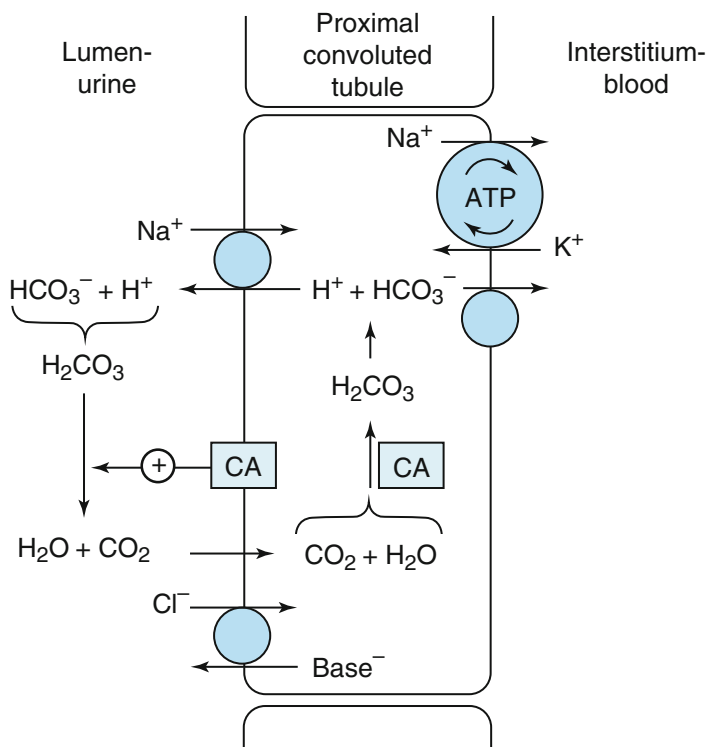
Topiramate is a newer anticonvulsant medication used for the treatment of partial seizures, Lennox-Gastaut syndrome, and for generalized tonic-clonic seizures. Off label uses include cluster headaches, essential tremor, binge eating disorder, acute mania, Tourette's syndrome, neuropathic pain, and bipolar disorder [56, 57].

Biochemistry and Clinical Pharmacology

The complete mechanism of action of topiramate is not fully elucidated because of actions at many receptors [58, 59] (Fig. 1).

Absorption is rapid (81–95% bioavailability) and release preparations are unaffected by food [48, 55, 58]. Extended release preparations are affected by a high fat meal which increases the

Fig. 1 Physiology of carbonic anhydrase (CA) (http://www.uky.edu/~mtp/Diuretic_Drugs.htm)



maximum concentration and shortens the time to maximum serum concentration to approximately 8 h. Protein binding 15–41% and inversely related to plasma concentrations.

Metabolism occurs in minor amounts (20%) in the liver via hydrolysis, hydroxylation, and glucuronidation to inactive metabolites, so it is primarily eliminated (70%) unchanged in the urine [59]. The elimination half-life is 20–30 h [55]. Topiramate inhibits CYP2C19 which can cause increased phenytoin concentrations when coadministered. It also decreases estrogen production of oral contraceptive pills and decreases digoxin serum concentrations. The typical inducing anticonvulsants, phenytoin, phenobarbital, and carbamazepine cause a 50% reduction in topiramate serum concentrations. Valproic acid will decrease the topiramate serum concentration, by 10–15% [55].

Pathophysiology of Toxic Effects

Seizures and other neurological effects have been consistently reported after topiramate overdose and even supratherapeutic dosing [56, 57, 60–62]. The mechanism of the pathophysiology of seizures after exposure to an anticonvulsant is unclear. A mouse study suggests early after exposure, topiramate has proconvulsant effects, but has anticonvulsant effects after more prolonged exposure, similar to an overdose and its therapeutic effect [63] (Grade III).

Clinical Presentation and Life-Threatening Complications

The central nervous system is the primary target of toxicity from topiramate in supratherapeutic and

acute or acute on chronic overdose. Reported effects in adults and children include somnolence, slurred speech, ataxia, hallucinations, coma, seizures, and status epilepticus or nonconvulsive status epilepticus [56, 59–62, 64–66]. Hypotension responsive to intravenous crystalloid has been reported as well [62] (Grade III).

Topiramate is structurally similar to the carbonic anhydrase inhibitor acetazolamide, causing a non-anion gap hyperchloremic metabolic acidosis [62] (Fig. 1). Unpredictably, patients have presented with a severe metabolic acidosis, with or without seizure activity [57, 62]. The metabolic abnormalities have been reported to persist after neurological improvement, 72 h from ingestion [56] (Grade III).

A year review of 567 calls to US poison centers for single topiramate exposures was 90% unintentional pediatric (age ≤ 4 years old) cases [28]. The most common finding was no symptoms (62%). The most common symptom was drowsiness (16%). Only one patient had acidosis recorded and there were no reports of seizures. The most serious effects were seen after intentional overdoses. One patient required mechanical ventilation for lethargy and another was reported to have bradycardia and conduction abnormality. There were no fatalities (Grade III).

Another poison center study of topiramate exposures older than 15, found 56 single topiramate cases over 9 years [7]. They could not statistically find a correlation between dose of topiramate reported and clinical outcomes. None of their patients had seizures, 25% had CNS depression, 11% had metabolic abnormalities or cardiac effects, but no patients were treated with vasopressors. Two patients required mechanical ventilation and four sedation or intravenous fluids. Overall less severe effects, but intentional and unintentional exposures are included together.

The only fatality connected to topiramate was a 44-year-old male found dead in his bed [67]. Cerebral and pulmonary edema were discovered on autopsy. A central blood concentration of

170 mg/L was found postmortem. Ethanol, phenobarbital, and methotrimeprazine were also detected but felt not to be the cause of death by the authors. Without an accurate account of the premorbid events and clinical effects it is difficult to definitively determine topiramate was the cause of death with other confounding sedatives present (Grade III).

Diagnosis

Serum topiramate concentrations can be measured, but some clinical facilities may be limited in this capacity. The reported normal range of serum concentration is 5–25 $\mu\text{g/mL}$ [68]. Serum concentrations are almost never available in a timely fashion to assist in clinical decision-making. EEG monitoring is indicated if nonconvulsive status epilepticus is suspected (Grade III).

Treatment

Considerations regarding gastrointestinal decontamination are similar to gabapentin outlined above (Grade III). There is no antidote for topiramate overdose. Seizures respond well to treatment with benzodiazepines, and if necessary intubation and mechanical ventilation [56, 59, 60, 62]. Mechanical ventilation may be required if lethargy or coma occurs (Grade III).

The metabolic acidosis has been treated with bicarbonate infusions [57]. This may not be necessary for a non-anion gap metabolic acidosis or if re-equilibration of the acid base balance occurs with crystalloid resuscitation. The goal of therapy with the bicarbonate infusion is to only maintain the serum pH within the normal range. It is not meant to enhance elimination (Grade III).

Hypotension can be treated in the usual fashion starting with intravenous crystalloids. If this fails, norepinephrine is theoretically the vasopressor of

choice because of its effects on cardiac contractility and peripheral vasoconstriction (Grade III).

Enhanced elimination of topiramate with hemodialysis is feasible due to its properties of low protein binding and small volume of distribution [55]. Hemodialysis would only be indicated if there was prolonged coma or seizures, hypotension, or metabolic acidosis [23] (Grade III).

Special Populations

Clearance of topiramate is higher in pediatric patients [55]. The clinical effects include more sedation and ataxia but also include seizures in supratherapeutic dosing and overdose [64–66]. Gastrointestinal decontamination has the most benefit early after the acute overdose. It is not warranted in an unintentional pediatric exposure due to low toxicity. The same supportive treatment used for adults should be used in pediatric patients. Hemodialysis is unlikely to be required.

Topiramate crosses the placenta and is considered teratogenic. Topiramate has a strong association with cleft palate in offspring of women taking topiramate in the first trimester [69].

The dose of topiramate may need to be decreased in the elderly because of increased mental impairment, ataxia, and slurred speech [17]. Because topiramate is primarily excreted renally, the dose will need to be adjusted by 50% if creatinine clearance decreases below 70 mL/min [55].

In therapeutic doses, topiramate may cause increased renal calculi, metabolic acidosis, acute glaucoma, weight loss, and hyperthermia [17].

Indications for ICU Admission with Topiramate Toxicity

- Coma
- Status epilepticus
- Hypotension
- Severe metabolic acidosis

Key Points Regarding Topiramate Toxicity

- Unintentional pediatric exposures will often cause only sedation.
- Intentional overdoses most often have sedation, but can also have seizures, status epilepticus, hypotension, and metabolic acidosis that require critical care.
- It is currently difficult to predict the clinical effect from the dose.
- Non-anion gap metabolic acidosis may occur due inhibition of carbonic anhydrase.

Criteria for ICU Discharge After Topiramate Toxicity

- Resolution of seizures
- Resolution of sedation
- Resolution of hypotension
- Resolution of metabolic acidosis

Pharmacokinetics of Topiramate

- Absorption T_{max} (1–4 h)
- Volume of distribution 0.6–1 L/kg
- Protein binding: 15–41% and is inversely related to plasma concentrations
- Mechanism of clearance: 70% is released as unchanged drug
- No active metabolites
- Elimination half-life: 20–30 h
- Hemodialysis can be used to enhance elimination

Common Errors in Management of Topiramate Toxicity

- Failure to recognize seizures or non-convulsive status epilepticus
- Failure to recognize topiramate can cause a hyperchloremic metabolic acidosis
- Renal failure may increase the duration of effect of topiramate
- Overly aggressive gastrointestinal decontamination is not necessary

Table 1 Key aspects of the clinical toxicology of second generation anticonvulsants

Anticonvulsant	CNS	CV	Enhanced elimination	Special property	Antidote
Gabapentin	++	–	HD	Enhanced toxicity in renal failure	None
Lamotrigine	+++ +	++ ++	HD	DRESS/AHS	Intralipid
Levetiracetam	+	–	HD	Enhanced toxicity in renal failure	None
Topiramate	+++	+	HD	Carbonic anhydrase inhibitor	None

Key

CNS = central nervous system

CV = cardiovascular system

“+” = degree of severity

“–” = no toxicity

HD = hemodialysis

DRESS = drug rash with eosinophilia systemic symptoms

AHS = anticonvulsant hypersensitivity syndrome

Table 2 Toxicokinetic and toxicodynamic interactions of second generation anticonvulsants

Drug	Increased toxicity	Decreased effectiveness
Gabapentin	Renal failure	
Lamotrigine	Concurrent valproic acid Elderly patient with decreased glucuronidation	
Levetiracetam	Renal failure	
Topiramate	Renal failure	Concurrent phenytoin, phenobarbital, carbamazepine, and valproic acid

See Tables 1, 2, and 3.

Requests

Structures of each anticonvulsant for each section.

Picture of carbonic anhydrase inhibition in the kidney.

Table 3 Summary of other newer anticonvulsants

Felbamate
Therapeutic indications: partial seizures and Lennox-Gastaut syndrome
Indications for ICU admission
Altered mental status
Renal failure with significant electrolyte abnormalities
Hepatic failure
Key points
Mechanism of action unclear [70]
Symptoms following felbamate overdose symptoms include ataxia, slurred speech, nausea, and vomiting [70–72]
Crystalluria (with unchanged felbamate, monocarbamate felbamate, mercapturic acid conjugates of the metabolite 2-phenylpropenal) and acute renal failure have occurred, that did not require renal replacement therapy [71, 72]
Felbamate urolithiasis with chronic administration [73]
Aplastic anemia and hepatic failure have been reported [74,75]
Criteria for ICU discharge
Normal mental status
Resolution of significant renal, hepatic, and electrolyte abnormalities
Pharmacokinetics[70,71]
Structurally similar to meprobamate, which causes coma
Mechanism of action is unknown
90% renal elimination

(continued)

Table 3 (continued)

Felbamate
Felbamate is sparingly soluble in water
Common errors in management
Failure to recognize felbamate can cause acute renal injury or urolithiasis
Failure to recognize felbamate as a cause of aplastic anemia
Lacosamide
Therapeutic indications: adjunctive treatment for partial-onset seizures and diabetic neuropathy
Indications for ICU admission
Dysrhythmias, that may include atrioventricular blocks, PR interval lengthening, atrial fibrillation/atrial flutter [76, 77]
Depressed mental status requiring intubation
Key points
Lacosamide modulates voltage-dependent sodium channels [78]
Higher doses (600 mg/day) have resulted in dysrhythmias such as atrial flutter/atrial fibrillation [77]
Lacosamide modulates voltage-dependent sodium channels [76, 78]
Neurologic symptoms such as dizziness and headache may occur at therapeutic doses [79]
GI symptoms such as nausea, vomiting may occur at therapeutic doses [79]
Criteria for ICU discharge
Resolution of dysrhythmias
Resolution of altered mental status
Pharmacokinetics
Lacosamide is excreted unchanged in the urine and undergoes minimal hepatic metabolism
Common errors in management
Increased risk of drug side effects with patients with cardiac and renal disease may occur
Express caution when lacosamide is used concurrently with other drugs known to prolong the PR interval, such as carbamazepine [77]
Tiagabine
Therapeutic indications: adjunctive treatment of refractory partial seizures [80, 81]
Indications for ICU admission [80, 82, 83]
Agitated delirium
Status epilepticus
Coma
Key points [82–85]
Mechanism of action of Tiagabine with selective inhibition of neuronal and glial GABA uptake that results in increased GABA-mediated inhibition in the brain
Seizures may occur after overdose ranging from a single seizure to status epilepticus

(continued)

Table 3 (continued)

Felbamate
Nonconvulsive status may also occur
Criteria for ICU discharge
Resolution of seizures or status epilepticus
Normal mental status
Pharmacokinetics [81]
Tiagabine is rapidly absorbed after oral administration and undergoes extensive hepatic metabolism
Metabolites are excreted into the bile
Common errors in management
Failure to recognize convulsive or nonconvulsive status epilepticus
Zonisamide
Therapeutic indications: treatment of partial and generalized seizures
Indications for ICU admission [86]
Significant CNS depression, possibly requiring intubation
QRS widening
QT prolongation
Key points
Zonisamide acts on voltage-gated sodium and calcium channels and has a modulatory effect on GABA-mediated neuronal inhibition
Neurologic side effects predominate at therapeutic doses such as somnolence, dizziness, headache, and nausea [85]
Zonisamide has an inhibitory effect on carbonic anhydrase and may lead to nonanion gap metabolic acidosis [86]
One case report demonstrated mild QRS conduction delay to 102 ms
Spontaneously improved to 85 ms on hospital day 3 [86]
Zonisamide is amenable to hemodialysis, with one study indicating 50% reduction in zonisamide concentration following one 4.5 h hemodialysis session [87]
Criteria for ICU discharge
Baseline neurological status
No cardiac conduction abnormalities
Pharmacokinetics [86]
Rapidly and completely absorbed after oral administration
Hepatic metabolism with primarily urinary excretion
35% excreted as unchanged drug
Common errors in management
Failure to recognize cardiac conduction toxicity
Failure to recognize hemodialysis can enhance the elimination of zonisamide
Failure to recognize nonanion gap metabolic acidosis may be related to zonisamide

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Pharmacokinetics of Valproic Acid

Volume of distribution:	0.22 L/kg
Protein binding:	93%
Mechanism of clearance:	0.0066 L/kg/h, liver
Plasma half-time (half-life):	Approximately 10 h
pKa:	4.60
Active metabolites:	Present, but in small concentrations
Methods to enhance clearance:	High-flux hemodialysis, multiple-dose Activated charcoal; may consider Hemoperfusion (evidence level II-3)

Valproic acid (VPA) was discovered by chance to have anticonvulsant activity when it was used as the vehicle for administration of other compounds that were being studied for antiepileptic activity. It now is used widely not only as an anticonvulsant but also in psychiatry as a mood stabilizer for patients with bipolar disorders. Valproic acid was approved for use in the United States in 1978 after more than 10 years of use in Europe. In recent years there have been advances in knowledge of the pathophysiology of VPA toxicology with potential implications for the management of poisoning and possible identification

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of genetic risk factors. In 2013 in the United States, the poison center voluntary reporting data showed 2,923 single exposures, of which 1,136 were intentional; there were two deaths [1]. There are various dosage forms: intravenous, 100 mg/mL (Depacon[®]); oral VPA capsules USP, 250 mg (Depakene[®] and generics); VPA syrup, 250 mg/mL (Depakene[®] and generics); divalproex (a stable coordination compound of VPA and sodium valproate in a 1:1 molar ratio) (Depakote[®] sprinkle capsules, 125 mg; Depakote[®] delayed-release tablets, 125, 250, and 500 mg; Depakote[®] ER extended-release tablets).

Biochemistry and Clinical Pharmacology

Valproic acid (*n*-dipropylacetic acid) is a branched-chain carboxylic acid. Its chemical structure is shown in Fig. 1. VPA is metabolized in humans to multiple metabolites (Fig. 2). A major portion of a daily dose is conjugated and excreted as glucuronides in urine. Beta-oxidation results in metabolites 2-en-VPA (2-propyl-2-pentenooic acid) and 3-keto-VPA (2-propyl-3-keto-pentanoic acid); both are major human plasma metabolites [2]. Beta-oxidation metabolites are the major metabolites found in urine (about 70%); omega-oxidation and omega-1-oxidation metabolites (3-hydroxy, 4-hydroxy, 5-hydroxy, mostly as glucuronides) are found in lesser amounts in the urine (about 30%) [3]. The hepatotoxic metabolite, 4-en-VPA, results from cytochrome P450 enzyme activity. Studies with human liver microsomes (smooth endoplasmic reticulum) indicate that the cytochrome P-450

isozymes CYP2C9 and CYP2A6 are responsible for 4-en-VPA formation [4]. Additional in vitro studies with human hepatoblastoma cells show that the p-450 isozyme CYP2E1 is responsible for further metabolism of 4-en-VPA to a reactive metabolite [5]. A carbon-centered free radical at the C-4 position in the VPA molecule probably serves as at least one key intermediate [6]. The 3-en-VPA is formed reversibly from 2-en-VPA by isomerization. In plasma, 2-en-VPA (less toxic than VPA or 4-en-VPA) is one of the major circulating metabolites of VPA. Valproic acid therapy (assessed after 3 weeks) results in a small (1.5–2 times) autoinduction of its own metabolism by beta-oxidation but not glucuronidation or 4-hydroxylation [7].

Valproic acid is highly (85–95%), but not tightly, bound to serum albumin [8, 9]; this less tight binding (lower avidity) correlates with clinical reports of clinically significant effectiveness of extracorporeal elimination in poisoned patients [10, 11]. Human brain-to-plasma ratios of VPA range approximately from 0.07 to 0.28. It is thought that an active transport process, the monocarboxylic acid transporter, regulates VPA distribution between plasma and brain [2, 12].

Cerebrospinal fluid (CSF) concentrations of gammaaminobutyric acid (GABA), a major inhibitory neurotransmitter, are increased with VPA treatment, with values of approximately 120 pmol/mL in untreated children compared with approximately 250 pmol/mL in treated children [11]. Elevated serum and CSF glutamine concentrations may correlate better with clinical signs of VPA toxicity than do serum ammonia concentrations [13]. VPA enters human CSF relatively rapidly after dosing. The time to maximum

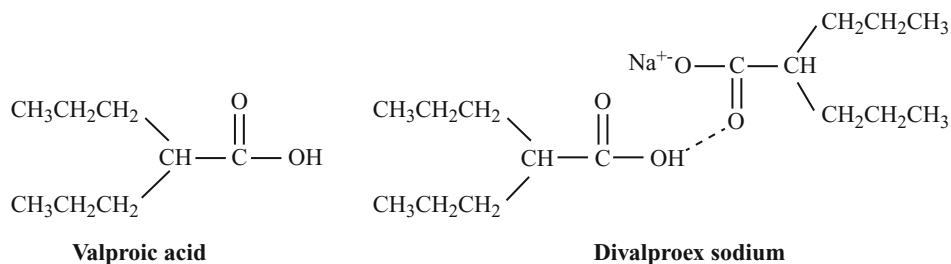


Fig. 1 Chemical structures of valproic acid (VPA) and the dimeric congener valproex sodium

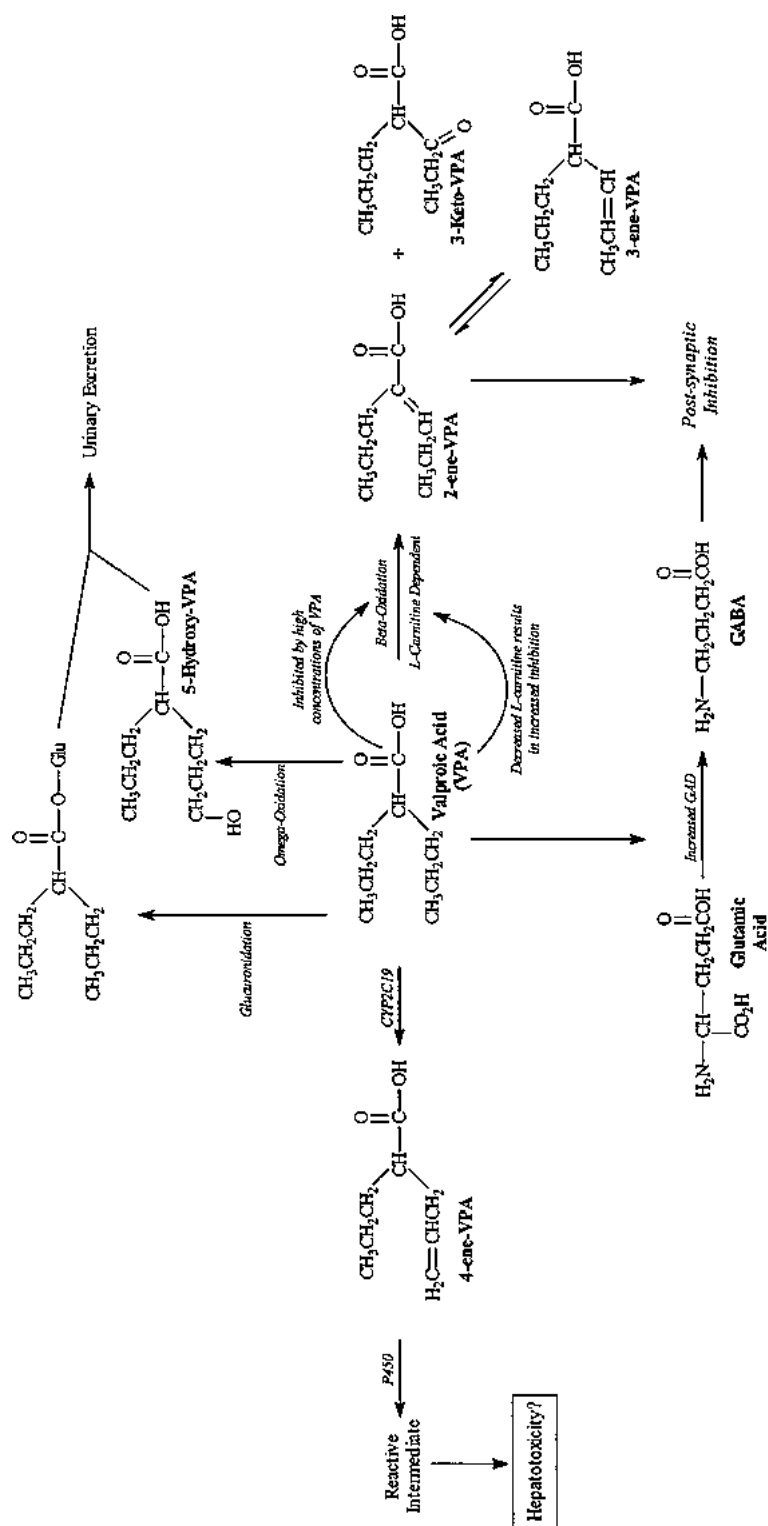


Fig. 2 Metabolism of valproic acid (VPA) in humans. *GABA* gamma-aminobutyric acid, *GAD* glutamic acid decarboxylase

human subdural CSF VPA concentration is 3.5–5.5 h (14.15). Recent studies have shown that VPA has neuroprotective actions that appear to be related to its inhibition of histone deacetylases [16–19].

Pathophysiology of Toxic Effect

The mechanism of anticonvulsant action of VPA seems to be elevation of brain GABA (see Fig. 2). Valproic acid-induced elevation of brain GABA in the substantia nigra is thought to be important because this area of the brain is involved in seizure control and propagation [14]. Laboratory animal data show that VPA increases the apoenzyme of glutamic acid decarboxylase, the enzyme that synthesizes GABA. Some laboratory animal data show that 2-en-VPA is more potent than VPA in potentiating brain GABA-mediated postsynaptic inhibitory responses [14]; 2-en-VPA may contribute significantly to the anticonvulsant effect of VPA in vivo. It is possible that the coma that characterizes VPA overdose also may be due to elevation in brain GABA and possibly 2-en-VPA's postsynaptic inhibitory effects. Other limited data suggest that clinical recovery correlates better with decline in elevated serum glutamine concentrations and EEG improvement rather than the decrease in elevated blood ammonia concentrations [13]. Ammonia is converted to urea and glutamine. Brain glutamine synthesis mostly occurs in astrocytes. In hyperammonemia, the excess glutamine is thought to impair astrocyte function. The osmotic gliopathy theory is that excess glutamine along with hyperammonemia result in osmotic stress which contributes to encephalopathy [15]. In view of this theory, future development of a glutamine synthetase inhibitor potentially may offer a beneficial treatment strategy.

Hepatotoxicity

Most fatalities from VPA poisoning are due to hepatotoxicity, although cerebral edema with deep coma, which may occur in acute toxicity or

as a consequence of hepatic encephalopathy, also poses a risk for death. Valproic acid hepatotoxicity may be dose dependent or idiosyncratic. Dose-dependent hepatotoxicity is more frequent, reproducible, and reversible, whereas idiosyncratic hepatotoxicity is unpredictable, is life threatening, has a long latent period, and is rare (estimated frequency <1 in 10,000). Risk estimates show 37 cases of the fulminant fatal form of VPA hepatotoxicity reported to the manufacturer for the 6-year period of 1978 through 1984. An estimated 400,000 patients were treated with this drug during this period. Of the 37 patients, 27 (73%) were between the ages of 5 months and 11 years. At highest risk for death were children 2 years of age or younger who were treated with multiple anticonvulsants and had significant disease in addition to seizures, such as congenital defects and mental retardation [16]. The fatality rate due to hepatotoxicity in these children was 1 in 500, whereas the fatality rate in the entire group was 1 in 10,000. Use of multiple anticonvulsant drugs in young children increased the fatality rate to 1 in 500 compared with 1 in 7,000 seen in children on monotherapy. Of the 37 patients with fatal hepatotoxicity, 17 also were receiving phenobarbital [14]. More recent reports further substantiate this epidemiological and risk factor data [17, 18]. Liver histology typically shows steatosis and necrosis. Liver ultrastructure findings include enlarged mitochondria with distorted matrix and fragmented cristae [19]. Three risk factors for VPA hepatotoxicity are young age, multiple antiepileptic drug therapy, and high VPA plasma concentrations [16]. An immediately preceding febrile illness is present in about half of children who develop VPA hepatotoxicity [20]. Decreased caloric intake often is associated with a febrile illness. This decreased intake results in increased levels of endogenous fatty acids, which may compete with VPA for beta-oxidation. It appears that the combination of factors of young age, polytherapy, status epilepticus, and febrile illness may result in mitochondrial dysfunction. Some epileptic children develop status epilepticus just before the onset of VPA hepatotoxicity [16] with implications for energy depletion in mitochondria.

The pathogenesis of VPA hepatotoxicity remains uncertain. Hypotheses for the biochemical basis of VPA hepatotoxicity include hyperammonemia, carnitine deficiency, preexisting inborn errors of metabolism, diminished free radical scavenger activity, and toxicity caused by unsaturated VPA metabolites. A polymorphism in a carbamoyl phosphate synthetase gene is reported to correlate with risk for hyperammonemia associated with VPA in whites but not in Japanese orientals [21, 22]. A polymorphism in superoxide dismutase is reported to correlate with an increased risk of elevation of liver serum aminotransferases and gamma-glutamyltransferase [23, 24].

L-Carnitine increases fatty acyl group transport into mitochondria (Fig. 2) and helps maintain the ratio of acyl to free coenzyme A (CoA). Patients receiving VPA therapy have an ongoing biochemical process that uses L-carnitine to maintain mitochondrial metabolism [19]. Mitochondrial metabolic stress induced by increased catabolism brought on by seizures or infection increases the risk of hepatic failure due to an insufficient reserve of L-carnitine, needed for mitochondrial metabolism, including VPA detoxification (see Fig. 2). One postulation is that L-carnitine supplementation may increase the beta-oxidation of VPA, thus decreasing cytosolic omega-oxidation and the production of toxic metabolites that are related to liver toxicity and ammonia accumulation.

The 4-en-VPA metabolite is thought to be at least in part mechanistically related to dose-dependent VPA hepatotoxicity. This metabolite, 4-en-VPA, has structural similarity to other known liver toxins, such as hypoglycin A (methylene cyclopropylacetic acid) and 4-pentenoic acid. These latter two compounds can produce microvesicular steatosis in the livers of laboratory animals, a characteristic feature of Reye's syndrome [25]. A large increase in VPA plasma concentration results in a large increase in 4-en-VPA. An extensive detailed study of VPA metabolism in cases of VPA hepatotoxicity concluded, however, that 4-en-VPA is not the decisive hepatotoxin [26]. In laboratory rats, 4-en-VPA is steatogenic but does not cause hepatocyte necrosis. In one study, younger patients had greater

formation of 4-en-VPA than older patients [20]. In another study, children younger than 2 years of age with VPA hepatotoxicity had lower plasma 4-en-VPA than children older than 2 years of age (whose age averaged 9.5 years) [26]. The ratio of human plasma 4-en-VPA to VPA increases as the total plasma VPA concentration increases. By contrast, the human plasma ratios of 2-en-VPA to VPA and 3-en-VPA to VPA decrease at high plasma concentrations of VPA. This decreased metabolic conversion of VPA to 2-en-VPA and 3-en-VPA at high plasma concentrations of VPA may be due to autoinhibition or saturation of mitochondrial beta-oxidation of VPA because VPA is an inhibitor of mitochondrial fatty acid beta-oxidation (see Fig. 2), with inhibition of 3-ketoacyl-CoA thiolase being most important. What follows is a limited capacity for mitochondrial beta-oxidation, which may become exhausted, leading to unknown metabolic reactions resulting in hepatotoxicity [27]. A 1.0 g oral dose or 400 mg intravenous dose of VPA administered to fasting human adults results in approximately a 75% decrease in plasma 3-hydroxybutyrate and an approximately 60% decrease in plasma total ketones, with increases of lactate, pyruvate, alanine, and glycerol [28]. Valproic acid decreases beta-oxidation of endogenous fatty acids. Clinically, VPA hepatotoxicity incidence is increased in patients who also are treated with other antiepileptic drugs, such as phenytoin, phenobarbital, and carbamazepine, which are known to induce cytochrome P-450. It is possible that cytochrome P-450 enzyme induction results in increased 4-en-VPA production from VPA and further metabolism of 4-en-VPA to a reactive intermediate metabolite. Patients treated with multiple P-450 enzyme-inducing antiepileptic drugs seem to have increased inhibition of beta-oxidation of VPA that may be due to reduced valproyl-CoA formation and greater depletion of carnitine [29, 30]. This altered VPA metabolic profile of production of 4-en-VPA and decreased beta-oxidation of VPA also is reported in patients with fatal VPA hepatic failure [31, 32]. Experimentally, VPA hepatotoxicity in laboratory rats can be predicted by the urinary excretion of total

4-ene-VPA (free plus glucuronide conjugate) [33]. Altered fatty acid metabolism occurs with VPA-induced hepatotoxicity; SREBP-1c (sterol regulatory element-binding protein 1c) and PPAR-alpha (peroxisome proliferator-activated receptor-alpha) are two transcription factors important in fatty acid synthesis and fatty acid degradation, respectively. VPA activates SREBP-1c resulting in increased mRNA expression of acetyl-CoA carboxylase 1, fatty acid synthase, and stearoyl-CoA desaturase 1; VPA inhibits PPAR-alpha resulting in decreased mRNA expression of 3-hydroxy-3-methylglutaryl-CoA synthase 2 and carnitine palmitoyltransferase 1A [34]. Thus, these biochemical actions may be a part of the mechanism of VPA hepatotoxicity. Coadministration of DHA (docohexaenoic acid, a polyunsaturated omega-3 fatty acid) with VPA decreases valproic acid hepatotoxicity in laboratory rats and increases VPA anticonvulsant action [35]. Additional studies of this interaction of potential therapeutic benefit are needed to determine possible clinical utility. Some human data suggest that cotreatment with both L-carnitine and pantothenic acid may offer increased protection against VPA hepatotoxicity compared to L-carnitine alone [36]. Laboratory rat studies show the potential of measuring selected substances to predict hepatotoxicity of valproic acid and other drugs in individual animals prior to the onset of clinical drug-induced liver injury (e.g., 8-hydroxy-2'-deoxyguanosine, octanoyl-carnitine, interleukin (IL)-1 beta, MCP-1/Ccl 2 (monocyte chemoattractant protein-1/CC-chemokine ligand Ccl 2) RNA, and others) [37–42].

Autoantibodies

Covalent plasma protein adducts of VPA and antibodies to these protein adducts are formed in humans (9 of 57 persons tested) but at low titers. This formation occurs because VPA acyl glucuronide nonenzymatically reacts with plasma proteins. Epileptic patients taking VPA chronically have measurable VPA plasma protein adducts at

concentrations of approximately 0.75 microgram VPA equivalents/mL [43].

Teratogenicity

Structure-activity studies in laboratory animals showed that other branched-chain carboxylic acid analogues also have anticonvulsant activity. Some of these do not have teratogenic activity, in contrast to VPA, which is a known human teratogen. VPA is associated with neural tube defects [44].

Clinical Presentation and Life-Threatening Complications

After an acute large overdose, drowsiness progressing to coma usually occurs relatively rapidly but may progress more gradually, particularly with the divalproate form. Metabolic acidosis, hypoglycemia, hypocalcemia, hypophosphatemia, and hypernatremia may become severe and potentially life threatening. Hyperammonemia and elevated serum liver enzymes may occur after either acute overdose or long-term chronic therapy [45, 46] and typically are not life threatening in most patients. Occasionally, severe life-threatening hepatotoxicity may occur, especially in patients on chronic therapy. Thrombocytopenia, occasionally requiring platelet transfusion, and leukopenia are potential risks. Delayed life-threatening cerebral edema appearing in a few to several days may occur in severely poisoned patients. In 133 VPA overdose patients with peak serum VPA concentrations averaging 380 mg/L (2,660 μ mol/L) and ranging from 110 to 1,840 mg/L (770–12,880 μ mol/L) (therapeutic range 50–100 mg/L [350–700 μ mol/L]), findings included lethargy in 94, coma in 19, tachycardia in 24, aspiration in 8, metabolic acidosis in 8, and hypotension in 4 [47]. Peak serum VPA concentrations greater than 850 mg/L (>5,950 μ mol/L) are more likely to be associated with coma; peak serum VPA concentrations

greater than 450 mg/L ($>3,150 \mu\text{mol/L}$) are more likely to be associated with moderate or major adverse outcome. Of 133 patients with transient thrombocytopenia 11 had peak serum VPA concentrations greater than 450 mg/L ($>3,150 \mu\text{mol/L}$) [47]. One of the highest reported serum VPA concentrations was 2,700 mg/L ($18,900 \mu\text{mol/L}$) in an adult patient with a fatal outcome [48].

Diagnosis

The diagnosis of VPA poisoning, similar to many drug poisonings, is helped enormously by an available and accurate history of ingestion. When a patient presents with an unknown ingestion and laboratory data are pending, differential diagnosis may be difficult. In this latter scenario, coma with or without metabolic acidosis may be present, and identification of VPA in urine or blood specimens may be required to support the diagnosis. This identification should be followed by quantitative plasma concentrations for confirmation. Plasma VPA concentrations greater than 100 mg/L ($700 \mu\text{mol/L}$) are of concern. Concentrations greater than 450 mg/L ($3,150 \mu\text{mol/L}$) and 850 mg/L ($5,950 \mu\text{mol/L}$) are of increasingly serious concern, although it is recognized that a close correlation between plasma VPA concentrations and clinical severity does not exist [47]. An initial level obtained shortly, 1–2 h, after overdose may be misleadingly low; therefore it is recommended to repeat a level to assess for delayed absorption.

Treatment

Treatment considerations include general supportive care, gastrointestinal decontamination with activated charcoal, selective high-flux hemodialysis, and also L-carnitine and N-acetylcysteine administration (evidence level II-2 and II-3). Some authors recommend the use of naloxone (evidence level III). All patients with VPA toxicity should be monitored closely for depression of mental status and need for airway protection.

Patients with an altered mental status should have their arterial ammonia blood concentration measured. Glucose should be monitored because of the possibility of hypoglycemia.

Gastrointestinal Decontamination

Activated charcoal given 5 min after an oral dose of 300 mg of VPA to six healthy human volunteers reduced absorption of VPA by 65% [49]. When multiple-dose activated charcoal was started 4 h after an oral dose of 300 mg of VPA (4–32 h after VPA, repeated doses of activated charcoal, total of 80 g, administered), there was no significant difference in the area-under-the-time-curve or plasma half-time (half-life) (20 h compared to 22 h) [50]. Single-dose activated charcoal given relatively soon after ingestion, but perhaps less likely multiple-dose activated, may be of benefit in patients with VPA overdoses (evidence level II-3). One patient with a fatal overdose of VPA had VPA concentrations in bile of 3,000 mg/L ($21,000 \mu\text{mol/L}$) [48], however, suggesting the possibility that multiple-dose activated charcoal in poisoned patients might provide some benefit in interrupting enterohepatic circulation. There are no published clinical prospective studies, from which to assess the efficacy of multiple-dose activated charcoal in patients with large acute ingestions or patients who have ingested an overdose of a delayed-release preparation. Life-threatening ingestions of VPA are many grams in amount such that VPA levels may rise despite attempts at giving MDAC. Therefore, The administration of activated charcoal may decrease gastrointestinal absorption if administered soon after ingestion. However, it is unknown if this affects either clinical course or outcome. Patients who ingest VPA may develop a decreased mental status while taking activated charcoal, and therefore it should be used cautiously, if at all, in nonintubated patients. Activated charcoal is unlikely to have an effect if given greater than 1 hour post ingestion.

Indications for ICU Admission in Valproic Acid Poisoning (Evidence Level III)

History of large-dose symptomatic acute ingestion

Rapidly decreasing level of consciousness
or presence of coma

Cerebral edema

Markedly abnormal liver function tests,
including elevated blood ammonia

Hypoglycemia

Metabolic acidosis

Cholestyramine does not decrease VPA gastrointestinal absorption clinically to a significant degree in humans [51].

Common Errors in the Treatment of Valproic Acid Poisoning

Omission of consideration of administration of L-carnitine

Omission of consideration of administration of N-acetylcysteine

Omission of consideration of use of high-flux hemodialysis

Monitoring for delayed absorption and toxicity

Hemodialysis

Despite the high percentage of VPA bound to plasma proteins at therapeutic concentrations, hemodialysis may have a role in VPA poisoning. High-flux hemodialysis alone without hemoperfusion was effective in one patient with coma, hypotension, lactic acidosis, and a serum VPA concentration of greater than 1,200 mg/L [52]. At high serum concentrations of VPA, its protein-binding fraction decreases owing to saturation of albumin binding sites. For example, 32% is bound at 1,400 mg/L (9,800 $\mu\text{mol/L}$) [53], resulting in the potential for greater effectiveness of hemodialysis than in patients with VPA

concentrations in the therapeutic range when it is 85–95% bound to plasma proteins. In one patient, high-flux hemodialysis of 6 h duration reduced serum VPA concentrations from 940 to 165 mg/L (6,580–1,155 $\mu\text{mol/L}$) [54]. Case reports of extracorporeal methods indicate that this approach rapidly decreases elevated VPA serum concentrations [55–58]. Peritoneal dialysis does not seem to be effective, however [59]. Although hemodialysis is effective in reducing plasma VPA concentrations, it may not affect outcome because most patients survive with supportive care, generally consisting of airway support and mechanical ventilation. In patients with extremely elevated VPA serum concentrations, hemodialysis perhaps may decrease the duration of coma and perhaps may reduce complications by enhancing drug clearance.

Naloxone

Anecdotal case report experience suggests that naloxone may provide some benefit in some, but not all, patients with VPA-induced coma and decreased ventilatory function (respiratory depression) [60]. Naloxone is relatively safe; its benefit-to-risk ratio is favorable for use in most patients with coma and ventilator depression. The fraction of patients with VPA poisoning who may respond at least to some extent to administration of naloxone is not reported.

L-Carnitine

VPA therapy and overdose both may result in decreased plasma carnitine concentrations, which decreases beta-oxidation [25, 61–65]. In patients with VPA-induced hepatotoxicity, L-carnitine treatment is reported to result in 48% survival in 42 patients compared with 10% survival in 50 patients treated with aggressive supportive care alone [66]. There was greater survival with intravenous L-carnitine compared with enteral L-carnitine, which is likely related to the 15%

enteral bioavailability of L-carnitine. The dose of L-carnitine recommended is 50–100 mg/kg/day typically for a few days until there is evidence of significant clinical improvement. The optimal dose has not been established. L-carnitine administration is reported to lower elevated blood ammonia concentrations toward the normal range in therapeutic dose VPA-treated children [67]. L-carnitine treatment, which is considered relatively safe, is recommended for patients with VPA hepatotoxicity (evidence level II-3). D-Carnitine is not active, and D, L-carnitine may be associated with a myasthenia-like syndrome.

L-carnitine administration may be considered for most patients with VPA poisoning because of the associated reduction in plasma concentrations of carnitine in these patients, which occurs even in some patients treated with therapeutic doses of VPA. Recommended oral doses of L-carnitine for carnitine deficiency are 50–100 mg/kg/day in children and 1–3 g/day in adults. L-Carnitine should be administered intravenously in VPA-poisoned patients. There are no published studies that establish optimal doses of intravenous L-carnitine to be administered to patients with VPA poisoning. More recent studies add further support for administration of L-carnitine to patients with VPA toxicity [68–70].

N-acetylcysteine

Because the liver toxic metabolite 4-en-VPA is produced by oxidant cytochrome P-450 mechanisms and 4-en-VPA seems to be metabolized further by a cytochrome P-450 (probably CYP2E1) to a reactive and perhaps toxic intermediate metabolite, use of N-acetylcysteine (NAC) has been recommended (evidence level III). There are no controlled published prospective randomized clinical studies outcome data that demonstrate NAC to be an efficacious treatment for VPA hepatotoxicity or VPA-induced cerebral edema [71]. NAC is a plausible therapy for VPA hepatotoxicity and for VPA-induced delayed cerebral edema because of cytochrome P-450

production of a toxic metabolite of VPA (i.e., further metabolism of 4-en-VPA) (see Fig. 2). NAC is reported to offer benefit for the treatment of liver failure from multiple causes [72, 73]. A dosing regimen for NAC similar to that for acetaminophen hepatotoxicity would seem to be a reasonable approach.

Criteria for ICU Discharge in Valproic Acid Poisoning

Patient is awake enough to protect their airway

Hemodynamic stability

Improving liver function

Children, pregnant women, and the elderly are treated similarly for VPA poisoning. There is some evidence that L-carnitine is transported across the human placenta (evidence level II-2) [74].

Key Points in Valproic Acid Poisoning (Evidence Level II-3)

1. Early recognition of hepatotoxicity in patients on long-term therapeutic dosing improves outcome.
2. Early use of L-carnitine improves survival in patients with VPA hepatotoxicity.
3. High-flux hemodialysis is efficacious in enhancing drug clearance. It is not known if it affects outcome.

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Part VIII

Medications: Neuromuscular

Steven J. Walsh and Kenneth D. Katz

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Parkinson disease, named after James Parkinson who first described the disorder in 1817, is a chronic, progressive neurologic disorder clinically characterized by a combination of tremor, rigidity, and bradykinesia [1, 2]. Estimates of the incidence of Parkinson disease range from 5 to 20 new cases per 100,000 individuals per year, occurring with a slightly greater frequency in middle-aged and elderly men of European and North American descent [1, 3]. The cause of Parkinson disease is unknown, but it has been observed in humans and induced in primates by exposure to 1-methyl-4-phenylpyridine (MPP⁺), a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which poisons complex I of the mitochondrial electron transport chain (Fig. 1) [4]. Other risk factors associated with the development of Parkinson disease include oxidant stress, reduced glutathione stores, tobacco smoking (linked inversely to the development of Parkinson disease), and caffeine consumption (correlated with reduced risk) [3, 4]. Current scientific evidence suggests that Parkinson disease does not have a substantial genetic component [3].

Pars compacta neurons located in the substantia nigra are responsible for dopaminergic input to the striatum, located within the basal ganglia (Figs. 2 and 3). Dopamine activates excitatory D₁ receptors in the striatum in a direct (monosynaptic) pathway and inhibits inhibitory striatal D₂ receptors in an indirect (polysynaptic) pathway (Table 1). With loss of dopaminergic nigral cells and subsequent striatal dopamine depletion, there is decreased activity of the direct pathway and increased activity of the indirect pathway. The net result of dopamine loss is reduced thalamic excitation of the motor cortex, resulting in the clinical manifestations of Parkinson disease [1, 5].

The hallmark clinical features of Parkinson disease are resting tremor, cogwheel rigidity, and bradykinesia. Patients with Parkinson disease may manifest other motor signs and symptoms, including masked facies and gait abnormalities. Nonmotor signs and symptoms such as sensory abnormalities, autonomic dysfunction, dementia, and depression are also characteristic [1].

Medical treatment of patients with Parkinson disease can be categorized as either symptomatic or preventive. Symptomatic therapy involves

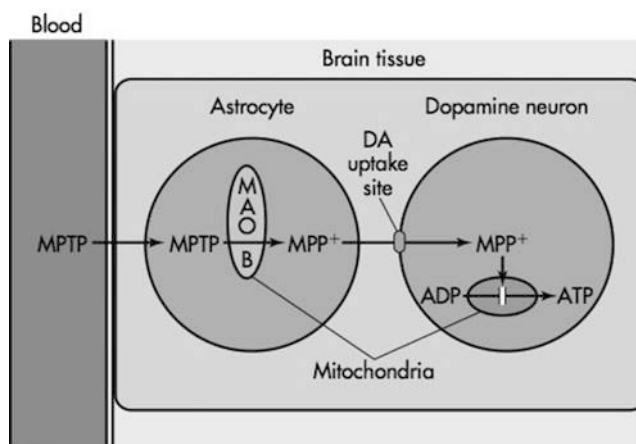


Fig. 1 Mechanism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced degeneration of nigrostriatal dopamine neurons. MPTP is converted by monoamine oxidase B (MAOB) within astrocytes or other nondopaminergic neurons to the reactive intermediate 1-methyl-4-phenylpyridine (MPP⁺). MPP⁺ is taken up into the dopaminergic neuron by the dopamine (DA) transporter. Within the dopaminergic neuron, MPP⁺ acts on

mitochondria to inhibit mitochondrial respiration, which results in cell death. ADP adenosine diphosphate, ATP adenosine triphosphate (From Gudelsky GA: Drugs for the treatment of Parkinson's disease. In Brody TM, Larner J, Minneman KP [eds]: Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, p 386)

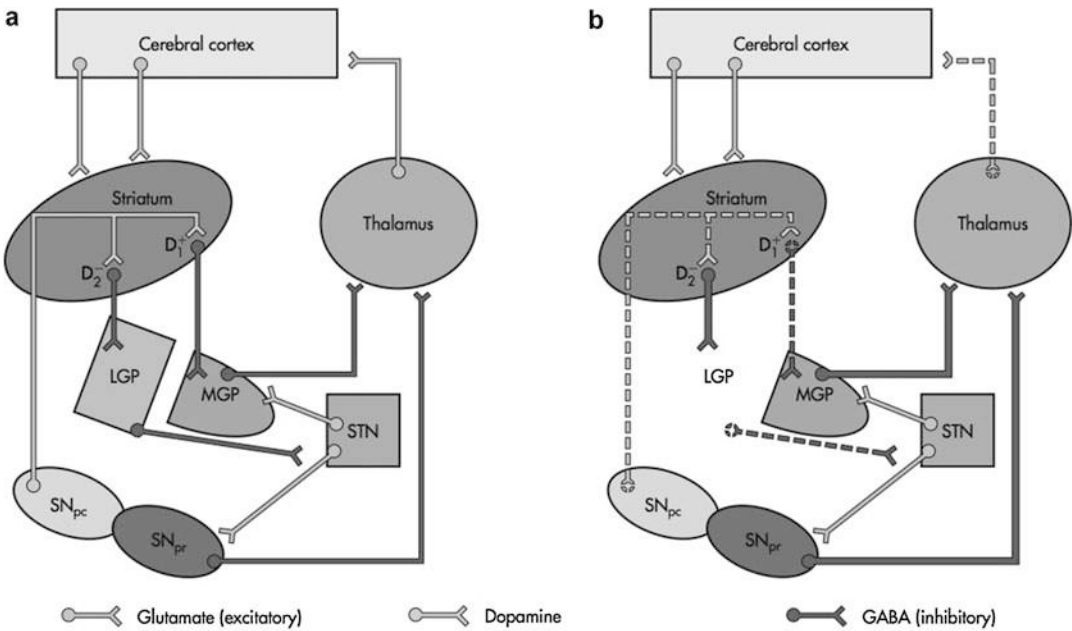


Fig. 2 Parkinson disease and the neural circuitry of the basal ganglia. (a) The striatum is the principal input structure of the basal ganglia. Striatal D₁-receptors mediate an excitation of a direct output pathway to the medial globus pallidus (MGP). Striatal D₂-receptors mediate an inhibition of an indirect output pathway projecting through the lateral globus pallidus (LGP) and subthalamic nucleus (STN) to the substantia nigra pars reticulata (SN_{pr}) and MGP. (b) Loss of dopaminergic input to the striatum resulting from degeneration of nigrostriatal dopamine neurons results in a decrease in the activity of the direct output

pathway and an increased activity of the indirect output pathway. The net effect is an increased inhibitory outflow from the SN_{pr} and MGP to the thalamus. This outflow ultimately results in reduced excitatory input to the cerebral cortex. *Thin lines* normal neuronal activity, *dashed lines* reduced activity, *thick lines* increased activity, SN_{pc} substantia nigra pars compacta (From Gudelsky GA: Drugs for the treatment of Parkinson's disease. In Brody TM, Lerner J, Minneman KP [eds]: Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, p 390)

Fig. 3 Dopamine pathways in the brain. Ac nucleus accumbens, Am amygdaloid nucleus, C cerebellum, Hip hippocampus, Hyp hypothalamus, P pituitary, Sep septum, SN substantia nigra, Str corpus striatum, Th thalamus (From Rang HP, Dale MM, Ritter JM, Gardner P: Other transmitters and modulators. In Pharmacology, 4th ed. Philadelphia, Churchill Livingstone, 2001, p 486)

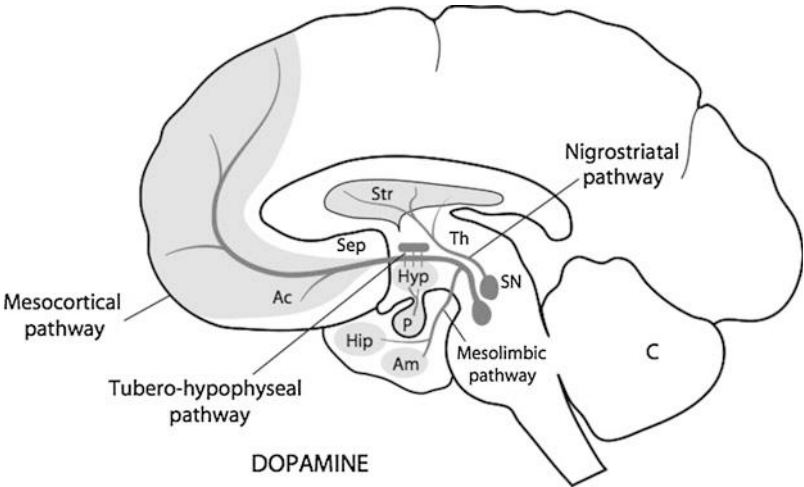


Table 1 Dopamine receptors

		D ₁ type		D ₂ type		
		D ₁	D ₅	D ₂	D ₃	D ₄
Distribution	Functional role					
Cortex	Arousal, mood	++	—	++	—	—
Limbic system	Emotion, stereotypical behavior	+++	—	+++	+	+
Basal ganglia	Motor control	++	+	+++	+	+
Hypothalamus	Autonomic and endocrine control	++	+	—	—	—
Pituitary gland	Endocrine control	—	—	+++	—	—
Agonists	Dopamine	+ (low potency)			+ (high potency)	
	Apomorphine	PA (low potency)			+ (high potency)	
	Bromocriptine	PA (low potency)			+ (high potency)	
Antagonists	Chlorpromazine	+	+	+++	+++	+
	Haloperidol	++	+	+++	+++	+++
	Spiperone	—	—	+++	+++	+++
	Sulpiride	—	—	+++	++	—
	Clozapine	+	+	+	+	++
Signal transduction		Increase cyclic AMP		Decrease cyclic AMP and/or increase IP ₃		
Effect		Mainly postsynaptic inhibition		Pre- and postsynaptic inhibition		
				Stimulation/inhibition of hormone release		

AMP adenosine monophosphate, IP₃ inositol 1,4,5-trisphosphate, PA partial agonist
From Rang HP, Dale MM, Ritter JM, Gardner P: Other transmitters and modulators. In Pharmacology, 4th ed. Philadelphia, Churchill Livingstone, 2001, p 486

administration of medications, including levodopa/carbidopa, anticholinergics/antihistamines, amantadine, dopamine agonists (e.g., bromocriptine, rotigotine, pramipexole), monoamine oxidase (MAO) B inhibitors (e.g., selegiline, rasagiline mesylate), catechol-*O*-methyltransferase (COMT) inhibitors (e.g., entacapone), antidepressants, and atypical antipsychotics. Preventive treatment is targeted at slowing or halting the development and progression of the disease and includes medications such as MAO B inhibitors, dopamine agonists, antioxidants, anti-inflammatories, and antiapoptotic agents. Novel therapies currently under investigation include injection of pluripotent stem cells in an attempt to regenerate degenerative nigra cells, as well as targeted gene therapies [6–8]. This chapter provides an overview of the

various classes of medications commonly implemented to treat patients with Parkinson disease and the tools with which to evaluate and treat toxicities associated with these medications in the critical care setting. Because patients who experience the toxic effects of antiparkinson agents are typically elderly, the critical care provider is advised to also consider the toxicity risks associated with advanced age (see ► Chap. 8, “Geriatric Poisoning”).

Levodopa/Carbidopa

The amino acid levodopa (L-3,4-dihydroxyphenylalanine, Fig. 4) is the metabolic precursor of all catecholamines and normally is produced from

tyrosine by the action of tyrosine hydroxylase (Fig. 5). It is decarboxylated to dopamine by dopa decarboxylase [9]. It has been stated that, “Levodopa is the most reliable and effective symptomatic treatment for Parkinson disease. Almost all patients with true idiopathic Lewy body Parkinson disease respond to levodopa treatment. Indeed, failure to respond suggests an alternative diagnosis” [4]. Treatment of Parkinson disease patients with levodopa is associated with decreased morbidity and mortality compared with treatment in the “pre-levodopa era” [2].

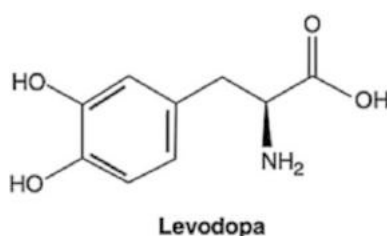


Fig. 4 Chemical structure of levodopa

Pharmacokinetics

Levodopa is well absorbed from the gastrointestinal tract, but drug bioavailability may be limited by many factors. Coingestion of other relatively large amino acids hinders levodopa absorption via saturation of the amino acid transport system in the proximal small intestine. Additionally, gut wall decarboxylase metabolizes 50–75% of orally administered levodopa before it reaches the systemic circulation. Delayed gastric emptying, which may occur with consumption of large meals or concomitantly administered anticholinergic medications, delays drug delivery to the small intestine and retards the onset of peak plasma concentrations [9].

The volume of distribution of levodopa is approximately 0.9–1.6 L/kg, with an apparent half-life of 0.78–1.74 h. It is metabolized in the periphery by COMT to the inactive metabolite 3-*O*-methyldopa (3-OMD) and is excreted primarily in the urine as unchanged dopa and in the form of several metabolites, including homovanillic acid and dopamine [9].

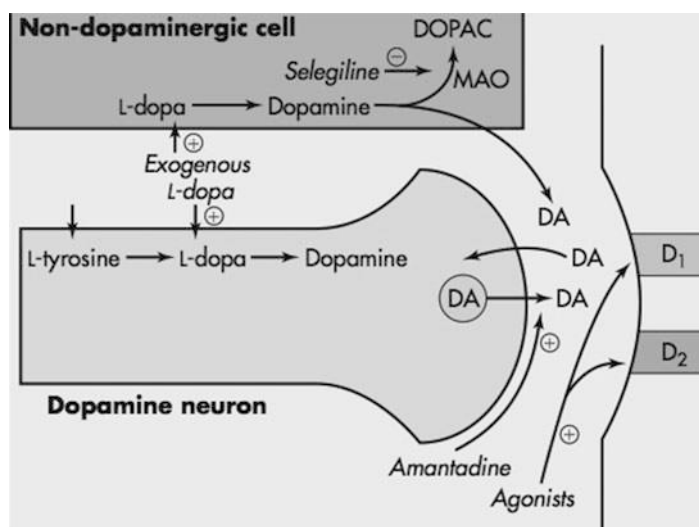


Fig. 5 Sites of action of antiparkinsonian agents to facilitate dopaminergic function. Levodopa (L-dopa) enhances the synthesis and ultimately the release of dopamine (DA). Amantadine facilitates the release of dopamine. Dopamine agonists directly activate dopamine receptors (D₁ and D₂) on the postsynaptic cell. Selegiline inhibits the metabolism

of dopamine in nondopaminergic neurons or glia or both (From Gudelsky GA: *Drugs for the treatment of Parkinson's disease*. In Brody TM, Larner J, Minneman KP [eds]: *Human Pharmacology: Molecular to Clinical*, 3rd ed. St. Louis, Mosby, 1998, p 388)

Levodopa effectively penetrates the blood–brain barrier. When administered alone, however, levodopa is decarboxylated nearly completely in the peripheral circulation to dopamine, which does not penetrate the blood–brain barrier. In addition, common gastrointestinal side effects of levodopa (such as nausea and vomiting) occur secondary to the conversion of dopa to dopamine in the periphery and resultant dopamine-mediated stimulation of postrema areas not protected by the blood–brain barrier [2]. Coadministration of a dopa decarboxylase inhibitor, such as carbidopa or benserazide, minimizes peripheral conversion of levodopa to dopamine, promoting maximal exposure of the brain to the desired agent and minimizing untoward gastrointestinal effects [10]. Another benefit gained from dopa decarboxylase inhibitor administration is the 70–80% reduction in daily levodopa dose needed for clinical efficacy [9].

Pharmacokinetics of Levodopa (Dopar; Sinemet, in combination with carbidopa)

Volume of distribution: 0.9–1.6 L/kg

Protein binding: none

Metabolites: dopamine, homovanillic acid, dopa

Plasma elimination half-life: 0.78–1.74 h

Clinical Presentation

Adverse Effects

Patients receiving therapeutic doses of levodopa commonly experience anorexia, nausea, and vomiting thought to be mediated by dopaminergic stimulation of the medullary emetic center [11]. Because dopamine is an active catecholamine possessing α - and β -adrenergic agonist properties, administration of levodopa may cause tachycardia, cardiac dysrhythmias, hypertension, and, later, orthostatic hypotension [11]. Additionally, patients receiving levodopa may develop behavioral disturbances, including confusion, delirium, hallucinations, anxiety, and depression [11]. Long-standing use of levodopa may result in the development of dyskinesias such as chorea,

dystonia, and myoclonus. Levodopa-induced dyskinesia occurs in approximately 50–75% of Parkinson patients after 5–10 years of therapy [12]. The mechanism of the dyskinesia has been suggested to be related to pulsatile stimulation of striatal dopamine receptors, with a resulting “downflow supersensitivity” [13].

Levodopa is a phenylethylamine compound and is structurally related to other central nervous system (CNS) stimulants and sympathomimetic drugs (e.g., amphetamine). Similar to other drugs in this class, levodopa is subject to abuse, which is well-described in Parkinson patients who desire a particular psychological benefit from the medication [14]. Slow discontinuation and then reintroduction of levodopa to the desired clinical endpoint may prove successful in treating this problem.

Significant drug–drug interactions with levodopa are relatively uncommon; however, any substance or medication that alters gastric motility or emptying (e.g., presence of food, anticholinergic medications) may change levodopa absorption and plasma concentrations. Penicillamine increases plasma levodopa levels by greater than 50% by enhancing levodopa absorption [15]. Several other drugs have been shown to accentuate the clinical manifestations of Parkinson disease and may interfere with levodopa therapy. Reserpine and tetrabenazine can reduce dopaminergic function by depleting presynaptic dopamine stores and may compromise and interfere with levodopa’s efficacy. Methylodopa, after conversion to methyl dopamine by dopa decarboxylase in presynaptic dopaminergic nerve terminals, can serve as a partial dopamine agonist and can competitively interfere with levodopa at the D_2 dopamine receptor. Coadministration of dopamine antagonists, such as high-potency neuroleptics or metoclopramide, can offset levodopa efficacy and exacerbate manifestations of underlying Parkinson disease. Calcium channel-blocking agents (flunarizine, verapamil, diltiazem, amlodipine, manidipine) also may exacerbate parkinsonism due to interference with presynaptic striatal dopamine release [15]. Several other medications, including amiodarone, valproic acid, vigabatrin, cytosine, methotrexate, dacarbazine, cisapride, meperidine, isoniazid, and amoxapine, may cause or worsen parkinsonism [15].

There is a hypothetical concern regarding levodopa neurotoxicity after long-term administration resulting from the propensity of the drug, once metabolized, to form free radicals. This potentially toxic phenomenon has been shown *in vitro* but has not been substantiated clinically [2, 16].

Overdose and Toxicity

Although the adverse effects of levodopa therapy are well described, there is a relative paucity of literature describing acute levodopa overdose. Delmas et al. [17] described a case of a patient who ingested carbidopa; additionally, Hoehn and Rutledge [18] described a 61-year-old Parkinson disease patient who ingested approximately 100 g of levodopa and presented with marked confusion, agitation, “jerking movements,” restlessness, and initial hypertension followed by orthostatic hypotension. Both patients did well with supportive care. A case report of a woman with no previous history of Parkinson disease who ingested approximately 15–17 tablets of levodopa/carbidopa (Sinemet®), ibuprofen, carisoprodol, and hydrocodone/acetaminophen described her as lethargic with choreiform movements. These choreiform movements were unaffected by administration of morphine sulfate and diazepam; pancuronium was administered intermittently for almost 60 h until the patient’s dyskinesias resolved. She was treated supportively and recovered without apparent sequelae [11].

Additionally, Parkinson patients can present not only after levodopa overdose but also with other levodopa-induced problems. Dyskinesias and motor fluctuations are common late complications of Parkinson disease and may be related not only to progression of disease but also to fluctuations in serum levodopa concentrations [19]. Levodopa-induced dyskinesias may be ballistic, dystonic, myoclonic, or choreoathetotic and can affect any muscle group, including muscles involved with ventilatory function. Motor fluctuations range from “on” stable intervals, during which Parkinson symptoms are controlled, to “off” periods, when the patient may experience disabling immobility, tremor, or postural instability. In addition, during the “off” periods, nonmotor features such as autonomic instability,

confusion, anxiety, and (rarely) neuroleptic malignant syndrome from relative lack of central dopamine may be seen [19]. Several emergent complications may arise from these various disorders, including rhabdomyolysis and respiratory failure from aspiration or ineffective ventilation.

Acute dystonic reactions and neuroleptic malignant syndrome, thought to stem from D₂ receptor antagonism, can be seen in patients in whom levodopa is withdrawn abruptly [20, 21]. This syndrome generally responds to reinstitution of levodopa therapy [22]. Neuroleptic malignant syndrome is discussed in detail in the chapter by that name.

Diagnosis

The initial diagnostic approach to a poisoned patient relies heavily on the history and physical examination. For a patient who has overdosed, it is recommended that several initial laboratory studies be obtained, including serum electrolytes, serum acetaminophen and salicylate assays, and an electrocardiogram (ECG). Occasionally, a urine toxicological assay may be deemed necessary. The general diagnostic considerations in the evaluation of overdose patients are discussed in ► Chap. 2, “The Diagnostic Process in Medical Toxicology.” The toxicological differential diagnosis is broad and includes poisoning by sympathomimetic agents (e.g., amphetamines (see ► Chap. 72, “Amphetamines and Their Derivatives”), salicylates (see ► Chap. 63, “Salicylates”), or thyroid hormone.

In the case of acute ingestion of levodopa, the diagnosis is reached primarily by history and physical examination. Stuerenburg and Schoser [23] reported the value of measuring plasma concentrations of levodopa and 3-OMD (resulting from the ortho-methylation of levodopa) to the diagnosis and care of a patient who overdosed on levodopa/carbidopa. Hoehn and Rutledge [18] reported the utility of measuring levodopa metabolites, such as dopamine dihydroxyphenylacetic acid, homovanillic acid, and norepinephrine, in urine to confirm levodopa exposure and to follow the eventual clearance of levodopa as it parallels clinical improvement. The availability of these assays

in most clinical care settings is limited, however, and they are not essential to patient management, which is almost entirely supportive.

Parkinson disease patients presenting with possible levodopa-induced clinical findings should be evaluated for other nontoxicologic diagnoses such as sepsis. An infectious disorder, such as pneumonia or urinary tract infection, or another systemic disease process such as heart failure can alter the patient's sensitivity to levodopa, triggering fluctuation in motor function [19]. Appropriate diagnostic and laboratory tests should be tailored to the individual clinical presentation and may include a chest radiograph (also frequently needed for aspiration concerns), complete blood count, blood cultures, cardiac enzymes, and urinalysis, in addition to those studies previously mentioned. Additionally, severe dyskinesia and neuroleptic malignant syndrome may promote rhabdomyolysis and myoglobinuric renal injury; serum creatine phosphokinase, electrolytes, blood urea nitrogen, and creatinine concentrations should be considered among the laboratory values obtained. Given the increased risk for thromboembolic disease in those patients with chronically decreased mobility, noninvasive vascular studies, such as lower extremity Doppler ultrasound, may be indicated.

Treatment

Treatment of the acutely levodopa-poisoned patient is largely supportive. The experience with levodopa overdose is limited, and suggestions regarding management of toxicity are based mainly on theoretical concerns. In the few instances of levodopa overdose that are documented in the medical literature, patients did well with supportive care alone.

**Indications for ICU Admission
in Antiparkinsonian Drug Toxicity**
Levodopa/Carbidopa
Severe agitation
Autonomic instability
Altered level of consciousness
Uncontrollable severe movement disorder
Neuroleptic malignant syndrome

As in all poisonings, attention initially should be focused on the patient's airway and circulatory status. If agitation is severe and uncontrollable, the airway should be secured. A dose of oral activated charcoal may reduce further systemic drug absorption when administered within the first few hours of ingestion. It is unknown, however, whether the administration of activated charcoal alters the clinical course or outcome in these patients. There is no published evidence to support efficacy or clinical benefit of gastric lavage.

Hypertension has been described in the acute phase of levodopa overdose and generally has been transient [11, 18]. If hypertension is persistent and severe, however, intravenous short-acting direct vasodilators such as sodium nitroprusside may be preferred over β -blockers because of the theoretical concern for unopposed α -adrenergic effects of levodopa poisoning. Hypotension should be treated initially with intravenous crystalloid and then, if hypotension is persistent, with intravenous direct vasopressor (such as norepinephrine) infusion. Catecholamines with relative α -adrenergic potency generally are preferred because dopamine-induced, β -adrenergic-mediated vasodilation may occur in patients with hypotension refractory to volume resuscitation (Evidence Level III).

Agitation and dyskinesia may be managed initially with intravenous benzodiazepines, such as lorazepam or diazepam, titrated to mild sedation. If necessary, neuromuscular blockade may be implemented for control of extreme movement disorder or severe combativeness.

Treatment of other acute, subacute, or chronic manifestations of levodopa poisoning should be carried out on the basis of the specific presentation. Associated medical illness such as an infectious process must always be considered and treated expeditiously. Another essential facet of therapy is directed at modification of the patient's antiparkinsonian maintenance regimen, which may include discontinuation or reduction of levodopa dosage during periods of dyskinesia or increased levodopa administration during clinical "off" periods. Additionally, implementation of other antiparkinson drugs (see the remainder of this chapter), such as dopamine agonists or

COMT inhibitors, may be indicated, depending on the clinical situation. Benzodiazepines and atypical neuroleptics may be helpful in reducing the severity of dyskinesia. In the case of Parkinson disease patients with acute psychosis, all antiparkinsonian medications should be withheld, and benzodiazepines should be administered for agitation [19]. Standard neuroleptics probably should be avoided because of their potential proparkinsonian effects. Consultation with a neurologist is recommended when adjustments are being made to the patient's medications.

Key Points in the Evaluation and Treatment of Antiparkinsonian Drug Toxicity
Levodopa/Carbidopa

1. Clinical toxicity is similar to that of sympathomimetic drugs (see ► [Chap. 41, "Sympathomimetic Agents"](#)), including delirium, dyskinesia, tachycardia, and hypertension.
2. Abrupt withdrawal after long-term administration may result in acute extrapyramidal manifestations.
3. Treatment of acute toxicity is mainly supportive.

Anticholinergic Agents

Anticholinergic medications have been used in the treatment of Parkinson disease dating to the mid-nineteenth century and include trihexyphenidyl (Artane[®]), procyclidine (Kemadrin[®]), biperiden (Akineton[®]), orphenadrine (Disipal[®], Norflex[®]), and benztropine (Cogentin[®]). The use of anticholinergic drugs in Parkinson patients is directed at the imbalance between cholinergic and dopaminergic tone in their basal ganglia and is supported by their clinical efficacy. The anticholinergic agents employed are competitive antagonists at cholinergic muscarinic receptors throughout the body [24] and, in some cases, are inhibitors of dopamine reuptake, potentially exerting a dual action in restoring CNS neurotransmitter balance. The

actual mechanism of action of anticholinergic medications in Parkinson disease is uncertain, however [2].

Pharmacokinetics

In general, anticholinergic antiparkinsonian medications are well absorbed from the gastrointestinal tract, with peak plasma concentrations reached within 1–3 h [9]. A paucity of published data exists regarding the distribution and metabolism of these drugs. Trihexyphenidyl seems to follow a two-compartment model after ingestion with first-order terminal elimination kinetics [9]. Procyclidine may undergo "some first-pass metabolism, presumably in the liver, based on estimates of oral bioavailability." [9] Biperiden is eliminated via hepatic metabolism "with no unchanged drug being excreted in the urine" [9].

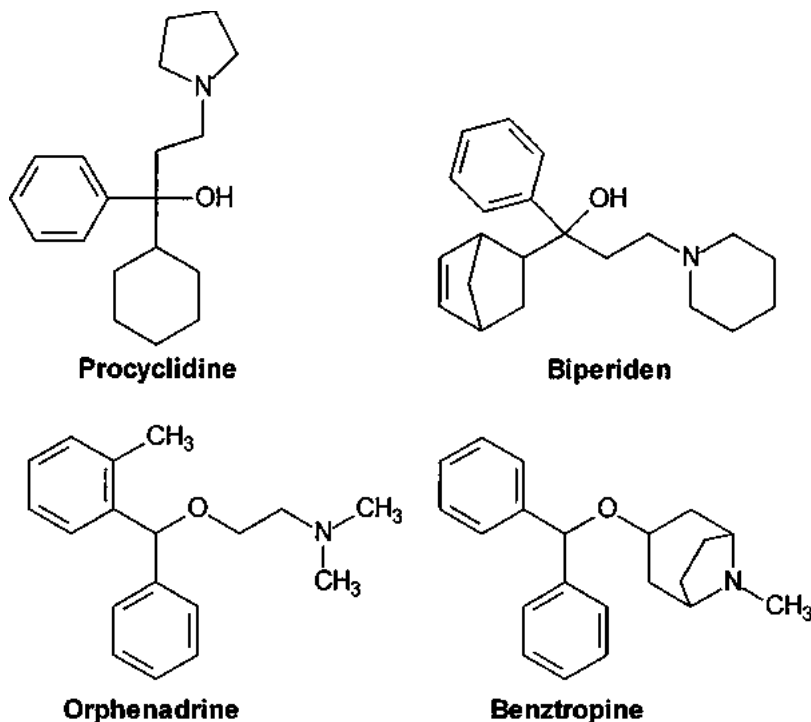
Some anticholinergic medications, such as benztropine and orphenadrine (Fig. 6), are structurally similar to the antihistamine diphenhydramine. Orphenadrine is the *O*-methyl analogue of diphenhydramine, allowing for prediction of additional toxicities (e.g., sodium channel blockade at high doses) based on shared structure–activity relationships [9].

Clinical Presentation

Adverse Effects

Adverse effects of anticholinergic medications are encountered commonly by patients and frequently limit their utility in clinical practice. This situation is particularly true in elderly patients, in whom side effects may be pronounced because of a myriad of concomitant physiologic perturbations (such as the presence of dementia or autonomic insufficiency) and other prescribed medications. Central anticholinergic effects include confusion, memory difficulty, sedation, and hallucinations. Peripheral effects secondary to muscarinic inhibition include dry mouth/mucous membranes, constipation, urinary retention, precipitation of glaucoma, blurry vision, anhidrosis, and tachycardia [2, 24].

Fig. 6 Chemical structures of procyclidine, biperiden, orphenadrine, and benztropine



With the exception of the potential effects of anticholinergic drug-induced gastrointestinal dysmotility on absorption of other drugs, pharmacokinetic drug–drug interactions generally are not clinically relevant to their use in Parkinson patients. There are innumerable prescription and over-the-counter medications, however, that possess anticholinergic properties, adding to the adverse pharmacodynamic effects of these agents.

Overdose and Toxicity

Intentional overdose and abuse of anticholinergic agents used to treat Parkinson disease commonly are described in the medical literature. Drugs such as benztropine and trihexyphenidyl are abused for their hallucinogenic and euphoric effects [25].

The clinical presentation of anticholinergic toxicity results from blockade of central and peripheral muscarinic cholinergic receptors [25, 26]. Confusion, hallucinations, incoherent speech, and agitation are hallmark central effects of anticholinergic drugs. The peripheral effects include hyperthermia, tachycardia, dry axillae, decreased bowel sounds,

and urinary retention [25, 27]. In addition, the antihistaminic properties of benztropine and orphenadrine may cause lethargy and sedation. Benztropine-induced dystonic and dyskinetic reactions, similar to those of antipsychotics, also have been reported [28]. The anticholinergic syndrome is described in detail in the chapter on that syndrome.

Special mention is warranted regarding orphenadrine poisoning. In addition to its antihistamine and anticholinergic properties, orphenadrine has relatively potent sodium channel-blocking effects on the cardiovascular system, with significant potential in overdose for producing cardiac conduction disturbances, depressed myocardial contractility, hypotension, and ventricular dysrhythmias [29, 30].

Diagnosis

The diagnosis of anticholinergic syndrome is based on a thorough history and careful physical examination, focusing on features that may

distinguish acute antimuscarinic effects from features reflecting the presence of other toxidromes, particularly hyperadrenergic states. In the case of acute overdose, measurement of serum electrolytes and acetaminophen/salicylate concentrations is generally considered appropriate. Under some circumstances, additional diagnostic tests aimed at searching for coingestants may be indicated (see ► [Chap. 2, “The Diagnostic Process in Medical Toxicology”](#)). An ECG should be performed to assess cardiac rhythm and the presence of significant interval (e.g., QRS or QTc) prolongation, especially when dealing with orphenadrine poisoning.

Serum benztropine concentrations, although not readily obtainable in most clinical care settings, may be helpful in patients poisoned with this medication. Fahy and colleagues [27] reported following serial benztropine concentrations in a 38-year-old man who ingested a vial of 1-mg benztropine tablets; levels peaked at 100 µg/L (325 µmol/mL), and anticholinergic symptoms persisted until the serum concentration reached 9 µg/L (29 µmol/mL). A specific laboratory approach to anticholinergic poisoning may not only aid in the diagnosis of uncertain clinical presentations but also provide prognostic value.

Treatment

The chapter on the anticholinergic syndrome discusses the treatment of that syndrome in detail. In general, meticulous supportive care, including maintenance of an airway, supplemental oxygen, intravenous fluids to correct intravascular volume deficits, cardiac monitoring, and bladder catheterization, is indicated in most patients with anticholinergic syndrome [24, 31]. Particular attention should be focused on the detection of rhabdomyolysis secondary to agitation and impaired thermoregulation [27].

Decontamination with activated charcoal historically has been considered helpful because some anticholinergic medications, such as benztropine, undergo enterohepatic metabolism

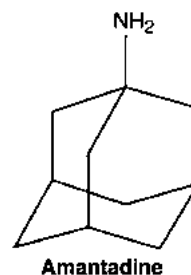
and recirculation [24]. It is unknown, however, whether activated charcoal effectively absorbs benztropine [27]. Furthermore, activated charcoal has not been demonstrated to alter the clinical course or outcome of poisoned patients.

Physostigmine, a reversible inhibitor of central and peripheral cholinesterase activity, increases acetylcholine concentrations at nicotinic and muscarinic synapses [31, 33]. This drug has been used not only as an aid in the diagnosis of anticholinergic syndrome but also in the control of its severe neuropsychiatric manifestations. Although most cases of anticholinergic syndrome can be treated successfully with supportive care alone, closely monitored, conservative administration of physostigmine may be beneficial in controlling severe anticholinergic agitation or convulsions or both [34]. Adverse effects of physostigmine include bronchospasm, seizures, and severe cardiac conduction abnormalities. The clinical pharmacology of physostigmine is discussed in the chapter in the Antidote section devoted to this agent.

Amantadine

Amantadine (Fig. 7) is an antiviral drug that, by fortuitous discovery, was found to possess antiparkinsonian efficacy. The mechanism of action of amantadine is unclear, but many actions have been suggested, including stimulation of catecholamine release, dopamine reuptake blockade, dopamine receptor stimulation, muscarinic antagonism, and *N*-methyl-D-aspartate (NMDA) receptor antagonism [11]. In clinical studies, amantadine administration has been found to alleviate bradykinesia, rigidity, and tremor in Parkinson patients [2].

Fig. 7 Chemical structure of amantadine



Pharmacokinetics

Amantadine is well absorbed after oral administration [32]. The volume of distribution of amantadine is large, with estimates ranging from 6 to 10 L/kg, and it is believed to be highly protein-bound [9]. It is not significantly metabolized and is excreted unchanged in the urine through glomerular filtration and tubular secretion [9]. The plasma elimination half-life is approximately 12–18 h in healthy adults. The half-life can increase twofold, however, in the elderly or in patients with renal insufficiency [9, 32].

Pharmacokinetics of Amantadine (Symmetrel)

Volume of distribution: 6–10 L/kg

Protein binding: 0.67%

Metabolites: unchanged

Plasma elimination half-life: 12–18 h

Clinical Presentation

Adverse Effects

The most common adverse effects experienced in patients taking amantadine are confusion, insomnia, hallucinations, and nightmares. Less-troublesome side effects include ankle edema and livedo reticularis, which generally are well tolerated and do not limit treatment. Additionally and importantly, there may be acute worsening of Parkinson disease when amantadine is withdrawn abruptly [2]. The adverse effects of long-term amantadine therapy may be exacerbated by coadministration of anticholinergics or drugs that reduce its renal clearance, such as hydrochlorothiazide/triamterene [32].

Overdose and Toxicity

The toxic effects of amantadine overdose principally involve the CNS and cardiovascular system. Patients typically present with agitation, psychosis, and restlessness, in addition to the other central and peripheral signs of anticholinergic poisoning (see ► Chap. 23, “Anticholinergic

Syndrome”) [33]. Amantadine-induced coma has been reported [34]. Claudet et al. [35] also reported a case of status epilepticus associated with overdose of this agent.

Cardiovascular effects of amantadine toxicity include hypotension, bradycardia, cardiac conduction defects, QTc prolongation, and malignant ventricular dysrhythmias including torsades de pointes [36]. These findings may be explained by amantadine’s tricyclic amine structure and similarity to cardiotoxic cyclic antidepressants [37, 38].

Diagnosis

Patients presenting with amantadine poisoning should be evaluated with routine laboratory tests and diagnostic studies previously mentioned for other antiparkinson medications. Patients should be placed on a cardiac monitor and an ECG obtained to detect the initial presence or later development of significant QRS widening, QTc prolongation, or dysrhythmia.

Serum amantadine concentrations have a confirmatory role in establishing the diagnosis of amantadine poisoning. Plasma concentrations greater than 1000 ng/mL (>6.6 nmol/mL) have been associated with CNS toxicity. The generally accepted therapeutic upper limit for this value is 300 ng/mL (2.0 nmol/mL) [32, 39].

Treatment

Treatment of amantadine poisoning consists mainly of supportive care. Intravascular volume replacement should be initiated and maintained at a rate that supports adequate urine output. Amantadine-induced ventricular dysrhythmias should be managed pharmacologically, first with lidocaine in standard treatment doses; class IA antidysrhythmics should be avoided because of their potential for exacerbation of cardiac conduction and repolarization abnormalities [37]. The management of torsades de pointes, discussed in ► Chap. 22, “Toxicant-Induced Torsade de Pointes,” is managed best with

defibrillation and subsequent parenteral magnesium sulfate or overdrive pacing. The onset of amantadine-induced cardiotoxicity may be delayed for 48 h after ingestion; it is recommended that symptomatic patients undergo extended cardiac monitoring [37].

Indications for ICU Admission in Antiparkinsonian Drug Toxicity

Amantadine

*Same as anticholinergic agents (see ► Chap. 23, “Anticholinergic Syndrome”)
Cardiac dysrhythmia (especially QTc prolongation, torsades de pointes)*

Administration of oral activated charcoal may reduce systemic absorption of amantadine if given within the first few hours after ingestion. Multiple-dose activated charcoal treatment has been described anecdotally for amantadine toxicity 24 h after ingestion [40]; however, it has not been subjected to further study in this setting and carries the risks associated with its use in anticholinergic poisoning (see ► Chaps. 3, “Therapeutic Approach to the Critically Poisoned Patient” and “► 23, Anticholinergic Syndrome”). Routine use of oral activated charcoal is not recommended.

Physostigmine has been used successfully for control of severe amantadine-induced agitation [41]. The use of physostigmine may lead to cholinergic crisis, however. Because physostigmine has been associated with asystolic arrest in cyclic antidepressant overdose, it should be avoided when significant cardiac conduction disturbance is evident [40]. A benzodiazepine, such as diazepam or lorazepam, would be the initial anticonvulsant of choice for amantadine-induced seizures.

Key Points in the Evaluation and Treatment of Antiparkinsonian Drug Toxicity

Amantadine

1. Major clinical manifestations of toxicity are anticholinergic syndrome, cardiac conduction disorder (e.g., QTc

prolongation), and ventricular dysrhythmia (e.g., torsades de pointes).

2. Administration of classes IA, IC, and III antidysrhythmic drugs should be avoided.

Selegiline

Monoamine oxidase is responsible for the central (intraneuronal) and peripheral (intestinal and hepatic) degradation of dopamine (Fig. 8). The enzyme exists in two forms, A and B, and is found in the CNS and in peripheral tissue [42]. MAO A activity is found predominantly in the liver and intestine, and MAO B activity is found mainly in the brain, liver, and platelets [43]. Irreversible and selective inhibition of MAO B by selegiline (Fig. 9) increases the duration of action of levodopa in Parkinson patients and may increase the “on” time in advanced cases [2]. This action also may reduce levodopa dosing requirements [2]. Selective MAO B inhibition occurs at therapeutic doses (10 mg/day), but selectivity may be lost at higher doses [15]. Selegiline also is used as a potentially neuroprotective agent in Parkinson patients based on its ability to block the MAO B-mediated oxidation of certain substrates (e.g., MPTP) to neurotoxic free radical species (e.g., MPP⁺) (Fig. 10; see Fig. 1) [2]. It has been speculated that administration of selegiline may retard striatal degeneration in Parkinson disease by inhibiting the formation of oxygen free radicals during CNS dopamine metabolism [2].

Pharmacokinetics

Selegiline is absorbed rapidly after oral administration and attains peak serum concentration within 0.5–2 h [42]. Selegiline has a volume of distribution of approximately 1.9 L/kg and exhibits an elimination half-life of approximately 2 h [44]. The drug’s major metabolites, L-methamphetamine and L-amphetamine, have longer half-lives of 29.5 and 17.7 h, respectively [45].

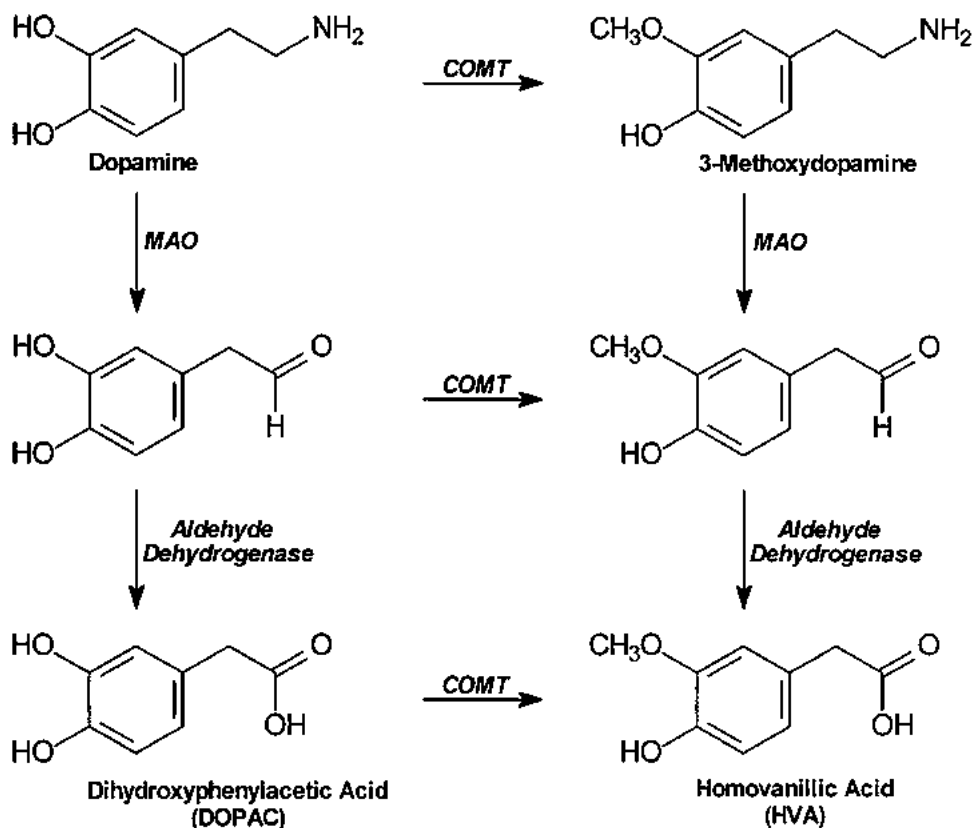


Fig. 8 The main pathways for dopamine metabolism in the brain. *COMT* catechol-*O*-methyltransferase, *MAO* monoamine oxidase

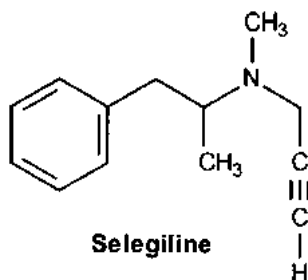


Fig. 9 Chemical structure of selegiline

Pharmacokinetics of Selegiline (Eldepryl)

Volume of distribution: 1.9 L/kg

Protein binding: 94%

Metabolites: L-amphetamine, L-methamphetamine

Plasma elimination half-life: 2 h

Clinical Presentation

Adverse Effects

Adverse effects of selegiline include CNS stimulation, insomnia, hallucinations, nausea, and vomiting. In addition, by inhibiting levodopa breakdown, selegiline may worsen levodopa-induced dyskinesia [45]. Orthostatic hypotension also has been reported with coadministration of selegiline and levodopa in Parkinson patients [46]. Additionally, if taken at higher daily dosages, selegiline may inhibit MAO A and exhibit toxicities similar to those of the less-selective antidepressant MAO inhibitors (see ► Chap. 50, “Monoamine Oxidase Inhibitors”).

Case reports have described significant drug–drug interactions of selective serotonin reuptake inhibitors, tricyclic antidepressants, and

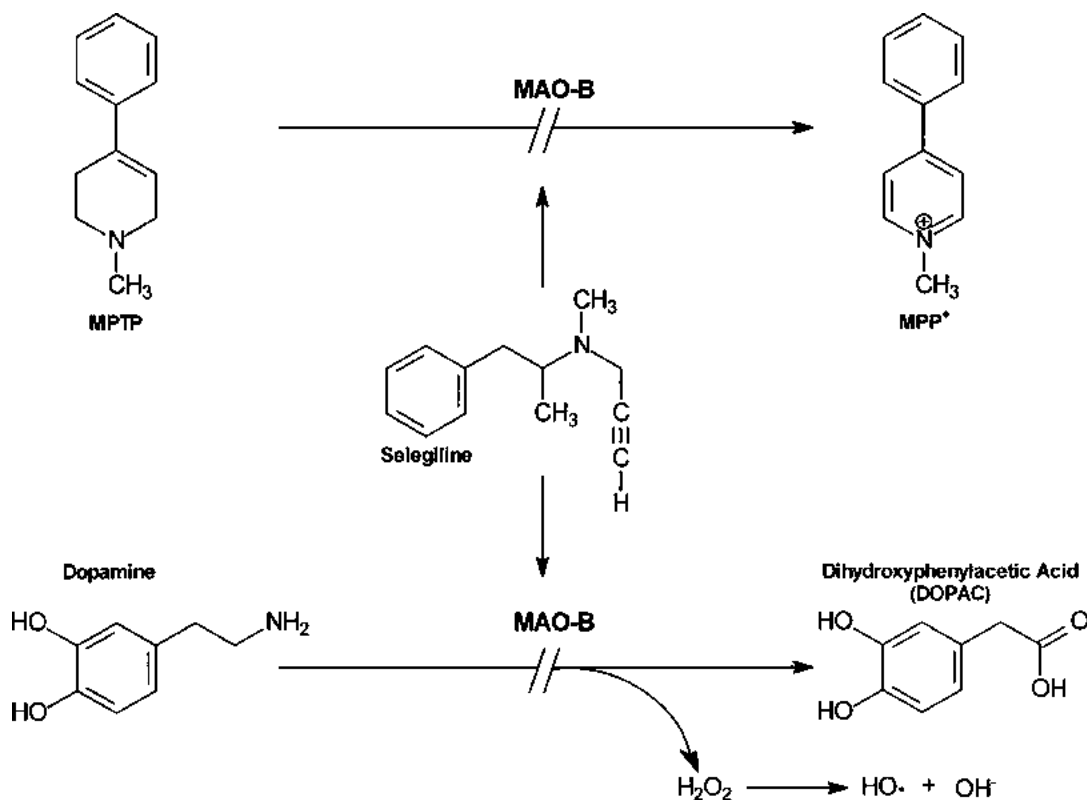


Fig. 10 Mechanism of the potential neuroprotective effect of selegiline on the progressive neurodegeneration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced toxicity and Parkinson disease. Selegiline, an

inhibitor of monoamine oxidase B (MAOB), blocks the formation of the reactive intermediate 1-methyl-4-phenylpyridine (MPP⁺) from MPTP and the formation of hydroxyl free radicals from the oxidation of dopamine

selegiline, causing signs and symptoms resembling serotonin syndrome, which is discussed in more detail in the chapter on that topic. This syndrome results from blockade of serotonin metabolism by MAO and excessive stimulation of brain stem and spinal cord 5-hydroxytryptamine (5-HT_{1A} and 5-HT₂) receptors [47, 48]. This type of clinical presentation has been described with concomitant use of selegiline and meperidine, causing restlessness, agitation, delirium, and hyperthermia [15].

Overdose and Toxicity

An extensive literature review, including multiple case series of MAO inhibitor overdoses, identified one published case of selegiline overdose. It is largely presumed and not supported by published clinical experience that selegiline overdose would

inhibit MAO A and MAO B and produce a syndrome clinically similar to that of an antidepressant MAO inhibitor overdose. Toxicity from MAO inhibitors is discussed in more detail in ► [Chap. 50, "Monoamine Oxidase Inhibitors"](#). Fujita et al. [49] described a case of a patient with reported selegiline overdose who developed hyperthermia and recovered with supportive care alone. Extensive quantitative analyses of L-amphetamine metabolites were performed; however, selegiline concentrations were not specifically measured.

Diagnosis and Treatment

Analysis of urine should detect the presence of methamphetamine and amphetamine after selegiline ingestion. So-called chiral assays that

can distinguish the illicit D- from the L-isomeric form associated with selegiline use are commercially available. Appropriate therapeutic interventions for acute MAO inhibitor poisoning and serotonin syndrome are outlined in the chapters dealing with those topics.

Indications for ICU Admission in Antiparkinsonian Drug Toxicity

Selegiline

Hyperthermia
Autonomic instability
Serotonin syndrome
Severe agitation
Delirium
Rhabdomyolysis

Key Points in the Evaluation and Treatment of Antiparkinsonian Drug Toxicity

Selegiline

1. Interactions with other agents (e.g., sympathomimetic compounds, selective serotonin reuptake inhibitors) may result in excess adrenergic or serotonergic tone, clinically manifested as a sympathomimetic toxidrome or serotonin syndrome.
2. Overdose is characterized by toxicity similar to that of other MAO inhibitors (see ► Chap. 50, “Monoamine Oxidase Inhibitors”).
3. Selegiline’s major metabolites, L-methamphetamine and L-amphetamine, can be distinguished readily from the frequently illicit dextrorotatory forms of the same compounds by isomeric (chiral) determination.

Dopamine Agonists

Dopamine receptor agonists used in the treatment of parkinsonism are medications that, because of their dopamine-like molecular structure, directly

stimulate striatal postsynaptic D₂ receptors. They are regarded as some of the most effective drugs to treat Parkinson disease, second only to levodopa [45]. Traditionally, dopamine agonists have been used as adjuncts to levodopa in patients with Parkinson disease. Initiation of dopamine agonists as first-line therapy may postpone the need for levodopa therapy, however, providing overall reduction of the risks of levodopa-induced dyskinesia [2].

There are several advantages of dopamine agonists over levodopa: (1) they do not require conversion to an active metabolite to exert their pharmacologic effect, (2) circulating amino acids do not compete for their absorption and transport to the brain, (3) they have longer half-lives, (4) they do not undergo oxidative metabolism and do not produce potentially damaging oxygen free radicals, (5) they can target specific dopamine receptor subtypes, and (6) they offer a larger therapeutic window with decreased risk of dyskinesia [2]. Several dopamine agonists are currently available, including bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), ropinirole (Requip), cabergoline (Cabaser, Dostinex), and lisuride (Dopergin) [50].

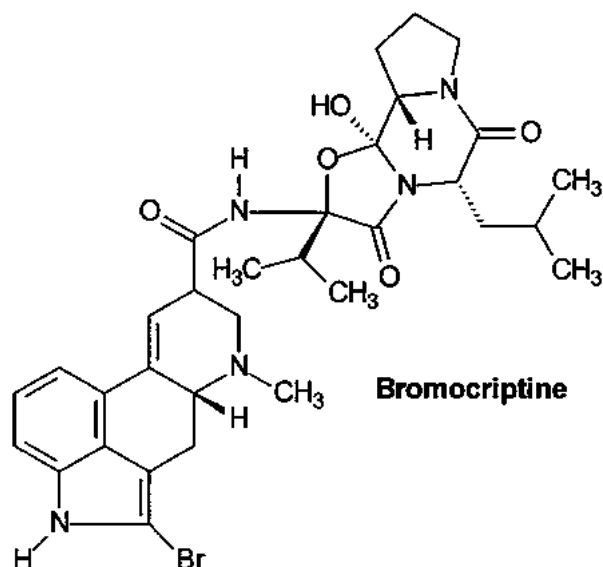
Pharmacokinetics

Bromocriptine (Fig. 11) is a potent D₂ receptor agonist, but it also possesses D₁ and 5-HT₂ agonist properties. It is absorbed rapidly after ingestion, is 90% metabolized by first-pass metabolism, and has a half-life of 3–8 h [50]. Bromocriptine is largely protein-bound and is excreted predominantly in the bile and feces [9].

Pergolide is almost ten times more potent than bromocriptine. It has a high affinity for D₂ receptors but also is a D₁, D₃, and α_2 receptor agonist [50]. Pergolide is well absorbed orally and has a half-life of approximately 3–7 h [10]. It is also 90% protein-bound [50].

Pramipexole binds to D₂ receptors primarily but also possesses affinity for a myriad of other receptors, including D₁, D₃, D₄, α_2 , acetylcholine, and serotonin receptors. Pramipexole has a half-life of

Fig. 11 Chemical structure of bromocriptine



about 8–12 h and is 15% protein-bound. Approximately 10% is metabolized, and the remainder is excreted unchanged in the urine [50].

Ropinirole binds to the D_2 receptor and has relatively insignificant agonist activity on other brain receptors. It is absorbed quickly and completely from the stomach and has an elimination half-life of approximately 6 h. Ropinirole is 40% protein-bound, metabolized by cytochrome P450 1A2 to inactive metabolites, and excreted in the urine [50].

Cabergoline is a D_2 agonist without effect on D_1 receptors. It has an elimination half-life of about 65 h [50].

Lisuride is a D_2 and 5-HT₂ agonist that has no D_1 activity. The onset of action is within 1 h after intravenous or subcutaneous administration. Lisuride exhibits an elimination half-life of approximately 1–7 h. There is no oral form because of minimal gastrointestinal absorption. Lisuride has effects comparable to those of dopa in treating Parkinson disease patients. This drug is available in Europe but not in the United States [50].

Significant drug–drug interactions may occur with the highly protein-bound dopamine agonists bromocriptine and pergolide. Coadministration of other highly protein-bound medications, such as warfarin or erythromycin, may result in elevation of dopamine agonist levels [15].

Pharmacokinetics of Dopamine Agonists

Bromocriptine (Parlodel)

Volume of distribution: 2 L/kg

Protein binding: 93%

Metabolites: –

Plasma elimination half-life: 3–8 h

Pergolide (Permax)

Volume of distribution: not available

Protein binding: >90%

Metabolites: extensive

Plasma elimination half-life: 27 h

Pramipexole (Mirapex)

Volume of distribution: 5.6–9 L/kg

Protein binding: 15%

Metabolites: 10

Plasma elimination half-life: 8–12 h

Ropinirole (Requip)

Volume of distribution: 7.5 L/kg

Protein binding: 40%

Metabolites: extensive

Plasma elimination half-life: 6 h

Cabergoline (Dostinex)

Volume of distribution: not available

Protein binding: 40–42%

Metabolites: extensive

Plasma elimination half-life: 65 h

Clinical Presentation

Adverse Effects and Chronic Toxicity

The side effects from dopamine agonists are similar to those of levodopa, including nausea, vomiting, orthostatic hypotension, hallucinations, psychosis, episodic somnolence (“sleep attacks”), and choreiform dyskinesias [2]. In addition, acute vasospastic crises (e.g., resulting in cerebral, coronary, or mesenteric ischemia), erythromelalgia, Raynaud’s phenomenon, and retroperitoneal and pulmonary fibrosis have been reported with the ergot dopamine agonists (e.g., bromocriptine) but are uncommon with the newer nonergot medications [2]. Serotonin syndrome theoretically may occur as a result of dopaminergic-mediated increase in serotonin release.

Overdose and Acute Toxicity

Most reported cases of dopamine agonist overdose involve bromocriptine. Taken in overdose, bromocriptine typically produces nausea, vomiting, hypotension, lethargy, paranoia, aggressive behavior, and hallucinations. The neuropsychiatric manifestations most likely can be explained by the fact that bromocriptine is a lysergic acid derivative, similar to LSD [51–53].

In a case report, a 17-month-old toddler who ingested her grandfather’s pramipexole exhibited lethargy, which resolved within 24 h [54]. Case reports of adult overdose printed in the manufacturer’s package insert describe ataxia, drowsiness, tachycardia, and vomiting, which all spontaneously resolved [54].

Diagnosis and Treatment

Indications for ICU Admission in Antiparkinsonian Drug Toxicity Dopamine Agonists

Uncontrolled agitation and delirium
Hypotension

Plasma bromocriptine concentrations vary widely among individuals on the same dose and do

not seem to correlate with clinical response or toxicity. Treatment of acute dopamine agonist overdose is largely supportive.

Key Points in the Evaluation and Treatment of Antiparkinsonian Drug Toxicity Dopamine Agonists

1. The presentation and treatment of acute and chronic bromocriptine toxicity are similar to that of other ergot alkaloids and include delirium, hallucinations, vasospastic crisis, and retroperitoneal/pulmonary fibrosis.

Catechol-O-Methyltransferase Inhibitors

Because levodopa is metabolized in the periphery by COMT to the inactive metabolite 3-OMD, the addition of the reversible COMT inhibitors tolcapone (Tasmar[®]) or entacapone (Comtan[®]) to Parkinson disease treatment regimens has provided effective adjuncts to levodopa therapy [2]. These medications also decrease formation of 3-OMD, which, at least theoretically, competes with levodopa for transport to the brain [2].

Pharmacokinetics

Tolcapone is absorbed rapidly from the gastrointestinal tract, with an elimination half-life of 2–3 h, and is >99.9% protein-bound. It is metabolized nearly completely by the liver with little parent drug excreted in the urine [55]. Interaction between tolcapone and other highly protein-bound medications has not been definitively demonstrated.

Entacapone is readily absorbed and is predominantly protein-bound (98%). The drug is also nearly completely hepatically metabolized, and small amounts of unchanged drug are found in the urine [56]. Similar to tolcapone, no significant interactions have been shown between entacapone and other protein-bound medications.

Catechol-O-Methyltransferase Inhibitors**Tolcapone (Tasmar)**

Volume of distribution: 0.10–0.14 L/kg

Protein binding: 99.9%

Metabolites: 3-*O*-methyl-tolcapone (>90%)

Plasma elimination half-life: 2–3 h

Entacapone (Comtan)

Volume of distribution: 0.24–0.56 L/kg

Protein binding: 98%

Metabolites: entacapone glucuronide (>90%)

Plasma elimination half-life: 0.4–0.7 h

Clinical Presentation**Adverse Effects**

Side effects of the COMT inhibitors are similar to those of levodopa and are related to increased levodopa availability. Severe and explosive diarrhea has been reported in approximately 5–10% of patients at therapeutic doses [2]. Harmless discoloration of urine also may occur. One potentially significant adverse effect of tolcapone is hepatotoxicity, an idiosyncratic effect found to occur in approximately 1–3% of patients taking this drug [2, 57]. The mechanism of liver injury seems to involve mitochondrial dysfunction [58]. Four cases of fulminant liver failure have been reported secondary to tolcapone, and, as a result, a “black box” warning has been issued in regard to this medication in the United States. Tolcapone is not available in Europe or Canada but can be obtained in the United States. Entacapone has not been associated with liver dysfunction [2].

Overdose and Toxicity

There are no reported human cases of overdose with either tolcapone or entacapone. Studies performed on healthy individuals taking larger-than-recommended daily amounts of both drugs resulted in minor symptoms that readily resolved on discontinuation of the medication. Theoretically, coadministration of a COMT inhibitor and

MAO inhibitor could result in central and peripheral catecholamine excess, presenting clinically as a sympathomimetic poisoning syndrome.

Diagnosis and Treatment**Indications for ICU Admission****in Antiparkinsonian Drug Toxicity****Catechol-O-methyltransferase inhibitors**

For signs of sympathomimetic toxicity, see ► Chap. 25, “Sympathomimetic Syndrome”.

No specific diagnostic tests are indicated in the setting of COMT inhibitor overdose. The emphasis of treatment should be on supportive care.

Key Points in the Evaluation and Treatment of Antiparkinsonian Drug Toxicity**COMT Inhibitors**

1. Chronic, dose-related adverse effects of COMT inhibitor treatment are similar to those of levodopa.
2. Hepatic toxicity is associated with tolcapone use.
3. Toxic interactions between COMT and MAO inhibitors are likely.

COMT, catechol-*O*-methyltransferase;
MAO, monoamine oxidase

Neuroprotective Agents

A broad variety of medications are aimed at protecting or preserving healthy striatal neurons in patients with Parkinson disease. These neuroprotective agents include free radical scavengers, iron chelators (e.g., deferoxamine), nitric oxide synthesis inhibitors, calcium channel blockers, anti-inflammatories, steroids, trophic factors, and antiapoptotic medicines. Many of

these agents, such as calcium channel blockers and deferoxamine, are discussed elsewhere in this text.

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In the central nervous system, γ -aminobutyric acid (GABA) is the main inhibitory neurotransmitter. Three major GABA receptors – GABA_A, GABA_B, and GABA_C – have been identified. Baclofen (β -(4-chlorophenyl)- γ -aminobutyric acid) is a GABA agonist, specific to GABA_B at therapeutic doses, that has been used to treat spasticity of various etiologies (e.g., multiple sclerosis, paraplegia, quadriplegia, cerebral palsy). It has also been used off-label for dystonia, jerking, restless legs, chorea, stiff-person syndrome, torticollis, tetanus, hiccups, trigeminal neuralgia, cluster headaches, and musculoskeletal pain; with more recent investigations for the management of rumination, supragastric belching, and gastroesophageal reflux; alcohol, opioid, and cocaine abuse disorders; bladder spasm; and in combined use with antimuscarinic agents for overactive bladder [1–28].

Recently, elevated doses of baclofen (up to 300 mg/day) were prescribed to treat craving in alcoholic patients, following the self-experience reported by a French physician [29]. This protocol is based on animal studies showing that, in contrast to other therapies, increasing doses of baclofen are able not only to reduce but also to suppress craving in animals chronically intoxicated with ethanol. Several RCTs are ongoing to demonstrate whether these elevated doses are efficient or not. This experience led to the development of severe poisonings due to the huge presumed ingested doses [30–32].

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Biochemistry, Pharmacology, and Pathophysiology

Baclofen is a structural analogue of GABA (Fig. 1) [33].

Pharmacokinetics

Baclofen is absorbed rapidly after oral administration, with a bioavailability of 70–85%. However, its central nervous system penetration is more limited, sometimes requiring relatively large oral doses to achieve therapeutic effects. Oral baclofen has a low therapeutic index, primarily because it is distributed evenly between spinal and supraspinal levels after oral administration. Peak blood concentrations occur 1–3.5 h after therapeutic ingestion; however, after overdose, absorption is prolonged and incomplete. Although signs and symptoms of toxicity can begin shortly after overdose, resolution can be protracted. After intrathecal or oral overdose, it may take days for the patient to become fully alert. Elimination of this moderately lipophilic GABA agonist from nerve and brain tissue is much slower than from serum, explaining the persistence of effects despite undetectable serum baclofen concentrations. Baclofen is excreted primarily by glomerular filtration, and its clearance is proportional to creatinine clearance. Generally, 50–85% of an ingested dose is eliminated unchanged in urine within 72 h. The remaining 15% is deaminated to β -(*p*-chlorophenyl)- γ -hydroxybutyric acid. However, large inter-individual variability has been observed in both elimination

and oral absorption processes [5, 15, 27, 33–50]. In addition, in large ingestions, there may be a delayed rebound in plasma concentration, and this can be associated with recurrence of effect [51–53].

Pharmacokinetics of Baclofen Poisoning

Protein binding: 30–35%

Volume of distribution: 0.8–2.6 L/kg

Serum half-life: 2–8 h (longer after overdose and renal insufficiency)

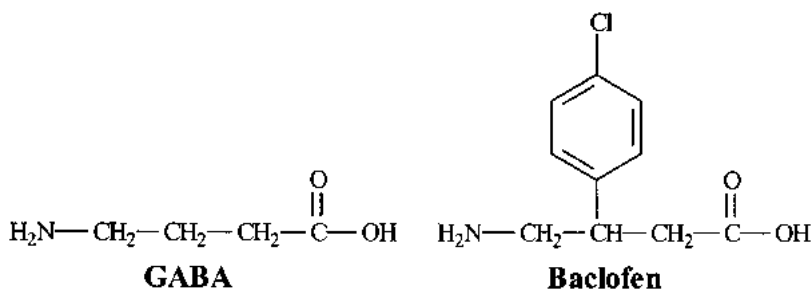
Mechanism of clearance: primarily renal

GABA_B Receptors and the Pathophysiology of Toxic Effects

GABA_B receptors are expressed widely in the brain and the spinal cord, including the cerebral hemispheres, diencephalon, brainstem, and dorsal horn of the spinal cord. The GABA_B receptor comprises two subunits and is coupled to G proteins. Activation of these receptors promotes a decline in calcium conductance and intracellular cyclic adenosine monophosphate production.

Baclofen binds to presynaptic and postsynaptic GABA_B receptors (Fig. 2). Presynaptic receptor binding of GABA or baclofen hyperpolarizes presynaptic terminals by closing calcium channels and decreases neurotransmitter (e.g., catecholamines, glutamate, substance P) vesicle release from excitatory spinal pathways Fig. 2b), producing an inhibitory effect. Presynaptic binding also occurs at GABAergic autoreceptors, hyperpolarizing presynaptic terminals and decreasing

Fig. 1 Chemical structures of γ -aminobutyric acid (GABA) and baclofen. Baclofen is a GABA analogue containing a *para*-chlorophenyl moiety in the β position relative to the carboxylate



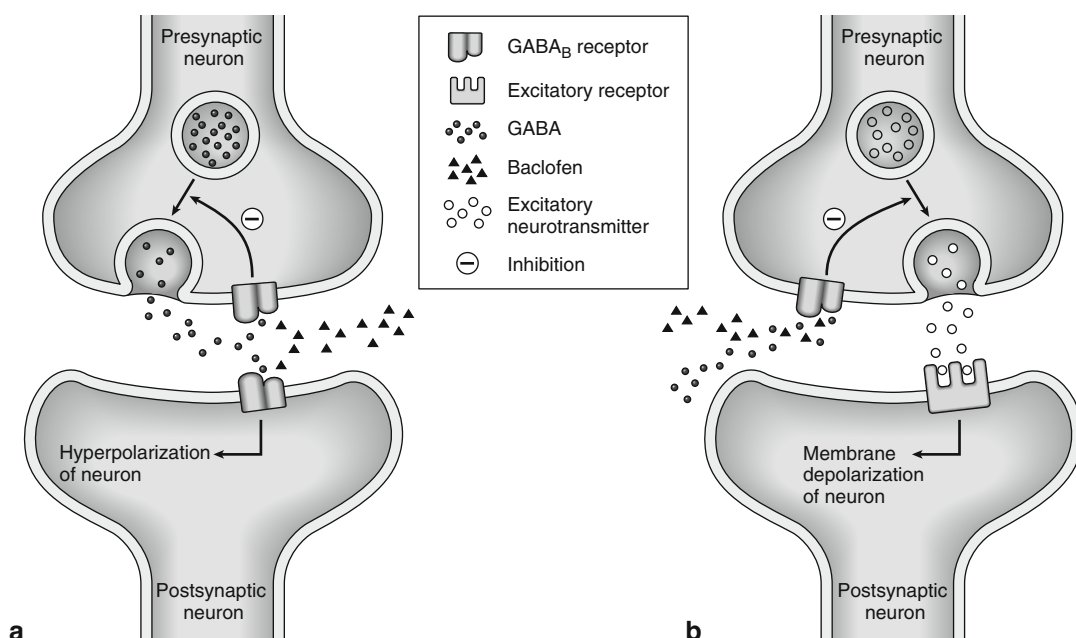


Fig. 2 Binding of γ -aminobutyric acid (GABA) and baclofen to GABA_B receptors. **(a)** GABA is released from presynaptic GABAergic neurons and may bind to GABA_B receptors on postsynaptic neurons, resulting in hyperpolarization of postsynaptic neurons. This has an inhibitory effect on the nervous system. GABA released from presynaptic GABAergic neurons also acts at GABA_B receptors on the presynaptic neurons, resulting in

decreased release of GABA from the neuron or autoregulation. This has an excitatory effect. **(b)** GABA_B receptors also are located on presynaptic neurons that release excitatory neurotransmitters. When GABA binds to these receptors, the release of excitatory neurotransmitters is diminished. This has an inhibitory effect. Baclofen can bind at all of these GABA_B receptors and produces an effect similar to that of GABA binding

GABA release (Fig. 2a), producing an excitatory effect. Postsynaptic binding to the GABA_B receptor hyperpolarizes the neuron via two separate actions, opening slow potassium channels and inhibiting dendritic calcium influx channels, and results in inhibition by creating a net negative membrane potential (see Fig. 2a). Inhibitory and excitatory effects may occur with the binding of baclofen to GABA_B receptors. Generally, when used therapeutically, the inhibitory effects prevail. The dual inhibitory and excitatory actions provide an explanation for the significant overlap of clinical manifestations (e.g., seizures) seen with overdose and withdrawal from baclofen.

Baclofen depresses γ and α motor neurons and inhibits monosynaptic extensor and polysynaptic flexor spinal reflexes. This activity accounts for the decreased muscle tone and the efficacy of

baclofen in treating spasticity. Baclofen affects afferent depolarization in the dorsal horn of the spinal cord and modulates nociceptive input from primary afferent fibers to neurons of the spinothalamic tract. This effect, along with the inhibition of substance P release, accounts for the efficacy of baclofen in the treatment of pain. Central and peripheral GABA receptors also are known to play a role in regulation of body temperature; this may account for the hypothermia generally seen after overdose and the hyperthermia generally seen in withdrawal from baclofen. Central nervous system depression secondary to baclofen may be attributed to stimulation of GABA_B receptors in the hippocampus, whereas respiratory and cardiovascular depression may result from stimulation of GABA_B receptors in the brainstem [6, 28, 33, 47, 54–62].

Clinical Presentation

Routes of Exposure

Oral

Acute ingestions of 300–970 mg in adults can be expected to produce serious intoxications, and doses of 1250–2500 mg have been fatal in adults [27]. Additionally, a retrospective database review of 23 cases of baclofen poisoning demonstrated baclofen ingestions of 200 mg or greater were predictive of more severe clinical manifestations and prolonged hospital stay than ingestions less than 200 mg [63]. Baclofen abuse has been reported in persons with a history of substance abuse and in adolescents seeking intoxication [64–66].

Intrathecal

Intrathecal administration is accomplished by a pump with a reservoir that is implanted surgically in the subcutaneous tissue of the abdominal wall. A catheter is threaded into the intrathecal space, allowing direct delivery into the cerebrospinal fluid. Complications include mechanical problems (dislodgement, disconnection, kinking, blockage), pump failure, and infection [33, 67–85]. In an 8-year study of 30 patients, the overall incidence of pump complications was 62%. The most frequent complication was catheter disconnection, followed by retraction of the intrathecal catheter [81]. Borrini and colleagues [70] attempted to assess the frequency and characterize complications related to intrathecal baclofen pump therapy in a cohort of 158 adult patients who were implanted before and during 2010. During 1 year of follow-up, the rate of adverse events was 0.023 per month, with 29% of cases related to the device and predominantly involving catheter dysfunctions [70]. Also, in a multicenter Japanese study of 400 patients with intrathecal baclofen pumps, catheter problems (migration, obstruction, kinking, and dislodgement) were observed in 8.5% of patients, pump malfunction in 1.8% of patients, and device-related and surgical wound infections in 3% of patients [86]. A study of 100 children and young adults demonstrated more frequent device-related complications in

those implanted with pumps with catheter access ports [78]. Separate from mechanical complications, intrathecal overdose has been reported in continuous infusion and after bolus injection [46, 56, 61, 87, 88].

Other Routes

Baclofen has also been used in topical formulations for the treatment of neuropathic pain; trialed in intravesical administration for bladder spasm; and proposed for subcutaneous, intravenous, and intraventricular delivery [17, 25, 35, 89, 90].

Clinical Manifestations of Baclofen Poisoning

Lee and colleagues [58] attempted to differentiate between acute and chronic baclofen poisonings, suggesting that acutely poisoned patients are more likely to present with encephalopathy (disturbances of consciousness or seizure or both), respiratory depression, muscular hypotonia, and generalized hyporeflexia. Chronically poisoned patients are more likely to present with hallucinosis, impaired memory, catatonia, or acute mania [58]. The same authors also noted that the acute intoxication syndrome has a faster onset, a shorter duration, more severe clinical manifestations, and a higher incidence of seizures compared with the chronic intoxication syndrome [58]. However, there is significant overlap in the clinical presentations of acute and chronic toxicity, as well as with the presentation of withdrawal, as discussed later.

Acute and Life Threatening Presentations

Neurologic. Headache, dizziness, incoordination, ataxia, myoclonus, fatigue, weakness, areflexia, flaccid extremities, encephalopathy, coma, and seizures, including status epilepticus, may occur [5, 27, 46, 47, 50, 56, 58, 61–66, 75, 88, 91–99]. The clinician needs to be aware of the risk of nonconvulsive (akinetic) status epilepticus [64, 97, 100]. Although baclofen has antiepileptic properties at low concentrations, it is proepileptic at high concentrations [56, 61, 96, 101]. Delayed psychosis and confusion with hallucinations have

been reported during the recovery phase [56, 63, 65, 95].

Pulmonary. Respiratory depression and failure may occur [5, 27, 46, 50, 56, 65, 75, 87, 91, 92, 95, 98, 102–105].

Cardiovascular. Hypertension or hypotension and tachycardia or bradycardia may occur. Tachycardia may alternate abruptly with bradycardia. Conduction abnormalities (including prolonged QT_c and first-degree heart block), premature atrial and ventricular contractions, supraventricular tachycardia, atrial flutter, and atrial fibrillation have been reported [5, 27, 46, 50, 56, 63, 65, 66, 75, 88, 95, 97–99, 103, 104].

Gastrointestinal. Nausea and vomiting may occur [5, 66, 91, 99, 103].

Ocular. Blurred vision, horizontal or vertical nystagmus, unreactive pupils, absent corneal reflexes, and absent doll's eye reflexes may occur. Pupils may be small or large [27, 50, 56, 58, 61, 63, 66, 92, 95–97, 103, 104].

Other. Hypothermia and hypersalivation may occur [27, 58, 66, 88, 97, 103]. Hyperthermia is reported rarely [58, 99] and is more likely to occur in baclofen withdrawal.

Chronic Intoxication

Toxicity can occur gradually after long-term intrathecal or oral dosing, especially in patients with concomitant renal insufficiency. Chronic intoxication may present with impaired memory, acute mania or catatonia, and hallucinosis; this has been called *chronic baclofen intoxication syndrome* [27, 58, 97]. Respiratory depression, apnea, bradycardia, tachycardia, hypotension, hypertension, tremor, weakness, hypotonia, areflexia, urinary retention, sedation, coma, seizures, orofacial dyskinesia, and hypothermia also have been reported as manifestations of chronic baclofen toxicity [15, 43, 48, 58].

Side Effects with Long-Term Use

Nausea, lightheadedness, vertigo, fatigue, drowsiness, confusion, and lethargy may occur as side effects of oral baclofen, owing to the narrow therapeutic margin [5, 48, 58, 61]. Occasionally, hypotension also is seen [48]. Other pharmacological complications of chronic baclofen use, particularly intrathecal use, have also been reported and

include: hypotonia, sexual dysfunction in males, constipation, and drug tolerance [106, 107].

Coma and the Diagnosis of Brain Death

Deep coma and brainstem dysfunction may mimic brain death in patients with severe baclofen poisoning. Despite these findings, patients with baclofen poisoning may survive neurologically intact if aggressive supportive care is provided. The diagnosis of brain death should be made extremely cautiously in patients with suspected baclofen toxicity. The American Academy of Neurology practice standards require the documentation of a proximate and irreversible neurologic injury prior to initiation of the brain death examination [108]. Several days of intensive care, serial neurologic examinations, and imaging studies to demonstrate irreversible brain injury should be pursued before pronouncing brain death in these patients [95]. Recovery has been reported after 5–7 days of coma [109]. A more detailed discussion of brain death determinations in this setting can be found in ► Chap. 13, “Poisoning Fatalities”.

Clinical Manifestations of Baclofen Withdrawal

Baclofen withdrawal may occur after diminished or discontinued oral administration or more commonly after intrathecal pump malfunction [5, 68, 76, 79, 82, 83, 110–113]. Withdrawal may occur shortly after recovery from baclofen toxicity when baclofen treatment is not reinitiated promptly in the long-term use [50, 104]. The withdrawal syndrome occurs within 12–96 h after cessation of use, and symptoms generally resolve within 24–72 h of resumption of treatment, although some improvement may be seen sooner [50, 72, 114].

Respiratory distress, tachypnea, hypotension or hypertension, bradycardia or tachycardia, dysrhythmias, heart block, sleeplessness, agitation, shaking, coma, areflexia, diplopia, dyskinesia, visual disturbances, loss of pupillary light and oculocephalic reflexes, hyperthermia, diaphoresis, and hypersalivation have been reported [5, 50, 57, 61, 67, 68, 71, 79, 83, 104, 110–112,

114–119]. Rhabdomyolysis, disseminated intravascular coagulation, renal failure, hepatic failure, cerebral ischemia, and brain death may ensue [57, 82, 115, 117, 119]. Elevations in liver transaminase, creatinine, creatine phosphokinase, white blood cell count, and prothrombin time levels have been reported [57, 113, 115]. Acidosis may occur [115]. Cases of reversible cardiomyopathies in the setting of baclofen withdrawal have also been reported [120, 121]. There is significant overlap in the clinical presentation of overdose and withdrawal (e.g., autonomic instability, coma, seizures, laboratory abnormalities), and differentiating between the two entities may be difficult [50]. One helpful clue is that spasticity and muscle spasms (likely to some degree an unmasking of an underlying condition) and hyperthermia are seen more commonly with withdrawal, whereas hypothermia and hypotonia is seen more commonly with overdose.

Baclofen withdrawal syndrome may appear clinically similar to benzodiazepine or ethanol withdrawal, serotonin syndrome, sympathomimetic syndrome, neuroleptic malignant syndrome, infection, other febrile illnesses, or multiorgan system dysfunction of other etiology [21, 57, 72, 113, 117, 119, 122, 123]. Infection of the pump pocket, meningitis, and sepsis must be considered in patients receiving intrathecal baclofen [57, 81, 83, 122]. Modern pumps have bacterial filters that generally prevent overwhelming intrathecal infection; however, infection still may occur [77, 81, 85]. Pump function can be assessed using computer program systems and by aspirating and measuring the amount of drug remaining in the system [57, 81, 119]. These maneuvers may help differentiate among withdrawal, toxicity, and infection [119].

Diagnosis

Laboratory Studies

Baclofen can be detected by gas chromatography–mass spectrometry and high-performance liquid chromatography [43, 45, 48, 64, 66, 93].

Plasma, rather than cerebrospinal fluid, concentrations generally are assessed [43]. In nonfatal overdose, plasma or serum concentrations of 0.5–15 mg/L have been reported [124]. In a single fatal overdose, the serum concentration was 17 mg/L [41]. Other laboratory abnormalities in poisoning may include elevated creatine phosphokinase, lactate dehydrogenase, glutamic oxaloacetic transaminase, alkaline phosphatase, amylase, blood glucose, and white blood cell count [45, 58, 97]. Analysis of cerebrospinal fluid should be considered to rule out other disease processes (e.g., meningoencephalitis).

Imaging Studies

Intrathecal pump systems are radiopaque. Radiographs may show loss of catheter integrity [76, 117, 119]. Imaging of the brain and spinal cord should be considered to rule out other disease processes (e.g., hemorrhage or infarction). Brain imaging is of particular importance when seizure occurs with focal-onset features.

Special Studies

Electroencephalography often reveals reversible abnormalities. Typical electroencephalography findings are diffuse slowing of background activity and burst suppression [56, 58, 61, 66, 94]. In more severe cases, periodic delta and triphasic waves and generalized epileptiform discharges suggestive of seizures are seen [47, 56, 58, 73, 94, 96]. Although some patients with severe baclofen toxicity may appear severely neurologically impaired by clinical and electroencephalography findings, these patients frequently recover fully with adequate supportive care.

Treatment

Generally, patients do well with aggressive supportive care. Fatalities have occurred, however, despite medical care [9, 45, 65]. Respiratory failure and deep coma should be managed promptly

and aggressively with intubation and mechanical ventilation.

Gastrointestinal Decontamination

Because of the rapid onset of coma, induction of emesis is not recommended. It is reasonable to administer oral activated charcoal without gastric lavage to patients with suspected ingestion of baclofen if an intact airway can be ensured [65]. The administration of activated charcoal has not been shown to alter the outcome of baclofen-poisoned patients, however. Administration of oral activated charcoal to patients who may develop a decrease in their level of consciousness should always be done cautiously. It is likely that any potential benefit of activated charcoal decreases as the time from ingestion increases, although delayed administration may be beneficial in the presence of documented persistent absorption [51] [Level III].

Cerebrospinal Fluid Removal

If a large bolus of baclofen accidentally is injected intrathecally, some cerebrospinal fluid may be removed immediately in an attempt to limit toxicity [56, 96, 98, 99, 125, 126] [Level III].

Extracorporeal Removal

Case series data indicate that duration of toxicity in patients with severe renal impairment may be shortened by hemodialysis [36, 127, 128] [Level III]. In contrast, in patients with normal renal function, hemodialysis seems not to modify the elimination half-life [51].

Specific Nonantidotal Treatments

Cardiovascular

Severe hypertension should be treated with short-acting agents because hypertension can

deteriorate rapidly to hypotension. If hypotension is unresponsive to intravenous fluid administration, vasopressor (e.g., norepinephrine) administration may be necessary [50, 56, 117]. Symptomatic bradycardia may respond to atropine [50, 65, 103, 105, 129] [Level III].

Indications for ICU Admission in Baclofen Poisoning

Evidence of toxicity after acute ingestion
Evidence of toxicity after recent pump adjustment or filling of reservoir
Evidence of significant toxicity after chronic exposure
Evidence of withdrawal symptoms after cessation of baclofen
Evidence of withdrawal symptoms with suspected pump failure

Neurologic

Seizures occur with baclofen toxicity and withdrawal. These seizures generally are brief and respond readily to treatment [65, 88]. Benzodiazepines have been used to control seizures and other symptoms of toxicity and withdrawal (e.g., unmasked spasticity of withdrawal) [63, 97, 114, 115, 119, 126]. Paralytic agents may be used to limit spasticity and convulsions, but there is a risk of status epilepticus going unrecognized clinically in a chemically paralyzed patient [119]. Electroencephalography monitoring is recommended if these patients are chemically paralyzed. Succinylcholine use should be limited; it should not be administered to patients who may have been comatose for prolonged periods, who have neuromuscular diseases, or who are suspected to be at risk of rhabdomyolysis or trauma. Patients with neuromuscular disease have altered muscle fiber receptors, resulting in hypersensitivity to hyperkalemia that may follow succinylcholine administration. Cardiac arrest may occur in these patients after the administration of succinylcholine [130, 131] [Level III].

Common Errors in Baclofen Poisoning

Failure to appreciate airway compromise

Failure to recognize the danger of succinylcholine administration in patients with neuromuscular disease

Failure to use short-acting agents when treating hypertension or hypotension and tachycardia

Failure to recognize nonconvulsive (akinetic) status epilepticus

Failure to consider the potential for prolonged, profound CNS depression with overdose

Failure to differentiate between toxicity, withdrawal, and infection

Failure to resume baclofen treatment after acute or chronic toxicity resolves, precipitating withdrawal

Withdrawal from intrathecal baclofen may be resistant to various treatments and may require reinstitution of intrathecal baclofen [68, 117, 126]. Case reports suggest that dantrolene may be helpful in treating baclofen withdrawal, but this is not well established [132]. It seems more sensible to resume baclofen promptly rather than initiate dantrolene therapy [115, 119]. Cyproheptadine has also been used in the treatment of baclofen withdrawal in both children and adults given its resemblance to serotonin syndrome in some cases [123, 133] [Level III].

Infectious

Pump infections may be treated by removal of the pump and intravenous antibiotic administration. Alternatively, antibiotics may be administered via the pump [77, 85] [Level III].

Specific Antidotal Treatments

In prior case reports of baclofen overdose, physostigmine has been administered as an antidote [96, 125, 134, 135]. Additionally, flumazenil has been

given alone [65, 92, 103, 136, 137] or with physostigmine [56] in similar reports of baclofen poisoning. However, at this point, there is no clear evidence that either agent is advantageous, and further study would be warranted to support specific indications for use in baclofen poisoning. Ondansetron also has been reported as an antidote in a case report, but this agent has not been studied further [91]. In a single study, intravenous lipid infusion was trialed in dogs for treatment of baclofen poisoning and seemed to have a favorable outcome [138] [Level III].

Criteria for ICU Discharge in Baclofen Poisoning

Resolution of altered mental status and seizures

Resolution of blood pressure, pulse, and temperature abnormalities

Resumption of baclofen initiated without evidence of withdrawal

Special Populations**Pediatric Patients**

Respiratory arrest occurred in a 22-month-old infant who ingested 10.9 mg/kg of baclofen [27]. Six children, age 2–6 years, presented after oral baclofen overdose; two children required intubation, and one child experienced seizures. Signs and symptoms were similar to those reported in adults [129]. An 8-year-old child presented with diminished responsiveness and vomiting then hypothermia, bradycardia, flaccidity, and areflexia after an intrathecal baclofen overdose [99]. In a case series of adolescents ingesting baclofen, 9 of 14 required intubation; their symptoms were similar to the symptoms seen in adults [65]. Another case involving an adolescent describes exam findings of coma and bradycardia in addition to seizures after abusive oral baclofen use [64]. Baclofen withdrawal syndrome also presents similarly in children and adults [57].

Pregnant Patients

Pregnant women and nursing mothers generally are excluded from baclofen treatment [5]. However, cases of intrathecal baclofen administration during pregnancy have been reported in the literature [139–141]. If a pregnant woman presents with baclofen toxicity, she should be treated supportively, as recommended for nonpregnant patients.

Elderly Patients

Peak plasma concentrations occur later after ingestion in elderly patients [43]. This delay may prolong the clinical course in elderly patients.

Other Patients

Patients with impaired renal function are at risk for developing toxic symptoms soon after initiating even low-dose baclofen. Patients on stable regimens of baclofen may develop toxicity if creatinine clearance declines [49, 94, 127, 142]. Serum creatinine levels may remain normal, despite diminished creatinine clearance [49].

Key Points in Baclofen Poisoning

1. Patients who receive aggressive supportive care generally survive baclofen toxicity.
2. There is no clinically available antidote that reliably reverses baclofen toxicity.
3. Seizures, resulting from either toxicity or withdrawal, generally respond to benzodiazepines.
4. Differentiating between baclofen toxicity and withdrawal can be difficult.
5. Generally, hypothermia suggests toxicity, whereas hyperthermia suggests withdrawal or possibly infection.
6. Baclofen toxicity can mimic brain death clinically.
7. Prompt resumption of baclofen administration is often essential for the prevention and treatment of baclofen withdrawal.

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The centrally acting muscle relaxants are a group of drugs that act in the central nervous system (CNS) to mitigate tension and spasm of skeletal muscles. Drugs within this group are structurally heterogeneous and act at a variety of receptors in the CNS. Muscle relaxants that act at the level of the spinal cord, such as baclofen, or peripherally, such as dantrolene, are discussed in their respective chapters.

Many of the centrally acting muscle relaxants have been available for decades. Carisoprodol, for example, was licensed in 1956 as a prescription, noncontrolled, centrally acting skeletal muscle relaxant. It is metabolized to the anxiolytic meprobamate [1, 2]. Others in the group may be compounded with analgesics: chlorzoxazone was first introduced in 1958 as the drug alone or in combination with salicylates or acetaminophen [3, 4]. Methocarbamol was reported in 1960 to effectively relieve muscle spasm in a patient with black widow spider poisoning [5] and in a case series of 100 patients with a variety of acute and chronic orthopedic conditions [6]. Metaxalone was patented in 1962 [7]. Diazepam, introduced in 1963, was the second benzodiazepine to be approved in the United States for humans, and has been used as an anxiolytic and anticonvulsant, as well as a centrally acting muscle relaxant [8, 9]. A 1964 double-blind investigation of 200 patients with low back pain and discomfort concluded that metaxalone diminished acute reflex skeletal muscle spasm [10]. Although a 1972 double-blind crossover trial of the tricyclic amine cyclobenzaprine demonstrated minimal improvement in patients with cerebral or spinal spasticity [11], a 1975 study of several animal models suggested that the drug could be used to mitigate excessive tonic skeletal muscle activity in humans [12]. Cyclobenzaprine has been available as a centrally acting muscle relaxant since 1977 [9].

Meprobamate and diazepam may be habit forming. The United States, for example, officially lists them as controlled substances [7]. Effective January 11, 2012, carisoprodol became a schedule IV controlled substance at the US federal level. Carisoprodol has been abused for its sedative and relaxant effects and to augment

the effects of other drugs [13]. In overdose, the centrally acting muscle relaxants are relatively safe when not combined with other agents. For example, a 1-year retrospective review of pure skeletal muscle relaxant exposure, including the centrally acting agents carisoprodol, chlorzoxazone, and cyclobenzaprine, revealed that morbidity and mortality were low [14].

Much of the clinical experience with muscle relaxants is limited to case reports and case series. Data reported in this chapter should therefore be interpreted cautiously.

Biochemistry and Pharmacology

The chemical structures of the agents discussed in this chapter are shown in Fig. 1. Their pharmacokinetics and metabolism are summarized in the accompanying box.

Pharmacokinetics of Centrally Acting Muscle Relaxants

Carisoprodol

Volume of distribution: unknown

Protein binding: 58%

Mechanisms of clearance: hepatic to hydroxycarisoprodol, hydroxymeprobamate, and meprobamate

Active metabolites: meprobamate (4.7% of dose)

Chlorzoxazone

Volume of distribution: unknown

Protein binding: unknown

Mechanisms of clearance: unknown

Active metabolites: none

Cyclobenzaprine

Volume of distribution: unknown

Protein binding: 93%

Mechanisms of clearance: hepatic to norcyclobenzaprine; may undergo enterohepatic cycling; 50% renally as inactive metabolites; via bile in feces as unchanged drug

Active metabolites: none

(continued)

Diazepam

Volume of distribution: 0.7–2.6 L/kg

Protein binding: 96–97%

Mechanisms of clearance: 4'-hydroxylation and conjugation; N-demethylation to nordiazepam

Active metabolites: nordiazepam

Meprobamate

Volume of distribution: 0.75 L/kg

Protein binding: 20%

Mechanisms of clearance: rapid hepatic; 8–20% in urine as unchanged drug; 10% as metabolites in feces

Active metabolites: none

Metaxalone

Volume of distribution: unknown

Protein binding: unknown

Mechanisms of clearance: unknown

Active metabolites: none

Methocarbamol

Volume of distribution: unknown

Protein binding: unknown

Mechanisms of clearance: O-demethylation and hydroxylation; conjugation; 99% excreted in 72-h urine

Active metabolites: guaifenesin

Orphenadrine

Volume of distribution: 4.3–7.8 L/kg

Protein binding: 20%

Mechanisms of clearance: extensive hepatic; demethylation; up to 30% may be eliminated unchanged in acidic urine; 60% excreted in 72-h urine

Active metabolites: nororphenadrine

Data from references [7, 9, 15, 16]

Chlorzoxazone

Chlorzoxazone is 5-chloro-2-benzoxazolinone and is derived from the more toxic zoxazolamine [3].

Cyclobenzaprine

Cyclobenzaprine HCl is a tricyclic amine salt, 3-(5H-dibenzo [a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride. It is structurally related to the tricyclic antidepressants; only a double bond on the central ring distinguishes it from amitriptyline [9, 17]. Cyclobenzaprine, which may undergo enterohepatic cycling, is metabolized in the liver to norcyclobenzaprine.

Diazepam

Diazepam is a benzodiazepine that undergoes 4'-hydroxylation and conjugation as well as N-demethylation to the active metabolite nordiazepam; other metabolites are the active but nonaccumulating 3-hydroxy derivatives temazepam and oxazepam [9]. The metabolism of diazepam is described in greater detail in ► Chap. 45, "Anxiolytics, Sedatives, and Hypnotics."

Methocarbamol

Like carisoprodol and meprobamate, methocarbamol is a member of the carbamate class. Its formula is 3-(*o*-methoxyphenoxy)-2-hydroxypropyl-1-carbamate [6]. The phenyl ring undergoes O-demethylation and hydroxylation; conjugation of the parent drug and metabolites follows. Guaifenesin, an expectorant, is an active metabolite [9].

Metaxalone

Metaxalone is 5-(3,5-dimethylphenoxy)-2-oxazolidinone [7].

Carisoprodol and Meprobamate

Carisoprodol is *N*-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate or isopropyl meprobamate [7]. It is hepatically metabolized to hydroxycarisoprodol, hydroxymeprobamate, and the active form meprobamate. Meprobamate is 2-methyl-2-propyl-1,3-propanediol dicarbamate [7].

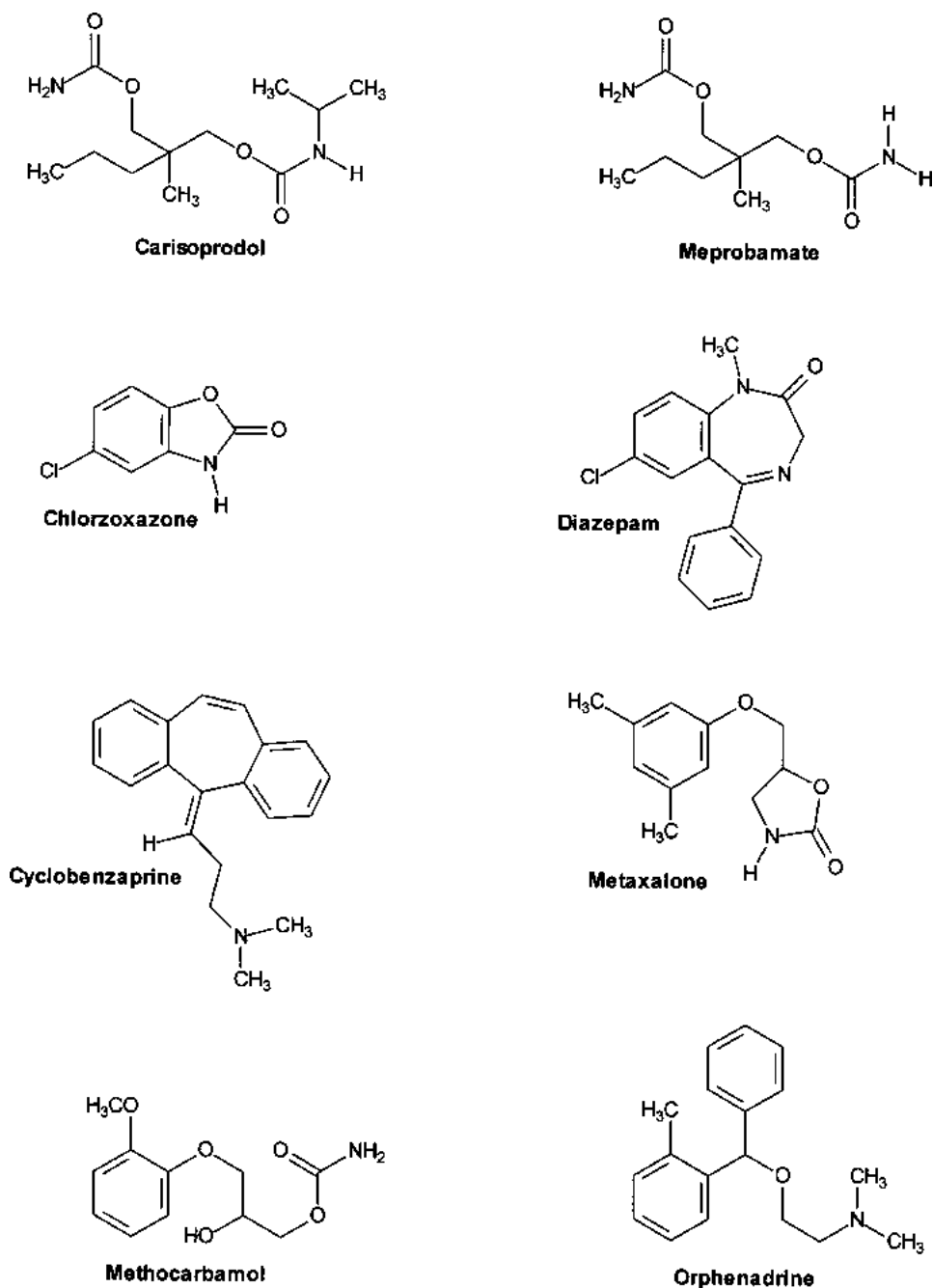


Fig. 1 Chemical structures of centrally acting muscle relaxants

Orphenadrine

Orphenadrine (*o*-methyldiphenhydramine) is classified as a skeletal muscle relaxant, anticholinergic, and

antihistaminic agent [7]. As a substrate for the cytochrome P-450 isoenzyme (CYP3)A4 and an inhibitor of CYP2D6, orphenadrine may have a number of unpredictable pharmacologic interactions [15].

Pathophysiology of Therapeutic and Toxic Effects

Carisoprodol and Meprobamate

Carisoprodol is active in the descending reticular formation and spinal cord, where it inhibits interneuronal transmission. Both carisoprodol and its active metabolite meprobamate are indirect γ -aminobutyric acid (GABA)_A receptor agonists that open the neuronal chloride channel and induce hyperpolarization. This mechanism is similar to that of the benzodiazepines (see Fig. 3 of ► Chap. 45, “Anxiolytics, Sedatives, and Hypnotics”) [1].

Chlorzoxazone

Chlorzoxazone inhibits polysynaptic reflex pathways that produce and maintain muscle tone in the subcortex and spinal cord, and it appears to relieve musculoskeletal spasm more effectively than neurogenic spasm [3, 4].

Cyclobenzaprine and Orphenadrine

Cyclobenzaprine relieves skeletal muscle spasm of local origin but does not exert its action directly on the skeletal muscle, at the neuromuscular junction, or at the level of the spinal cord. Rather, it acts on the brainstem to reduce tonic somatic motor activity [17]. In overdose, its toxicity is related to its antagonism of muscarinic acetylcholine receptors and the resultant anticholinergic syndrome. A similar toxic profile is seen with the diphenhydramine analogue orphenadrine [9]. However, orphenadrine is a more potent fast voltage-gated sodium channel antagonist than cyclobenzaprine, a property that may be important in the clinical manifestations of overdose.

Diazepam

The benzodiazepine diazepam has multiple therapeutic uses, one of which is skeletal

muscle relaxation. It increases the action of the inhibitory neurotransmitter GABA in the limbic and reticular systems and in the CNS in general (see Fig. 3 in ► Chap. 45, “Anxiolytics, Sedatives, and Hypnotics”) [8, 16]. The pathophysiology of benzodiazepine effects is described in detail in ► Chap. 45, “Anxiolytics, Sedatives, and Hypnotics.”

Metaxalone

Metaxalone has an unknown mechanism of action, although no direct effects on the striated muscle, the motor end plate, or the nerve fiber are reported [18]. As may largely be the case for several of the other agents discussed in this chapter, the drug’s sedative properties are most likely to explain its therapeutic effects [10].

Methocarbamol

This drug, which is believed to act primarily at the interneurons of the spinal cord, blocks multisynaptic reflexes [6].

Clinical Presentation and Life-Threatening Complications

The ingestion of pure centrally acting muscle relaxants is generally associated with low morbidity and mortality. The clinical manifestation of overdose is predominantly CNS depression. The available data on the clinical toxicology of these agents are relatively sparse, but several investigators have described their experience with certain members of this class. Logan and colleagues [19] compiled a series of 104 incidents of impaired driving in which the drugs carisoprodol and/or its metabolite meprobamate (used alone as an anxiolytic) were detected in the blood of drivers. Reports of erratic driving and symptoms consistent with CNS depression were common but may have been attributable to coingestion of ethanol. In 21 cases, however, such behavior was witnessed in the absence of drugs other than

carisoprodol or meprobamate. A retrospective review of carisoprodol-related deaths in Jefferson County, Alabama, over a nearly 12-year period found that the skeletal muscle relaxant was present in 24 cases. Although the mechanism of death in 82% of these cases was respiratory depression, consistent with the action of carisoprodol or its metabolite meprobamate, carisoprodol was never the only one detected at autopsy and was never determined to be the sole cause of death. Of note, propoxyphene, a cardiac and neuronal sodium channel blocking agent, was present in a third of the cases [20]. Carisoprodol has been reported in three cases of illicit use in which it was combined with the nonopioid, nonsteroidal tramadol [21]. Carisoprodol has also been implicated in a case report of myoclonic encephalopathy. After the ingestion of 35 g of carisoprodol, agitation, tachycardia, and myoclonus developed in a 39-year-old man. His plasma carisoprodol concentration was 71 mg/L, and the meprobamate concentration was 118 $\mu\text{mol/L}$ [22].

In cases of cyclobenzaprine or orphenadrine overdose, an anticholinergic syndrome may be the predominant clinical manifestation (see ► Chap. 23, “Anticholinergic Syndrome”). In a 5-year review of cyclobenzaprine exposure [23], toxicity appeared to be related primarily to anticholinergic effects, even if overdoses did not produce the neurologic and cardiovascular toxicity of the structurally related tricyclic antidepressants. Neurologic and cardiovascular complications may follow an overdose of orphenadrine. In a case report, a 3-year-old boy ingested an unknown quantity of orphenadrine and presented with tonic-clonic seizures and ventricular tachycardia [24]. A 2-year-old girl who ingested 400 mg also presented with seizures and an episode of ventricular tachycardia; her initial plasma orphenadrine concentration was 3.55 mg/L [25].

In a case series of severe meprobamate poisoning, coma, hypotension, and hypothermia complicated the clinical course in four patients, and one required resuscitation after cardiac arrest. Peak plasma concentrations ranged from 800 to 923 $\mu\text{mol/L}$ (176–203 mg/L) (therapeutic, 28–55 $\mu\text{mol/L}$ [6–12 mg/L]). Three were treated with charcoal hemoperfusion. All four survived

without sequelae [26]. Although the exact mechanism of meprobamate’s cardiac toxicity is not established, one study observed that none of the seventy-four patients with signs of meprobamate toxicity, including cardiac failure, had prolongation of their QRS on EKGs [27]. Of note, authors Buire et al. point out that patients who are tolerant to meprobamate may have higher plasma concentrations of the drug with relatively normal levels of consciousness, as assessed by their Glasgow Coma Scale [28].

Dependence and Withdrawal

Patients who are prescribed carisoprodol are at risk to become dependent on its metabolite meprobamate. In an uncontrolled Norwegian study of prisoners who had been taking carisoprodol for a minimum of 9 months, abstinence symptoms, including anxiety, insomnia, irritability, headache, and muscular pain, were observed when the drug was withdrawn over a 2-week period. No seizures or psychoses were noted [29]. Reeves et al. reported a case in which a patient abruptly discontinued the use of carisoprodol and presented with a variety of effects including visual hallucinations, bizarre behavior, and anxiety [30].

Diagnosis

The diagnosis of skeletal muscle relaxant overdose depends primarily on the history and physical examination.

Some hospital laboratories may be able to detect or even measure concentrations, for example, of carisoprodol or meprobamate, but it is more likely, particularly in smaller hospitals, that outside reference laboratories must be contacted to arrange these assays. Furthermore, the screening immunoassays commonly used by hospital clinical laboratories may indicate false-positive results for tricyclic antidepressants if cyclobenzaprine is present. Cyclobenzaprine and its metabolite norcyclobenzaprine are among a number of

polycyclic compounds that may cross-react with tricyclic antidepressants on immunoassay or high-performance liquid chromatography of blood, and cyclobenzaprine may have the same effect on a colloidal metal immunoassay of urine [17, 31]. The cholinergic agent physostigmine may serve as a diagnostic tool in cases of cyclobenzaprine or orphenadrine overdose. There are rare reports of seizures and asystole associated with physostigmine administration, usually in polypharmacy overdoses, and conclusions about a cause-and-effect relationship are questionable [16]. When appropriately administered it is a relatively safe drug. The clinical pharmacology of physostigmine is described in ► Chap. 161, “Physostigmine.”

Treatment

The cornerstone of treatment of toxicity with these agents is supportive care. Patients should be monitored on telemetry and may require ICU level of care based on their symptoms and signs.

Indications for ICU Admission in Poisoning by Centrally Acting Muscle Relaxants

Coma

Respiratory failure

Seizures, hypotension, and QRS prolongation, which may occur in cases of orphenadrine overdose

Hypotension, cardiovascular failure without QRS widening with meprobamate

Cardiogenic shock requiring catecholamine support or mechanical support such as extracorporeal membrane oxygenation

Gastrointestinal Decontamination

If a patient is seen shortly after ingestion, administration of activated charcoal may theoretically decrease drug absorption. However, there is no evidence that the administration of activated charcoal will affect either the clinical

course or outcome. Activated charcoal should be given cautiously, if at all, to patients who have ingested a drug that may cause a rapid decrease in level of consciousness and airway protection.

Extracorporeal Removal Techniques

Meprobamate has a small volume of distribution and limited protein binding; it is moderately dialyzable. In the case series of severe meprobamate poisoning noted earlier, charcoal hemoperfusion performed in three patients reduced the plasma half-life as much as threefold, from 8.3 to 2.6 h [26]. Data concerning the efficacy of other centrally acting muscle relaxants are limited, although extracorporeal removal techniques would not be expected to significantly hasten the removal of agents with large volumes of distribution and/or extensive protein binding.

Flumazenil

Carisoprodol and its active metabolite meprobamate act as indirect GABA_A agonists and, like the benzodiazepines, enhance GABA-mediated CNS neuronal chloride ion channel opening, thereby inducing hyperpolarization (see Fig. 3 in ► Chap. 45, *Anxiolytics, Sedatives, and Hypnotics*). Flumazenil was reported to reverse CNS depression in a woman who had a Glasgow Coma Scale score of 9 after carisoprodol ingestion. Her respirations were shallow at 18 breaths/min, and her pupils were reactive at 2 mm. She received two 2-mg naloxone doses without effect. Ten minutes later, she received flumazenil (0.2 mg intravenously over a period of 2 min), and within 2 min, she became more alert, with somewhat dysarthric speech. A second dose 5 min later normalized her mental status completely within 2 min [2]. Rarely reported in overdose, chlorzoxazone was cited in one case report of a patient who became comatose on two occasions after toxic ingestion of this skeletal muscle relaxant. Although the patient had only therapeutic to subtherapeutic benzodiazepine levels present,

flumazenil was used and appeared to at least transiently reverse the CNS depression of chlorzoxazone [4]. The presence of an unrecognized benzodiazepine may explain the observed effect of flumazenil. Based on the aforementioned case reports, however, routine use of flumazenil is not recommended in the management of overdose, particularly if the patient has been taking any of these agents chronically. A complete discussion of the clinical pharmacology of flumazenil may be found in ► [Chap. 148, “Flumazenil.”](#)

Physostigmine

Although case reports [24, 25] of orphenadrine overdose attribute the resolution of ventricular tachycardia to physostigmine, the empirical use of this potentially toxic cholinergic agent should not precede the institution of standardized protocols for dysrhythmias.

Prevention and Treatment of Carisoprodol or Meprobamate Withdrawal

There is no standard treatment regimen for patients with carisoprodol dependence and most patients are treated for the symptomatic complaints of withdrawal [13]. The authors of the Norwegian study noted earlier suggested that a gradual reduction in carisoprodol dosing may prevent withdrawal symptoms [29]. Similarly, if chronically administered carisoprodol or meprobamate is discontinued abruptly, prompt resumption of drug treatment may prevent withdrawal.

Criteria for ICU Discharge in Poisoning by Centrally Acting Muscle Relaxants

Patient awake with adequate airway protection
Patient otherwise hemodynamically stable
without electrocardiographic conduction disturbances

Key Points in Skeletal Muscle Relaxant Overdose

1. Consider skeletal muscle relaxant overdose in patients with anticholinergic signs such as hyperthermia, disorientation, hallucinations, delirium, seizures, sinus tachycardia, and mydriatic pupils.
2. Consider skeletal muscle relaxant overdose in patients with hypotension, bradycardia, depressed respirations, areflexia, hypotonia, myoclonic encephalopathy, or rapid onset of coma.
3. Most cases resolve with supportive care only.
4. Appropriate resumption of drug treatment may prevent carisoprodol/meprobamate withdrawal.

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Part IX

Medications: Analgesic/ Anti-Inflammatory

D. Nicholas Bateman

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Overview

Acetaminophen (paracetamol) was first discovered in Germany in 1887. It was initially rejected in favor of the structurally related phenacetin, as it was considered too toxic. It was only when restudied in the late 1940s that it was recognized as safer than alternative agents [1]. It was first marketed as an antipyretic and analgesic in the USA, as Tylenol, and UK, as Panadol, in the 1950s [2].

Toxicity from acetaminophen overdose was initially recognized in 1966, about 10 years after marketing, when the first cases were reported in Scotland [3, 4]. At that time there were no effective therapies, and morbidity and mortality from acetaminophen overdose climbed steadily as overdoses increased (Fig. 1) [5]. In the 1970s there were a significant number of cases in the Royal Infirmary poisons unit in Edinburgh, and Laurie Prescott and colleagues did important work, allowing rapid progress in knowledge. Initial studies showed the relationship of plasma concentration of acetaminophen to risk of toxicity (II-3) [6]. Animal studies had suggested both the mechanism of action of acetaminophen and potential antidotes. Studies were then done in the UK and North America evaluating three of these, cysteamine, methionine, and acetylcysteine. By the end of that decade the evidence was clear from UK data that acetylcysteine (*N*-acetylcysteine, NAC) was the antidote of choice (II-3) [7], but for many years there were differences in the approach to giving this antidote, as intravenous formulations were at that time not licensed for use in the USA [8, 9]. Despite an available antidote, which halted the increase in mortality, deaths did not subsequently decline. As a result, in the UK, changes were introduced in 1998 to the pack sizes available for over-the-counter sale (maximum 16 g in a pharmacy, 8 g in a general store sale), in an attempt to reduce mortality [10]. The magnitude of change in mortality and morbidity this has caused remains a topic of debate [11].

Because acetaminophen is available without prescription, “over-the-counter,” worldwide it is commonly used in overdose, but the precise number of deaths caused is uncertain. In the UK, for example, at least 150 deaths per annum may be attributed to ingestion of acetaminophen with and

without ethanol, and an almost equal number of deaths involve ingestion of acetaminophen as part of an overdose [5]. Acetaminophen remains the most common cause of acute liver failure as seen in hospitals in the USA and UK, and is important in many other countries [12, 13]. Among overdose patients, there are a number of patients who suffer from toxicity due to taking supratherapeutic doses. This is in part due to the confusion in labeling of acetaminophen-containing medications, the availability of different types of products containing acetaminophen, a lack of understanding in the community of what products contain acetaminophen [14], and the narrow therapeutic index of this compound. It may also be that factors such as acute starvation are as important in man as they are in animal models of acetaminophen toxicity. Repeat ingestion of supratherapeutic doses appears to result in a greater risk of liver damage than the same dose as a single ingestion [15].

Although antidote therapy is effective if given soon after ingestion of an overdose, it is clear that its efficacy declines over time and in patients who take multiple therapeutic doses in excess it is often too late for acetylcysteine to be effective (II-2) [16]. Although other approaches to therapy have been studied in animal models these are yet to be put into the clinic. In patients with severe liver injury liver transplantation may be effective. Present issues in clinical toxicology of acetaminophen include the use of safer, potentially shorter and simpler antidote regimens, better predictive tests for indicating which patients are at risk, and which therefore allow better risk stratification than the present nomograms that have been in use for 40 years.

The introduction of modified release preparations of acetaminophen has resulted in a problem in overdose management, since these make risk assessment more difficult, as the nomograms may not be applicable due to delays in acetaminophen absorption [17]. In addition over the past few years intravenous acetaminophen has become more widely used, particularly postoperatively, and sadly cases of toxicity have been associated with supratherapeutic use by this route [18].

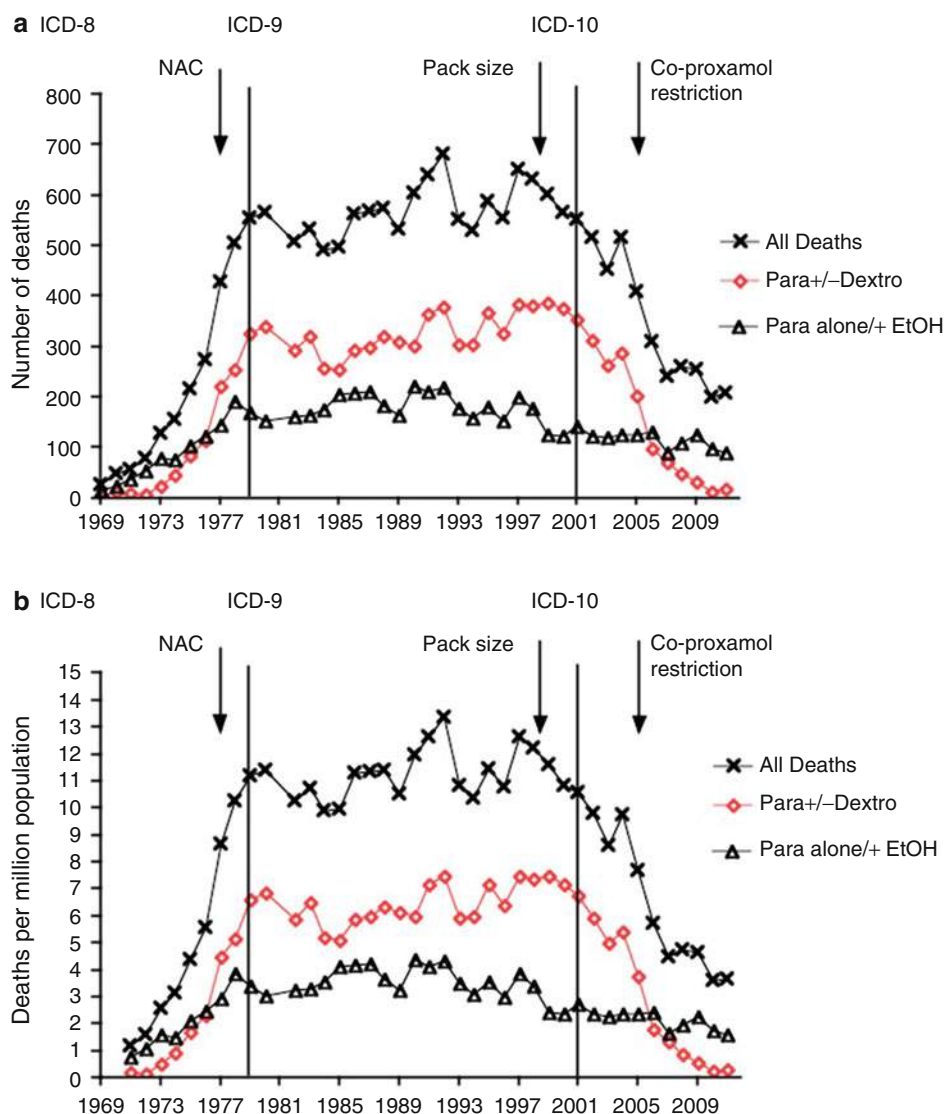


Fig. 1 Deaths from acetaminophen poisoning in England 1969–2011, (a) total numbers; (b) per million population. Down arrows indicate potential influences on mortality: introduction of acetylcysteine as an antidote in 1975; reduction in pack sizes available for sale over-the counter

in 1998; and withdrawal of propoxyphene containing acetaminophen codrug (coproxamol) over 2 years 2005–2007 (Data from Bateman 2014 Clin Tox 52 821–23, with kind permission of Prof R J Flanagan)

Clinical Pharmacology

Although acetaminophen has been used extensively for more than 50 years, its precise mechanism of action therapeutically remains unclear. While it has been shown to inhibit both cyclooxygenase 1 (COX-1) and cyclooxygenase

2 (COX-2) enzymes with a reduction in prostaglandin (PG) production [19, 20], its pharmacological effect appears to be primarily mediated via inhibition of COX-2 and prostaglandin E2 synthesis (PGE2) [21, 22]. In vivo, acetaminophen has similar effects to selective COX-2 inhibitors, with only mild COX-1 effects [23]. Animal

studies have suggested that acetaminophen inhibits COX-3, a variant of COX-1 [23, 24]. COX-3 encodes proteins with different amino acid sequences to COX-1 and COX-2, and so it is unlikely that it plays a significant role in PG-mediated pain and fever. Furthermore, the low level of expression of COX-3 in humans suggests that it may be of little clinical relevance [25].

Despite similarities with classic nonsteroidal anti-inflammatory drugs (NSAIDs), however, the anti-inflammatory effect of acetaminophen is weak [24]. This may be related to peroxide concentration, as acetaminophen-induced COX inhibition is less active at sites of inflammation where peroxide concentration is high, but more active centrally at sites of low peroxide concentration, probably in the brain [19, 26]. Animal models suggest additional analgesic effects may be mediated via serotonergic [27], opioid [28], or cannabinoid systems [29]. Animal studies using COX-2 knockout mice have also demonstrated that COX-2 is responsible for the febrile response [30], suggesting that the antipyretic mechanism of acetaminophen may be mediated via COX-2 inhibition. In overdose none of these pharmacological effects are likely to be important in the majority of patients, although increased kaliuresis with resultant hypokalaemia suggests an effect on renal function associated with the effects of acetaminophen on renal prostaglandins [31].

The kinetics and metabolism of acetaminophen at therapeutic doses are well understood. Gastric emptying is the rate-limiting step in absorption, and, as acetaminophen is absorbed rapidly from the small intestine, speed of absorption of acetaminophen has been used as a measure of gastric motility. Absorption is usually complete by 60–90 min after a therapeutic dose. Liquid preparations may be completely absorbed within 20 min [32]. With ingestion of excessive doses of standard-release preparations, absorption may be delayed but is almost invariably complete within 4 h. Coingested drugs that delay gastric emptying may delay absorption of acetaminophen. Thus a peak serum acetaminophen concentration occurring later than 4 h after overdose is

rare but has been noted, for example, after coingestion of drugs that impair gastric motility, such as the opioid propoxyphene [33] and anticholinergic diphenhydramine [34]. A major concern for clinical toxicologists has been the introduction by pharmaceutical companies of modified release acetaminophen preparations. As these are associated with peak plasma concentrations delayed more than 4 h after overdose they interfere with the use of the standard nomogram approach to assessing acetaminophen dose, and hence risk of toxicity [35–37].

In therapeutic dose acetaminophen elimination follows first-order kinetics. It has a half-life of 2–4 h, which is prolonged in patients with acute acetaminophen-induced liver damage. At therapeutic doses protein binding is 15–20%, and the volume of distribution is approximately 0.9 L/kg [32]. It is obviously more difficult to study these aspects in patients with overdose, as the dose actually absorbed is often uncertain. With the onset of liver injury the elimination of acetaminophen is delayed [6, 38]. More than 90% of acetaminophen is conjugated in the liver by a combination of sulfation and glucuronidation; approximately 4–7% is excreted unchanged in urine. The remainder (about 4% at therapeutic doses) is metabolized by the cytochrome P-450 mixed-function oxidase system [39], primarily by CYP2E1 with a smaller contribution by CYP1A2, to a toxic metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI).

Pharmacokinetics of Acetaminophen at Therapeutic Dose

Volume of distribution: 0.9 L/kg

Protein binding: 15–20%

Mechanisms of clearance (at therapeutic dose): hepatic >90%, renal 4–7%

Toxic metabolite: *N*-acetyl-*p*-benzoquinoneimine

Methods to enhance clearance: dialysis (may be appropriate to consider in massive overdose but is normally used in patients therapeutically for management of renal failure)

Pathophysiology

The basis of acetaminophen toxicity is its metabolic pathway and the availability of natural glutathione (Fig. 2). Acetaminophen is an example of a substance that undergoes hepatic metabolism to a toxic metabolite (other examples include carbon tetrachloride, methanol, and ethylene glycol). The metabolizing enzymes are distributed throughout the body, but the majority of these are found in the liver, with the highest concentration in the centrilobular region (zone 3), which is composed of hepatic acinar cells. A secondary area of increased concentration is in the kidneys. Neither acetaminophen nor its conjugated metabolites are harmful. However, the metabolite generated by CYP2E1 is potentially toxic [40–42]. This metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), is very short lived. It binds to the hepatic cell membrane and injures the lipid bilayer, if not neutralized by an antioxidant [43], and glutathione is the primary antioxidant naturally present in the liver that conjugates and detoxifies this metabolite [39, 42, 44–47].

Mitochondrial injury is a component of hepatic injury, and agents that prevent mitochondrial injury reduce liver injury from acetaminophen in animals [48].

At therapeutic doses, acetaminophen is an extraordinarily safe drug with minimal adverse effects. However, in an animal model of acetaminophen overdose, NAPQI begins to bind to hepatocytes and causes arylation, cellular injury, and possibly death when hepatic glutathione stores have been depleted to less than 70% of normal values [44].

Similar reactions are believed to occur in man. Serious liver damage after a single 75 mg/kg body weight dose of acetaminophen is rare, even in patients at increased risk. In patients without risk factors, a dose less than 150 mg/kg body weight is unlikely to cause serious liver damage [16]. Children younger than 6 years appear to be more resistant to acetaminophen toxicity than adolescents and adults on a weight basis. This may be because the liver is a proportionally larger organ in children than adults. Several large studies of young children have demonstrated that in this

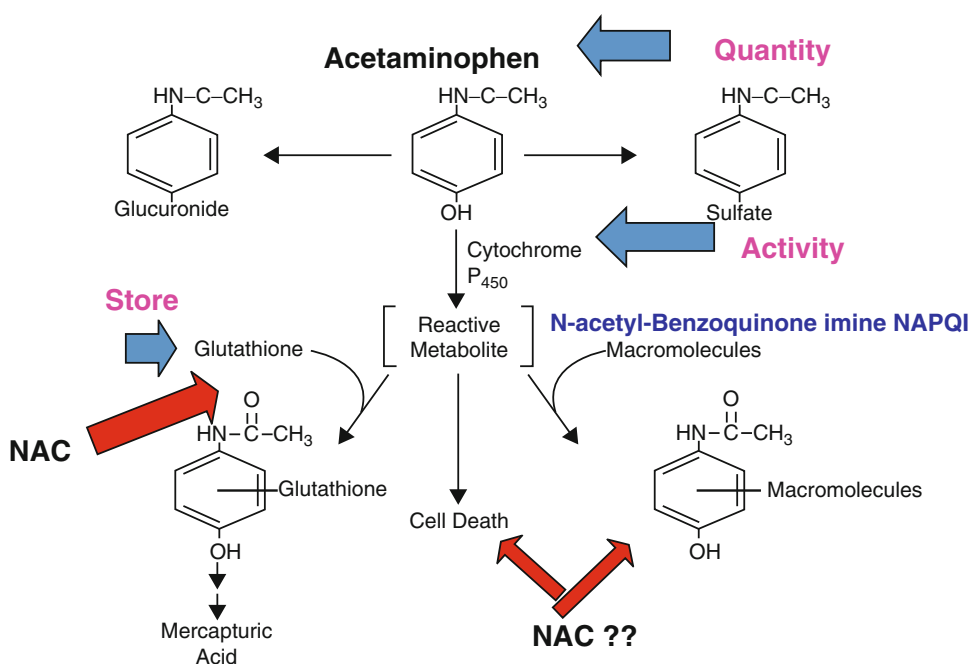


Fig. 2 Metabolism of acetaminophen showing main metabolites, mechanism of toxicity, and primary site of action of acetylcysteine (“?? NAC” indicates unknown mechanism of benefit in liver failure prophylaxis, see text)

age-group, a single ingestion of 200 mg/kg or less is highly unlikely to result in significant toxicity (II-3) [49–52].

Chronic supratherapeutic dosing of acetaminophen may also result in toxicity. The manufacturers' recommended daily amount is 4 g/day or less for adults and 75 mg/kg/day or less for children. Toxicity has been reported with ingestion of more than these recommended doses for a day or longer [53–55]. Retrospective case series in children have reported therapeutic doses (20–25 mg/kg/day) being associated with hepatotoxicity [56, 57], but the accuracy of these dose estimates is uncertain.

Whether chronic acetaminophen dosing at normal therapeutic doses causes liver damage is a subject which has been raised by studies suggesting small increases in ALT with chronic dosing in normal populations [58]. The clinical relevance of a small increase in ALT is likely very low, and others have suggested little evidence of any toxicity from such dosing [59].

Modulators of Toxicity

Toxicity results when the amount of NAPQI produced from acetaminophen metabolism overwhelms the capacity for glutathione-mediated detoxification. Theoretically, any compound that induces CYP2E1 could increase the amount of NAPQI produced and thus increase the likelihood of toxicity. Inducers of CYP2E1 include ethanol, rifampicin, isoniazid, and carbamazepine (II-3) [60]. Clinical series suggest that patients who chronically ingest drugs that induce CYP2E1, or smoke tobacco, may have poorer outcomes than the general population after acetaminophen overdose (II-3) [61–64]. In addition coingestion of opiates seems to be associated with increased toxic effect in acetaminophen overdose [65]. Patients with depleted glutathione stores from malnutrition, such as chronic alcoholics, may also be at increased risk (II-3) [15]. There is some evidence that coexisting conditions, in particular myopathies, may increase toxicity risk in overdose (II-3) [66]. Acute starvation also seems to increase risk of hepatotoxicity, as in patients

with acute dental pain. In contrast, concomitant ethanol and acetaminophen ingestion may decrease the effects of acetaminophen overdose because of inhibition and competition for CYP2E1 activity [67]. Phenytoin, which is not a CYP2E1 inducer, does not appear to increase the risk of acetaminophen-induced hepatotoxicity and, in fact, may offer hepatoprotection by increasing glucuronidation [68].

Age is also a modulator of toxicity. Young children appear to be more resistant to the toxic effects of acute acetaminophen overdose. Additionally, the incidence of hepatotoxicity is much lower than that observed in the general population [69]. The corollary to this is the increased risk of hepatotoxicity in the elderly (II-3) [15, 70, 71].

Clinical Presentation and Life-Threatening Complications

The clinical manifestations of acetaminophen toxicity can vary significantly, depending on the dose, time of presentation, and whether the toxicity results from acute or chronic ingestion. Patients who undergo medical evaluation within several hours after an acute ingestion may be asymptomatic or have only minor symptoms. Nausea, vomiting, and occasionally lethargy may occur early (typically within several hours of ingestion) in moderate to severe acetaminophen poisoning. In our experience, these symptoms usually decrease within 12–18 h and may possibly reflect direct effects of the parent compound (because resolution occurs with declining acetaminophen levels). Metabolic acidosis is a feature of evolving liver failure, but it and even coma have been reported within 4–6 h of a massive overdose, although coma is extremely rare, and should alert the physician to alternative diagnoses or coingestions such as opioids or benzodiazepines [72–74]. It is important to exclude hypoglycemia caused by acetaminophen-induced liver injury. Patients who first come to medical attention after the onset of signs of liver injury – generally at least 24 h after acute ingestion – may initially present with abdominal pain, encephalopathy, coagulopathy, and renal failure.

Hepatocytes are the primary target after an acetaminophen overdose. Given NAPQI's ultra-short half-life, its initial toxicity is limited to cells that synthesise it. Most of the life-threatening complications of acetaminophen poisoning are a direct result of acute liver injury and the systemic complications of liver failure. The role of inflammatory response is also important in the pathogenesis of liver damage, as inhibition of this process in laboratory animals results in less toxicity [75]. The clinical course most commonly observed with acute acetaminophen hepatotoxicity is hyperacute liver failure, which has been defined as the development of encephalopathy within 7 days of the onset of jaundice (although rarely in very severe acetaminophen poisoning cases death may occur before jaundice is apparent) [76–78]. Liver failure is the result of NAPQI-induced hepatocellular injury. The early histopathologic finding after acetaminophen overdose is centrilobular hepatic necrosis (zone 3) with periportal sparing [79, 80]. The centrilobular region is chiefly composed of zone 3 hepatic acinar cells, the site of highest metabolic activity. Hepatic necrosis results in the release of a wide range of substances into serum and severe metabolic derangements (e.g., acidosis, hypoglycemia, and hyperammonemia) from the loss of functioning liver.

It is also now clear that there is a consequent molecular signaling and response with necrosis, apoptosis, and an inflammatory response caused by an influx of inflammatory cytokines [81, 82]. In animal models drugs that affect this inflammatory response reduce hepatotoxicity. Coagulopathy and renal failure usually accompany liver failure, although the extent of different organ involvement may vary. Sepsis (both bacterial and fungal), cardiovascular collapse, and terminal ventricular dysrhythmias may also develop in patients with ALF. The injured liver has an ability to regenerate, and ALF is thus potentially reversible if the patient can be supported through the acute phase of poisoning, particularly in the case of acetaminophen poisoning, because hepatic regeneration occurs from cells situated in the periportal regions (zone 1), which tend to be

Table 1 Clinical characteristics of encephalopathy

Grade I	Slowed thought processes, slurred speech, untidy appearance, slight tremor
Grade II	Increased drowsiness, inappropriate behavior, easily elicited tremor
Grade III	Hypersomnolent, incoherent speech, marked confusion
Grade IV	Coma, no response to painful stimuli

unaffected by all but the most massive of acetaminophen overdoses.

Hepatic encephalopathy is the hallmark of ALF and develops in severe cases of acetaminophen-induced hepatotoxicity. In a series of 171 patients, grade II (Table 1) encephalopathy was noted at a median of 72 (range 38–120) h after an acute acetaminophen overdose. Grade IV encephalopathy was noted within 89 (range 51–141) h following an overdose occurring 12 (range 3–96) h after grade II encephalopathy [83]. Patients with grade III encephalopathy are at significant risk for cerebral edema. Death is most likely to occur 72–96 h after an overdose, although it may be delayed for up to 10–14 days. Death occurs most frequently as a complication of cerebral edema or sepsis. Patients who survive do not have permanent liver damage.

Renal failure in the setting of acetaminophen poisoning may be due to a direct renal effect of NAPQI, prerenally mediated acute tubular necrosis, and/or hepatorenal syndrome. Because CYP2E1 is present in renal tubules, NAPQI is generated in the kidney. Renal injury manifested by hematuria, proteinuria, and modest elevations in blood urea nitrogen and creatinine have been reported in as many as 8.9% of patients [84]. It typically develops within the first 24–48 h but is easily missed as the process takes a few days to peak. The injury is normally transient but may progress to anuric renal failure and require dialysis [84, 85]. Oliguric renal failure necessitating dialysis has been reported to occur in 1% of patients [86]. Renal failure associated with liver failure is typically delayed 48–72 and is a feature of severe outcome (II–3) [15, 85]. Clinically

significant nephrotoxicity in the absence of hepatotoxicity has been reported but is rare [87–89].

Other clinical manifestations associated with acetaminophen toxicity include pancreatitis and cardiotoxicity. Pancreatic inflammation, defined as serum lipase three times the upper limit of the normal laboratory value, may be found in 30% or more of patients with acetaminophen hepatotoxicity [90]. However, clinical pancreatitis is rare [85]. Cardiotoxicity, manifested by nonspecific electrocardiographic changes and alterations consistent with pericarditis, is also rare [85, 91]. The mechanisms responsible for these less common findings are unclear but in some cases may have been due to other undetected coingestants, such as propoxyphene causing cardiac effects [92].

Chronic Acetaminophen Overdose

The manufacturers' recommended maximum daily doses of acetaminophen are 4 g of acetaminophen in adults and 75 mg/kg in children. Ingestion of larger supratherapeutic quantities may result in hepatotoxicity. This is most common in the context of acute pain syndromes, as in dental pain, where toxic risk may be increased by acute starvation. In young children, although hepatotoxicity has been reported after as little as 150 mg/kg/day, the general experience is that due to a proportionally increased hepatic mass in children toxicity is less likely than in adults [56, 93, 94]. Medication error is an important potential risk in children [95], but Munchausen's-by-proxy must also be considered.

Chronic acetaminophen excess is usually a therapeutic misadventure. Common scenarios include those involving patients who increase their daily intake because they believe that it is safe, patients who use combination products such as acetaminophen and codeine along with acetaminophen, or caretakers who substitute adult for pediatric suppositories in a young child. The incidence of hepatotoxicity after chronic excess has not been extensively studied. Certain populations may be at risk, including patients who are fasting or who have ingested alcohol in the preceding 5 days [55]. Numerous cases of hepatotoxicity

have been reported in alcoholics after chronic acetaminophen excess, although the apparent frequency may be due in part to ascertainment bias [54]. A randomized, double-blind, placebo-controlled trial of 201 long-term alcoholic patients, failed to show liver injury by conventional blood tests when recommended doses of acetaminophen were not exceeded [96].

The clinical presentation of chronic acetaminophen toxicity is variable. Many patients initially come to medical attention during routine medication review and are taking excess for reasons such as acute or chronic pain disorders. These patients generally have no symptoms directly related to excessive acetaminophen use. Rarely cases may present as altered mental status from incipient ALF, but these usually seem to have had an acute recent increase in dose. This raises a possibility of adaption to regular excess acetaminophen dose, and most experienced clinicians will have come across patients who routinely take additional acetaminophen above recommended limits without apparent harm.

Diagnosis

Patients normally present in one of three scenarios:

- (i) With a history of a single overdose as part of an act of self-harm
- (ii) With a history of multiple ingestions as an act of self-harm
- (iii) As a result of therapeutic excess, as in the case of an acute pain syndrome treated with a cocktail of remedies, or confusion over the content and quantities of acetaminophen in different cold remedies

Occasionally therapeutic misadventure may occur in hospital environments, as with excess IV acetaminophen, or from regular excess oral dosing in underweight, nutritionally challenged patients.

Patients are often asymptomatic but with chronic therapeutic or repeat deliberate ingestion may present with right upper quadrant abdominal

tenderness, vomiting, or jaundice. *De novo* presentation with hepatic encephalopathy is extremely rare.

Laboratory Evaluation

Determination of risk in acetaminophen overdose is dependent on the time from the ingestion. Within the first few hours the acetaminophen blood concentration is currently the best predictor of outcome (II-2). A number of nomograms were produced in the 1970s based on a series of patients in Edinburgh who were not treated for their overdose. These lines start from the plasma concentration taken at least 4 h after ingestion in an attempt to avoid any misinterpretation due to measuring acetaminophen during the absorption phase. All have a half-life of 4 h, even though this is longer than that seen in normal therapeutic doses. The lines derive from graphs drawn by hand and eye that divide patients with and without hepatotoxicity as defined by a rise in ALT over 1000 IU/L. No deaths occurred in 54 patients in this series of 70 in those with a plasma concentration below a line commencing at 300 mg/L acetaminophen 4 h after ingestion, with the proportion of patients who developed an ALT over 1000 IU/L increasing from 23% at 100 mg/L to 60% at 200 mg/L [97]. Prescott used these data to develop a nomogram for the UK with a 4 h concentration of 200 mg/L (200 µg/mL; 1323 µmol/L) to determine treatment at a time when antidotes were being developed (II-3) [7]. Rumack and Matthew also published a similar nomogram that was reduced by the FDA to 150 mg/L for clinical use (150 µg/mL; 992 µmol/L) [8, 98]. Subsequently in the 1990s in the UK a risk assessment approach was adopted in patients with concentrations between lines drawn from 100 to 200 mg/L (662 and 1323 µmol/L) at 4 h (III) [99]. This assessment included determining whether patients were alcoholic, taking enzyme-inducing drugs, or were malnourished. Patients with these features were treated at the 100 mg/L nomogram line. In Australia a decision was made to move from the 200 mg/L nomogram to the 150 mg nomogram in 2008 [100].

In the UK in 2012 policy was changed by the UK regulator, the MHRA, in view of the death of a young woman who had not been thought to be high risk. All patients in the UK are currently treated using the 100 mg/L nomogram [101].

Whichever nomogram is being used it is important to have an accurately timed acetaminophen concentration and be aware of the units being used to report. Confusion can arise when different laboratories use mass and molar units; in the UK there has been standardization to mass units (mg/L) to avoid confusion, and potential failure to treat [102] (Fig. 3).

It is generally accepted that the accuracy of the nomogram for prediction becomes less reliable beyond 15 h, since the original dataset used had very few patients who presented late. Furthermore since the elimination of acetaminophen is reduced by liver injury [6] it would in theory be possible to use estimates of the half-life of the drug based on two or more times blood samples to establish whether injury to the liver had occurred. This is rarely used in practice but may be useful in managing individual patients, for example, those who wish to self-discharge against medical advice, or refuse antidote therapy.

A potential confounder is the accuracy of acetaminophen measurement at concentrations below 10 mg/L (66 µmol/L). Some laboratories have even higher cutoffs for reporting undetectable concentrations, and this may cause problems in interpretation of results in patients presenting late after their overdose. Some countries have also licensed modified release products of acetaminophen, and the nomograms are not likely to be accurate in this situation [17].

Other blood tests should be routinely measured at presentation, since these will be necessary to interpret progress in patients who are determined to require treatment with antidote. These include a measurement of renal function, normally creatinine, liver function tests, in particular transaminase activity, and prothrombin time, often measured as INR. Admission tests may be predictive of outcome [15, 103]. Other tests have been suggested to be abnormal in more severe poisoning, including urinary phosphate, urinary potassium, and plasma lipase. These have not been

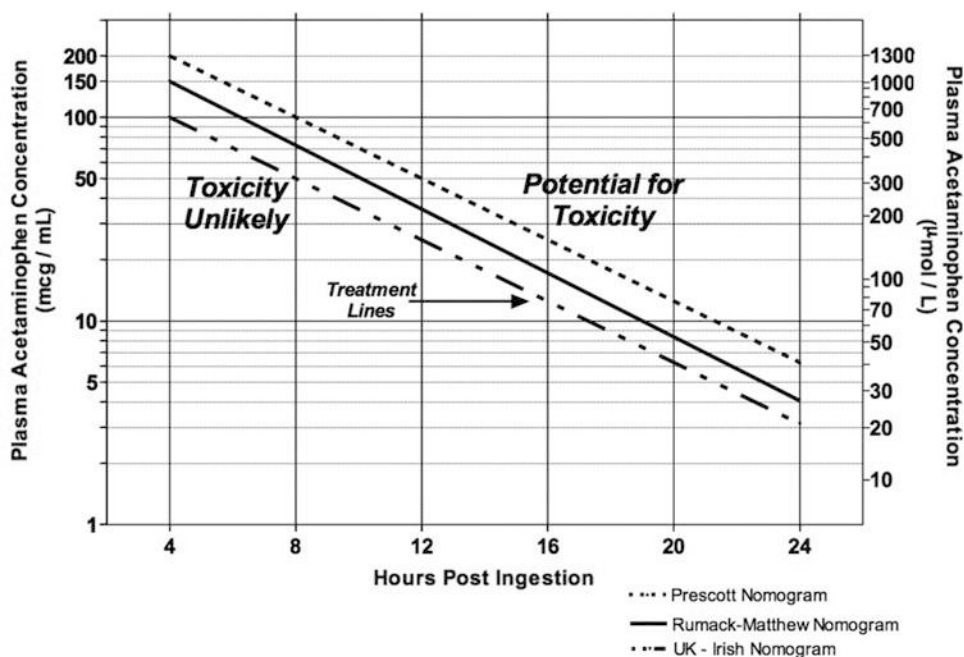


Fig. 3 Acetaminophen treatment nomograms. Treatment is recommended if the plasma acetaminophen concentration is above the *solid* (150 mg/L at 4 h) line in North

America and Australia. In the UK and Ireland the *dotted-dashed line* (100 mg/L at 4 h) is used to determine therapy with acetylcysteine

adopted in routine practice. Some patients will have compensated or uncompensated metabolic acidosis shortly after ingesting a significant overdose [104]. This acidosis has been associated with increased lactate formation and has been postulated to occur as a consequence of impaired mitochondrial respiration at the level of ubiquinone by acetaminophen or NAPQI [105, 106]. This early-onset acidosis tends to resolve spontaneously within hours [104]. In patients whose clinical condition continues to deteriorate, however, acidosis often recurs and is highly predictive of lethality once ALF has developed.

ALT is a sensitive marker of liver injury, and traditionally an ALT of >1000 IU/L has been regarded as an index of “severe” hepatotoxicity in acetaminophen poisoning [107]. This definition was based on the requirement at that time to dilute samples with ALT above this activity to determine the result accurately. It is in reality poorly correlated with outcome, and ALT measurement is not part of the standard criteria now used to determine prognosis. However it remains a useful cutoff

point to use in clinical decisions regarding the severity of illness. Rate of rise of ALT is more important than its actual value, as rate of rise is better linked to extent of acute liver injury.

Prothrombin time (usually measured as INR) is one of the best readily available markers of functional hepatic damage, since unlike ALT, which provides information on cell injury, PT provides information about hepatic synthetic function. A rise in INR indicates a decrease in hepatic synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, X). A rising PT in the setting of falling transaminase levels is an ominous finding. Serum transaminase concentrations will generally fall in both a patient who recovers from hepatic injury and one who develops ALF and massive hepatic necrosis. PT, however, will not usually improve if a patient has progressive liver injury, and it generally continues to rise in cases of ALF, especially in the absence of clotting factor replacement. The finding of a slightly elevated PT within hours after an acute overdose is common and usually the result of direct reversible

inhibition by acetaminophen of vitamin K–dependent clotting factor synthesis and not a marker of hepatic injury (II-2) [108].

In patients who have taken a single overdose and have acetaminophen concentrations below the nomogram limits, risk of serious hepatic damage is low; they can normally be discharged. Care should be taken, however, in patients who have recently consumed more than one ingestion (within a 24 h period) of acetaminophen, and in those coingesting drugs that may alter gastrointestinal motility and delay gastric emptying such as opioids or antihistamines [109]. It is wiser in these patients, and indeed a sensible precaution in all patients, to take account of the history of dose ingested, and where there is disparity between this and blood results clinicians should be cautious in their decision regarding early discharge, and double-check timings of ingestion and samples (III). Kinetic studies suggest a correlation between dose and concentration across a wide dose range [110], and historic case series indicate that history correlates with measured plasma acetaminophen concentration (II-3) [111, 112].

The product of acetaminophen and ALT has been suggested as a tool to better identify those patients at increased risk of serious liver injury [113]. Novel biomarkers are now being evaluated that appear to give earlier indications of liver injury than present laboratory tests; a lead candidate is the microRNA miR 122. Other biomarkers, of apoptosis and cell necrosis, may also have a future role (Fig. 4) [82].

Differential Diagnosis

Although acetaminophen is currently the primary cause of ALF, a number of other toxic and nontoxic etiologies must also be considered. Toxic causes include intrinsic, dose-related hepatotoxins such as carbon tetrachloride, chloroform, cyclopeptides from fungi (α -amanitin), copper sulfate, yellow phosphorus, and various herbal products. Botanicals that have been implicated as intrinsic hepatotoxins include pennyroyal oil from *Mentha pulegium*, chaparral, germander, Jin Bu Huan, and pyrrolizidine alkaloids from

Heliotropium, *Senecio* (tansy ragwort), *Crotalaria*, and *Symphytum* (comfrey) species. ALF may also result from idiosyncratic adverse drug reactions from, for example, phenytoin, valproic acid, isoniazid, halothane, or nonsteroidal anti-inflammatory agents. Idiosyncratic hepatotoxicity is not dose related and may occur after therapeutic dosing. Liver failure from methylenedioxymethamphetamine (MDMA) has also been described and may occur in association with severe MDMA-induced heatstroke, or be due to contaminants in the tablets [114]. Other causes of fulminant liver failure include viral hepatitis, sepsis, hypovolemic shock, cardiogenic shock, heatstroke, and Reye's syndrome [115]. Serology, clinical history, and occasionally histopathology help differentiate these entities.

The time course and the clinical and biochemical characteristics of shock liver may appear remarkably similar to acetaminophen-induced hepatic failure. Shock liver generally results from hemorrhage, hypovolemia, and the resultant hypotension secondary to trauma and operative procedures. Differentiating between shock and acetaminophen as the primary hepatic insult may prove challenging, especially in situations in which hypotension may have occurred and the patient has been taking therapeutic amounts of acetaminophen.

In light of the increasing number of reports of hepatotoxicity associated with chronic supratherapeutic dosing, acetaminophen should always be considered in cases that might otherwise be attributed to cryptogenic ALF. For any patient admitted to the critical care unit with ALF of unknown etiology, the earliest available blood specimen should be retrieved and tested for acetaminophen to assess whether it might be an etiologic factor. However, depending on the timing of the last acetaminophen dose, the plasma concentration may be low or nondetectable and cannot reliably exclude acetaminophen as the cause. Furthermore, in the setting of severe hyperbilirubinemia (≈ 25 mg/dL; 1.46 μ mol/L), some conventional acetaminophen assays performed by enzyme assay (GDS Diagnostics, Elkhart, IN) may cross-react with the bilirubin and result in a falsely elevated or false-positive acetaminophen

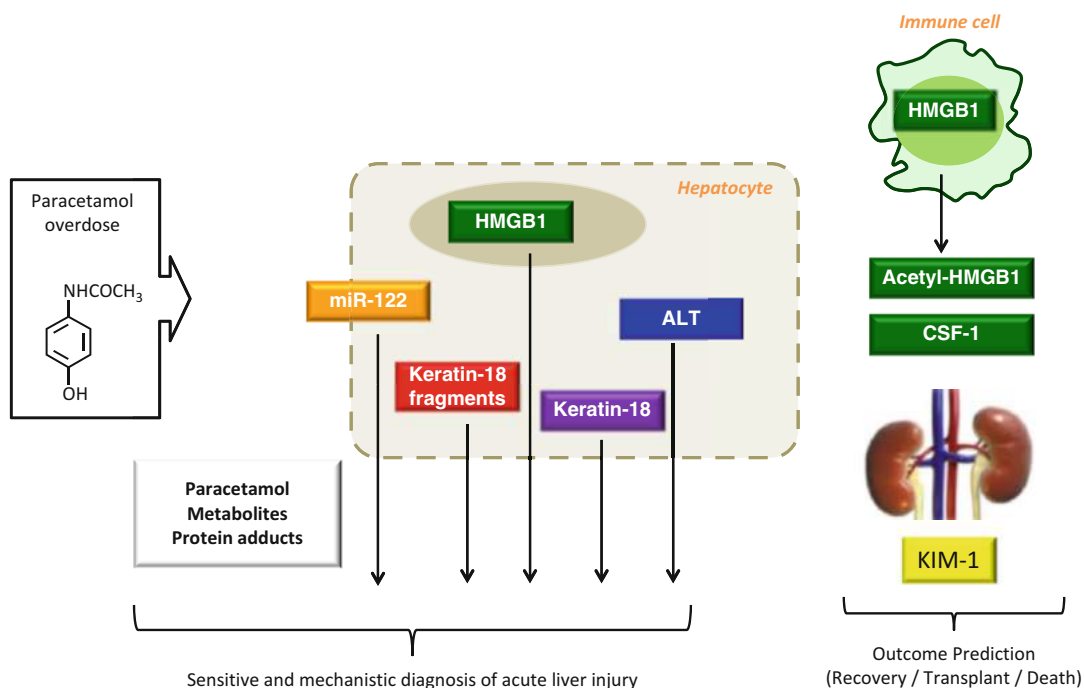


Fig. 4 Schematic diagram illustrating a range of novel markers that may have utility in prediction of hepatic toxicity and hepatic recovery in acetaminophen overdose. Measurement of biomarkers may identify acute liver injury early (miRNA-122, HMGB1, K18 isoforms) or provide prognosis of liver injury (Acetyl-HMGB1). In view of the multicellular and many aspects of acetaminophen-induced

liver injury, the use of this panel-based approach, alongside current markers, may enable patient stratification for the treatment and assessment of efficacy of novel therapeutic intervention strategies (*HMGB1* high-mobility group box-1) (Based on Dear and Antoine. 2014 Expert Rev. Clin. Pharmacol. Early online, 1–9)

determination. Measurement of plasma levels acetaminophen-protein adducts may be a useful adjunct tool to assess recent acetaminophen intake and may be of use in indicating that acetaminophen is a cause of acute liver failure of uncertain origin [116, 117].

Treatment

Acute Single Oral Ingestion

Decontamination with a single dose of activated charcoal should be performed if the patient is seen within 1 h of ingestion (II-2) [118]. It is unknown if activated charcoal alters the outcome in patients who have ingested excessive doses of acetaminophen. Caution should be exercised in patients who may have ingested other substances that might

reduce their conscious level while activated charcoal is being given, as there is a risk of aspiration in such patients. In the past, there was concern about activated charcoal and use of the oral antidote NAC, but the amount of acetylcysteine adsorbed was not considered clinically important.

Use of NAC is mandatory in all those patients above the nomogram line used in the country of treatment (II-2). This currently varies between “150 mg/L line” used in most countries and the “100 mg/L line” used in UK and Ireland. Use of this very conservative threshold in the UK has had major resource implications which have been questioned [119].

Acetaminophen intoxication by itself does not typically produce cardiorespiratory compromise unless the patient is in hepatic failure. Presence of such features should lead to a consideration of other causes, particularly coingested drugs. Rare

instances of patients presenting in coma and requiring endotracheal intubation shortly after an overdose have been reported [72]. This procedure should, however, not interrupt or delay the use of intravenous NAC. Acetaminophen is removed by dialysis, but this modality has little role in most overdoses given the efficacy of NAC as an antidote. In patients with renal failure haemodialysis will remove acetaminophen, and also NAC, with a doubling of the dose of NAC recommended [120].

Multiple Ingestions and Therapeutic Error

Assessing the need to treat patients in this scenario is more challenging, as there are no agreed criteria internationally. It is necessary to use a combination of history of dose ingested and blood tests taken on admission to determine treatment. As an example of the approach used in the UK, in patients who present less than 24 h after the last ingestion treatment with NAC is generally started if the history suggests an amount in 24 h greater than local guidelines. This dose may vary between 75 mg/kg in 24 h and as much as 200 mg/kg in 24 h in different countries. In patients who are not jaundiced, do not have right upper quadrant abdominal pain, and have had their last ingestion of acetaminophen more than 24 h previously it is reasonable to withhold NAC therapy until blood results are available, since the efficacy of the NAC falls with time. Treatment is then based on presence of acetaminophen in blood, or of evidence of liver injury using ALT and INR (prothrombin time). Decisions on stopping treatment will depend on the results of blood tests; if these suggest potential toxicity they should be repeated at the end of an appropriate time interval of NAC therapy, usually a full 21 h course of antidote.

Intravenous Acetaminophen Overdose

There is much less experience of use of NAC in IV acetaminophen overdose, but this has become more often as this route has become more widely used. The usual nomograms cannot be applied in

the situation of IV dosing, as the dose is given rapidly and the nomogram 4 h interval of assessment may not be correct. These patients may be subject to therapeutic errors, but also may be suffering acute starvation [18, 121]. There is uncertainty as to whether the much higher acetaminophen concentrations that result immediately following IV dosing have toxic significance as more toxic metabolites could be formed if conjugation pathways are overwhelmed. In addition many patients receiving IV acetaminophen have been fasted preoperatively, or are in intensive care units and not receiving full nutrition. Similar concerns may apply to those in intensive care with muscular dystrophies who are ventilated and receive acetaminophen (oral or IV) therapy for muscular dystrophies [66]. For these reasons some authors have suggested a lower dose threshold for intervention with NAC [18].

Acetylcysteine (*N*-acetylcysteine)

NAC is a highly effective antidote when administered soon after an acetaminophen overdose. It was selected from a range of potential glutathione donors in the 1970s. It acts as a glutathione substitute in addition to enhancing glutathione synthesis and increasing the amount of acetaminophen that undergoes sulfation (see Fig. 2) [45]. Its efficacy is primarily a function of time elapsed since the overdose. NAC is most effective when administered within the first 8 h after an acetaminophen overdose, and its effectiveness decreases incrementally every hour thereafter (II-2) [8, 97].

Indications for ICU Admission in Acetaminophen Poisoning

Significant acidosis

Any grade of encephalopathy

Coagulopathy requiring treatment

Significant renal failure

Different approaches to using NAC were developed in the UK and USA. In the 1970s an intravenous formulation of NAC was licensed in the UK for management of airways disease, and this was therefore used to administer the drug in

Table 2 Acetylcysteine regimens

Regimen	Loading dose	Followed by	Total dose
21 h IV	150 mg/kg over 1 h	50 mg/kg over 4 h	300 mg/kg
		100 mg/kg over 16 h	
72 h PO	140 mg/kg	70 mg/kg every 4 h for 17 doses	1330 mg/kg

acetaminophen overdose [7]. In the USA an oral formulation had to be used. The UK regimen developed by Prescott and colleagues in Edinburgh was a 20.25 h IV protocol, delivering 300 mg/kg of NAC over the duration of treatment, with 150 mg/kg given in the first 15 min, 50 mg per kilogram over 4 h, and 100 mg/kg over 20 h. The regimen used in North America was 140 mg/kg initially followed by 70 mg/kg every 4 h for 17 doses [8]. Case series using longer intravenous [122, 123] and shorter oral regimens have also been reported. The standard North American IV regimens subsequently developed use a 21 h protocol, with the first infusion, similar in dose to the original Prescott regimen, being given over 1 h (Table 2). Recently in the UK regulatory decision has been made to also move to the 1 h initial IV dose [101]. In view of the relatively low lipid solubility of acetaminophen and the relationship between NAC dose and adverse event risk some authorities advise using a maximum weight of 110 kg in obese patients and pregnancy when calculating NAC dose [124]. A recent study in comparing patients with weights above and below 100 kg did not show an excess of ADRs in the heavier patients [125], although detected rates of ADRs were very much lower than seen in prospective studies, throwing some doubt on the validity of these findings.

The Danish approach to acetaminophen poisoning has been very different to anywhere else worldwide. They have historically treated all patients with paracetamol excess [126]. This is not a cost-effective approach, and risks excess NAC anaphylactoid effects in patients with low acetaminophen concentrations [127].

NAC is effective if given early after acetaminophen ingestion but is recognized to lose efficacy the longer the interval between acetaminophen dose and treatment (II-2) [8]. No parallel study

has been done comparing oral and IV antidote use, but comparing historical groups there is no strong evidence of the major difference in the efficacy of different regimens (II-2) [128]. There is a theoretical risk, based on calculations of the potential hepatic production of NAPQI in acetaminophen overdose, that the dose of NAC in the current IV regimen is less than would be required to provide full antidote efficacy in very large overdoses of acetaminophen (e.g., 4 h acetaminophen concentrations >600 mg/L) (III) [9]. Some toxicologists advise a doubling of NAC in such patients; however, this practice is controversial since the metabolic interaction between antidote and acetaminophen reactive metabolites at these concentrations is unknown. Potential confounders include substrate inhibition within the liver and saturation of the capacity to generate glutathione from NAC.

Adverse effects to NAC have been recognized since the antidote was first used. Major adverse effects seen are nausea and vomiting and anaphylactoid reactions. Death has been reported, but this is most likely due to overdosage with IV NAC due to miscalculation and confusion in the dosage form in the 1980s. Rates of adverse reactions are variously reported and are likely to depend on the methods used to ascertain them [129]. Prospective close monitoring results in far higher estimates than retrospective analysis [130]. Nausea and vomiting requiring treatment with antiemetics seems to occur between 20% and 30% of patients [127]. Symptoms of nausea are far more frequent, reaching 70% in prospective studies (I) [131]. The incidence of nausea and vomiting does not seem related to the quantity of acetaminophen ingested. In contrast, anaphylactoid reactions are inversely related to the plasma concentration of acetaminophen (II-3) [132, 133]. Thus, recent changes in the UK to treat patients with lower plasma concentrations of acetaminophen have resulted in increasing risk of adverse effects from the antidote [133]. Anaphylactoid reactions seem due to histamine release [130] and can be treated successfully using antihistamines, with the addition of beta-receptor agonists when bronchospasm is present. As the mechanism is not immunological there is no necessity to use corticosteroids in managing

this reaction. In severe cases adrenaline may be required, and in patients with hypotension additional fluid should be given intravenously. Nausea and vomiting should be treated with a standard antiemetic, although it would seem prudent to avoid ondansetron in view of the signal of toxicity when used in acetaminophen overdose [131].

A recent clinical trial studied the effect of a shorter, 12 h, IV protocol delivering 100 mg/kg NAC over 2 h and 200 mg/kg over 10 h. This study was primarily to examine effects on adverse reactions to NAC and was not powered to assess relative efficacy against the 20.25 h regimen used as control; however, it suggested no lack of inferiority of the shorter regimen [131]. Further work using this protocol is needed before it can be used widely in clinical practice; nevertheless, it suggests potentially even shorter treatment may be possible in selected patients. This is perhaps not surprising bearing in mind the short half-life of acetaminophen at therapeutic dose [32].

Most patients who are treated worldwide will now receive a standard 21-h intravenous protocol of NAC. The oral regimen should only be considered in those in whom IV access is impossible or in situations where IV therapy is unavailable. Methionine [107], an alternative oral antidote, seems of less efficacy based on historic studies, but is still used in some countries.

Blood samples need to be taken at the end of the treatment period to ensure that the patient is fit to discharge. Mandatory tests include measurement of transaminase (usually ALT), serum creatinine, and prothrombin time. Many clinicians will also wish for a repeat acetaminophen concentration to ensure that the drug has been eliminated. In the USA for patients who have taken a large overdose, or who have a prolonged half-life, such measurement of acetaminophen concentrations prior to discontinuing therapy is essential, and the standard of care, to ensure that NAC is not stopped while significant levels of acetaminophen are still circulating.

Interpretation of blood tests post treatment is relatively straightforward. The rate of rise in transaminase is related to the severity of toxicity, and therefore very small perturbations in measurements are normally insignificant clinically

[134]. Many clinicians will use a doubling in ALT to determine whether hepatotoxicity is likely. Acetylcysteine interferes with the measurement of INR [108, 135], and thus a small rise (e.g., to less than 1.4) with a normal ALT can usually be ignored. Acetylcysteine continuation should be considered in those with a rising ALT, or other features suggesting impending liver failure. Hepatotoxicity in acetaminophen poisoning was traditionally defined as an ALT over 1000 IU/L [107]. This cutoff is rather arbitrary, and many patients will recover without liver unit care at this concentration. Acetylcysteine can be discontinued when ALT starts to improve and INR begins to recover. Extensive clinical experience by the author in several thousand cases has shown that it is not necessary to treat until normal values have returned. Jaundice is a late feature in acetaminophen-induced liver failure, and measurement of bilirubin is of most value in the management of acute liver failure.

Interpretation of serum creatinine is also affected by the use of acetylcysteine since it impairs the synthesis of creatinine. Rising creatinine above 10% of baseline should therefore be regarded as potentially indicating onset of renal impairment. In this circumstance it is prudent to recheck the blood test since patients with renal damage may not show the full clinical syndrome of renal failure until 3–5 days after acetaminophen overdose.

In patients who go on to develop liver injury it is important to continue to administer NAC, as there is evidence that this is protective in hepatic coma (II-2) [136, 137]. Monitoring progress requires regular measurement of liver and renal function and clotting tests. As liver injury develops synthesis of clotting factors is impaired, and those with the shortest half-life (factors V and VII) disappear most rapidly. Measurement of the concentrations of individual clotting factors may therefore be considered in patients with incipient hepatic failure in an attempt to estimate severity.

Patients who develop renal injury and hepatic injury in combination seem to have a far worse prognosis, and those who present with renal injury have a high mortality (II-3) [15]. It is sensible to discuss patients with significant hepatic damage,

for example, rapidly rising ALT, clotting disturbance and renal injury, with a liver unit as some patients may go on to require hepatic transplantation. The King’s College criteria are widely used as an assessment tool in this situation.

Liver Transplantation and Management of Fulminant Hepatic Failure

In patients in whom ALF develops from acetaminophen toxicity, the most pressing question is whether orthotopic liver transplantation (OLT) is necessary for their survival. Patients need to be discussed early with a local liver unit, and transfer of the patient will be determined by local criteria. In patients with severe coagulopathy, renal failure, acidosis, hypoglycaemia, and encephalopathy care in a liver unit is mandatory. Most hepatologists will consider rate of disease progression, patient age, and laboratory markers. Thus a prothrombin time that is greater in seconds than the hours after overdose is used in the UK as a marker of poor prognosis. In patients with overdose there may also be psychological aspects to consider in relation to managing patients post transplant that may influence decision to transplant.

To date there is little evidence that artificial liver devices have a benefit in this clinical situation. Transplantation is therefore a key treatment methodology in severe cases. To make an informed recommendation with regard to OLT it is necessary to consider the natural history of patients who do not undergo transplantation, as well as the utility of prognostic indicators. Most patients in whom ALF develops from acetaminophen toxicity survive and fully recover without transplantation. The King’s College group reported their experience in 1255 patients with ALF and 908 with acute liver injury (ALI) from acetaminophen toxicity treated at their center between 1973 and 2008 [71]. Those with ALF were older, more likely to be female, and to have renal injury at admission to the liver unit. The majority survived without OLT, and only 147 were transplanted, survival from which improved significantly over the 35 y period of the study to the order of 80% [71]. The presence of overt encephalopathy was strongly associated with poorer outcome. The capacity for liver

recovery is better in acetaminophen poisoning than other causes of acute liver failure [138].

The search for highly sensitive and specific prognostic factors continues. Reliable indicators are critically important because patients may have sudden clinical deterioration and die before transplantation can take place. The window of opportunity for successful transplantation is often less than 24 h. In contrast, transplantation should be avoided in patients expected to survive because liver function recovers completely and transplantation unnecessarily dooms the patient to a lifetime of immunosuppressive therapy.

Auxiliary transplantation is a technique in which a partial liver graft is placed while the patient’s liver recovers, and which can then be allowed to reject or be removed. It seems attractive in theory but is technically demanding and experience is limited in acetaminophen overdose [138].

Prognostic Indicators

Several groups have studied prognostic indicators to develop criteria for transplantation. The most widely published transplant criteria were derived at the King’s College Hospital liver unit in London (Table 3). According to these criteria, patients should be considered for liver transplantation if their arterial pH is less than 7.3 at 24 h or later after acetaminophen ingestion despite fluid resuscitation and treatment with sodium bicarbonate or if they have a combination of grade III or IV encephalopathy, serum creatinine level higher than 3.4 mg/dL (300 μmol/L), and INR longer than 6.5 [138]. These criteria were originally derived from 310 acetaminophen-poisoned patients studied between 1973 and 1985 [139]. They were later validated by the same investigators in a group of 120 patients treated between 1990 and

Table 3 Original King’s College Criteria for Transplantation

PH < 7.25 24 h after overdose despite fluid resuscitation and sodium bicarbonate
Concurrent presence of grade III-IV encephalopathy, creatinine >3.4 mg/dL (300 μmol/L), and INR more than 6.5

1994. The positive predictive value of these criteria for a fatal outcome is 88%, and the negative predictive value is 65% [140]. An alternative scoring system is the MELD score suggested as an improvement, and more recently the Acute Liver Failure Group Index has been used. The latter includes coma grade, laboratory results (INR, bilirubin, and phosphorus) and an apoptosis marker (M30) and is reported as an improvement on the Kings College Hospital criteria [141]. Present UK criteria for emergency transplantation in acetaminophen poisoning are

1. pH < 7.25 despite fluid resuscitation
2. Severe coagulopathy (INR > 6.5) and renal failure (anuria or serum creatinine > 300 μ mol/L) and grade 3–4 encephalopathy
3. Serum lactate > 3.5 on admission or > 3.0 after fluid resuscitation
4. Any two criteria from category 2 combined with clinical deterioration in the absence of sepsis [141]

O'Grady has also suggested some criteria when transplantation is contraindicated, and these include compromised brainstem function, invasive fungal infection, rapid increasing need for inotropes, and severe pancreatitis [141]. Long-term quality of life is impaired in those receiving transplants, further emphasizing the need to carefully assess the use of this therapy in acetaminophen-induced liver failure [142].

Psychiatric Assessment Before Orthotopic Liver Transplantation

Psychiatric assessment for transplant feasibility is an essential aspect of the transplantation evaluation [143]. OLT is a major operative procedure, and its ultimate success is in part dependent on the transplant recipient's compliance with post-transplant care, including the need for lifelong immunosuppressive therapy. Although a suicide attempt or a history of ethanol or substance abuse by itself does not preclude transplant suitability, skilled assessment by a psychiatrist who has a close working relationship with the transplant

team is essential to determine the likelihood of long-term post-transplant compliance. Ongoing substance abuse is a probable contraindication to this procedure. The long-term medical and psychiatric outcomes in those with hepatic transplantation for acetaminophen overdose seem similar to other groups [144].

Medical Management

Aggressive medical management is warranted for patients with ALF in an attempt to stabilize the patient and prevent further deterioration. Medical issues that arise include treatment of coagulopathy, renal failure, encephalopathy, cerebral edema, sepsis, cardiovascular collapse, metabolic derangements, and respiratory failure.

Coagulopathy

Coagulopathy will develop in many patients as demonstrated by an increased PT and INR. However, given the use of PT/INR as an indicator for the need for liver transplantation, many recommend that vitamin K and factor replacement with fresh frozen plasma be withheld unless the patient has frank bleeding or requires an invasive procedure such as an arterial line, central line, or insertion of an intracranial pressure monitor. The efficacy of vitamin K therapy in patients with acetaminophen-induced hepatic synthetic dysfunction is of uncertain value, and as the primary problem is failure to synthesize clotting factors this is not unexpected. Active hemorrhage, most often upper gastrointestinal bleeding, necessitates treatment with fresh frozen plasma and red blood cell transfusion as needed. The use of H₂-blockers may reduce the risk of such bleeding.

Renal Failure

Renal failure occurs in more than 75% of cases of ALF from acetaminophen overdose and is an indicator of adverse outcomes [15]. Decreased urine output may be the sign of acute renal failure, hepatorenal syndrome, and/or undertreated hypovolemia. Fluid resuscitation in these cases

may inadvertently lead to fluid overload and pulmonary edema. Hemodialysis may be warranted, although the criteria for initiation are not well established [120]. Venovenous hemofiltration is an alternative therapy and regularly used to support renal and metabolic complications. Low-dose dopamine (2–4 $\mu\text{g/kg/h}$) may improve renal perfusion and function. Nephrotoxic drugs should be avoided, and dosing of medications undergoing significant clearance by the kidney should be adjusted for renal insufficiency.

Encephalopathy

Because the most common cause of death in patients with ALF is intracranial hypertension, with resultant brain herniation, the onset of hepatic encephalopathy is an ominous finding. Blood ammonia concentrations are usually elevated, but the degree of ammonia elevation correlates poorly with the extent of encephalopathy. Computed tomography of the head should be performed if the patient's mental status deteriorates suddenly to evaluate for evidence of intracranial hemorrhage or cerebral edema.

Sepsis and Shock

Patients with ALF who survive the first 4–5 days after an acute overdose remain at risk for complications of systemic inflammatory response syndrome (SIRS), sepsis, and hemodynamic collapse. SIRS is associated with worsening encephalopathy and a poorer prognosis. Susceptibility to infection, both bacterial and fungal, appears to be as common in ALF secondary to acetaminophen overdose as in other etiologies [145, 146]. Infections are thought to be the direct cause of death in around 20% of patients with ALF. The most common sites of infection are the respiratory tract, urinary tract, and blood. Bacteremia may be a direct result of seeding from a catheter or from decreased integrity of gastrointestinal mucosa. Endotoxemia, macrophage activation, and cytokine and tumor necrosis factor release may all occur and lead to a clinical

condition resembling septic shock. Because the only early sign of infection may be worsening encephalopathy or renal dysfunction, a high index of suspicion for infection, including daily cultures of blood, urine, and other fluids, has been recommended. The administration of broad-spectrum antibiotics is warranted if there is evidence of fever or other signs of infection. Antifungal agents may also need to be given to patients who do not respond rapidly to antibiotics. The use of prophylactic antibiotics and antifungals in these patients remains controversial.

Hemodynamic collapse and sudden death may also occur in patients with ALF secondary to acetaminophen overdose. Measurement of central venous pressure may prove useful to optimize fluid management. Continuous cardiac monitoring is essential. Norepinephrine or epinephrine infusions may be used to keep mean arterial pressure above 60 mmHg.

Hypoglycemia

Hypoglycemia from impaired gluconeogenesis and decreased hepatic glycogen stores is one of the most significant metabolic derangements in patients with ALF. Hypoglycemia develops in more than 40% of these patients, and therefore frequent glucose monitoring is critical. Patients with hypoglycemia may require 10% dextrose infusions. The delivery of more concentrated glucose solutions through a central line may be necessary in patients with refractory hypoglycemia. Metabolic acidosis should be aggressively corrected with sodium bicarbonate infusion. Hypophosphatemia is also common and should be corrected.

Sedation

Careful consideration must be given to which agents should be used for sedation in patients with ALF. No controlled studies have been conducted that address this issue. If drugs are used, an agent that does not have active metabolites may be preferable. Offset of drug effect may be prolonged.

Criteria for ICU Discharge in Acetaminophen Poisoning*Resolution of major metabolic abnormalities**Improving coagulopathy**Resolving encephalopathy***Special Populations****Pregnant Patients**

Acetaminophen is the preferred analgesic/antipyretic during pregnancy because it is safe at therapeutic doses and there is no evidence that it is teratogenic [147]. However, while there is potential for fetal toxicity after a maternal overdose the major determinant of fetal outcome is the health of the mother. A Scandinavian study suggested an excess of spontaneous abortion in those with a range of acute overdoses in pregnancy and 3 months before conception (13 acetaminophen). Spontaneous abortion was 10% more frequent, but there was no excess in malformations. Acetaminophen freely crosses the placenta, and the fetal liver is capable of elaborating detectable amounts of NAPQI by about 14 weeks' gestation [148]. NAC also crosses the placenta; after a maternal overdose it was found in the cord blood of delivered infants ($n = 4$) at concentrations equivalent to those in maternal blood [149]. Acetaminophen overdose in pregnancy has been reported to result in fetal morbidity and mortality; treatment delay is significantly correlated with fetal loss [148, 150]. Pregnant women who have ingested a potentially toxic amount of acetaminophen should receive treatment as per nonpregnant patients. It seems prudent to use the patient's actual weight when determining the dose of NAC (to a maximum of 110 kg). Other interventions such as emergency cesarean section are not usually warranted. However, cesarean section may be contemplated for near-term infants if the mother has substantial acetaminophen-induced hepatic necrosis. Liver transplantation has been reported successfully in pregnancy in the second trimester, though with fetal loss in this case [151].

Neonatal Patients

Neonates have been safely and effectively treated with IV NAC. Data from a 55-day-old infant born at 29 weeks of gestation indicate slower metabolism in preterm infants in keeping with kinetic predictions [152]. Care must be taken to not give excessive free water, which can result in hyponatremia, and specific regimens for managing infants are published: for example, using 3 ml/kg/h of 50 mg/ml NAC for 1 h followed by 2 ml/kg/h of 6.25 mg/ml NAC for 4 h and then 1 ml/kg/h NAC of 6.25 mg/ml for 16 h, normally given in either 5% glucose or 0.9% sodium chloride [101, 124].

Patients with Myopathies

There are data suggesting that children with myopathies are at greater risk of liver damage from acetaminophen. Both children in this report were in intensive care, one post operatively and the other having a chest infection. The reason for the toxicity is unclear; starvation is an obvious risk factor, and both children were under 60 kg in weight (40 and 55 kg) [66]. Particular care is needed in use and dose of acetaminophen to avoid toxicity in such patients.

Key Points in Acetaminophen Poisoning

1. IV NAC is a highly effective antidote when given shortly after an acute overdose and is the treatment of choice.
2. Decision to treat should be based on a nomogram assessing concentration of acetaminophen taken at least 4 h after a single ingestion.
3. In patients presenting more than 8–10 h after a single ingestion history of ingested dose should be used to assess need for therapy with NAC.
4. In those taking multiple overdoses, or therapeutic excess, the decision to treat is based on history of dose ingested, usually

(continued)

in the last 24 h, on blood results or on presence of symptoms suggestive of liver injury.

5. History of dose ingested correlates well with the plasma concentration of acetaminophen in most patients. If in doubt (e.g., the timing or amount of ingestion) err on the side of prompt treatment with NAC, and revise treatment once blood tests are available.
6. Oral NAC may be used in patients in whom IV therapy is not possible, but care needs to be taken in preventing vomiting.
7. Time to treatment is a key determinant in patient outcome, and delay should be avoided, particularly more than 10 h after acetaminophen ingestion.
8. Most patients with significant hepatotoxicity (AST >1000 IU/L) and coagulopathy after acetaminophen overdose survive without liver transplantation.
9. Presence of acute renal injury at presentation is a marker of poor prognosis.
10. It is essential to check blood results after a course of NAC, and only discharge patients if these are within acceptable limits.
11. Further doses of NAC are indicated in those with abnormal liver function.
12. Patients who survive an acetaminophen overdose have no residual liver damage.
13. Unless clinically indicated, fresh frozen plasma and vitamin K should not be given if the patient has an elevated PT because the PT is an important prognostic indicator.
14. NAC can decrease morbidity and mortality when administered to patients with fulminant hepatic failure after an acute acetaminophen overdose.
15. Selective use of liver transplantation as a treatment modality for patients with fulminant hepatic failure from acetaminophen toxicity, especially in the presence of acidemia, may prove beneficial.

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Introduction

Methotrexate (amethopterin, 4-amino-10-methylpteroglutamic acid) has been a widely used folate antagonist, initially as an antineoplastic agent, and later on as an anti-inflammatory and immunomodulation agent. Aminopterin was the first folate antagonist successfully used for induction of temporary remission in acute leukemia in children [1]. Methotrexate, a safer related agent of aminopterin, replaced it as an antileukemic drug [2]. Since then, methotrexate has been increasingly used as a monotherapy and in combination with other antineoplastic agents for a variety of hematologic and non-hematologic malignancies in children and adults. Its anti-inflammatory and immunomodulation properties were found to be also efficacious in a broad range of dermatologic, rheumatologic, and other disease states (e.g., ectopic pregnancy, graft vs. host disease). The main clinical applications of methotrexate are shown in Table 1 [3].

There are no comprehensive epidemiological data on the incidence, circumstances, and severity of methotrexate overdose and poisoning. However, it may be deduced from the available literature that methotrexate poisoning can occur in the following settings:

1. High-dose methotrexate (HD-MTX) administered to cancer patients. This regimen involves high doses of methotrexate (usually ≥ 500 mg/m²) that can lead to severe toxicity and death, even if no medication error occurred; the mortality associated with HD-MTX before using methotrexate drug monitoring and adjusted dose of folinic acid (Leucovorin) was 4.6–13.6%. HD-MTX-induced renal failure can still cause substantial morbidity and mortality [4–6].
2. Low-dose methotrexate (LD-MTX) used for nonmalignant diseases such as rheumatoid arthritis and psoriasis. It is considered a relatively safe treatment. However, medication

Table 1 Methotrexate main clinical applications

	FDA approved	Non-FDA approved
Malignancies	Acute lymphoid leukemia	Acute myeloid leukemia
	Meningeal leukemia	Carcinoma of the bladder
	Non-Hodgkin's lymphoma	Carcinoma of the penis
	Mycosis fungoides	Carcinoma of the stomach
	Breast cancer	Chronic myeloid leukemia
	Head and neck epidermoid cancer	Hodgkin's lymphoma
	Lung cancer	Malignant epithelial tumor of the ovary
	Osteosarcoma	Soft tissue sarcoma
	Gestational trophoblastic neoplasia	Cutaneous lymphoma
		Meningeal lymphoma
Inflammatory/ immunologic	Rheumatoid arthritis	Crohn's disease
	Juvenile rheumatoid arthritis; polyarticular	Asthma
	Juvenile idiopathic arthritis; polyarticular	Lupus erythematosus
	Psoriasis	Dermatomyositis
		Graft versus host disease
		Multiple sclerosis
		Polymyalgia rheumatica
		Primary biliary cirrhosis
		Sarcoidosis
		Uveitis
		Wegener's granulomatosis
		Ectopic pregnancy
Obstetric		Termination of pregnancy

errors (iatrogenic or patient noncompliance) can lead to toxicity and even death, depending on dose, risk factors, delay in diagnosis, and adequacy of treatment [7, 8].

3. Unintentional overdoses, mainly in children not treated with methotrexate; infrequently reported [9, 10].
4. Attempts at self-harm; rarely reported [9]. The National Poison Data System (NPDS) of the American Association of Poison Control Centers refers to antineoplastic agents without specifying methotrexate. In addition, the NPDS does not list methotrexate or antineoplastic agents as a category or substance with a large number of fatalities [11].

Most methotrexate-induced toxicities are related to therapeutic regimens, mainly HD-MTX, which are managed by hemato-oncologists without medical toxicology or poison center consultation. The mainstay of the management of methotrexate poisoning is appropriate dose tailoring, prevention, identification of risk factors, early detection of errors, vigorous hydration, urinary alkalinization, rescue with folinic acid, enzymatic cleavage of methotrexate with glucaripidase (carboxypeptidase G₂), and extracorporeal enhanced elimination [6, 12].

The molecular structures of folic acid, folinic acid, and methotrexate are shown in Fig. 1.

Clinical Pharmacology

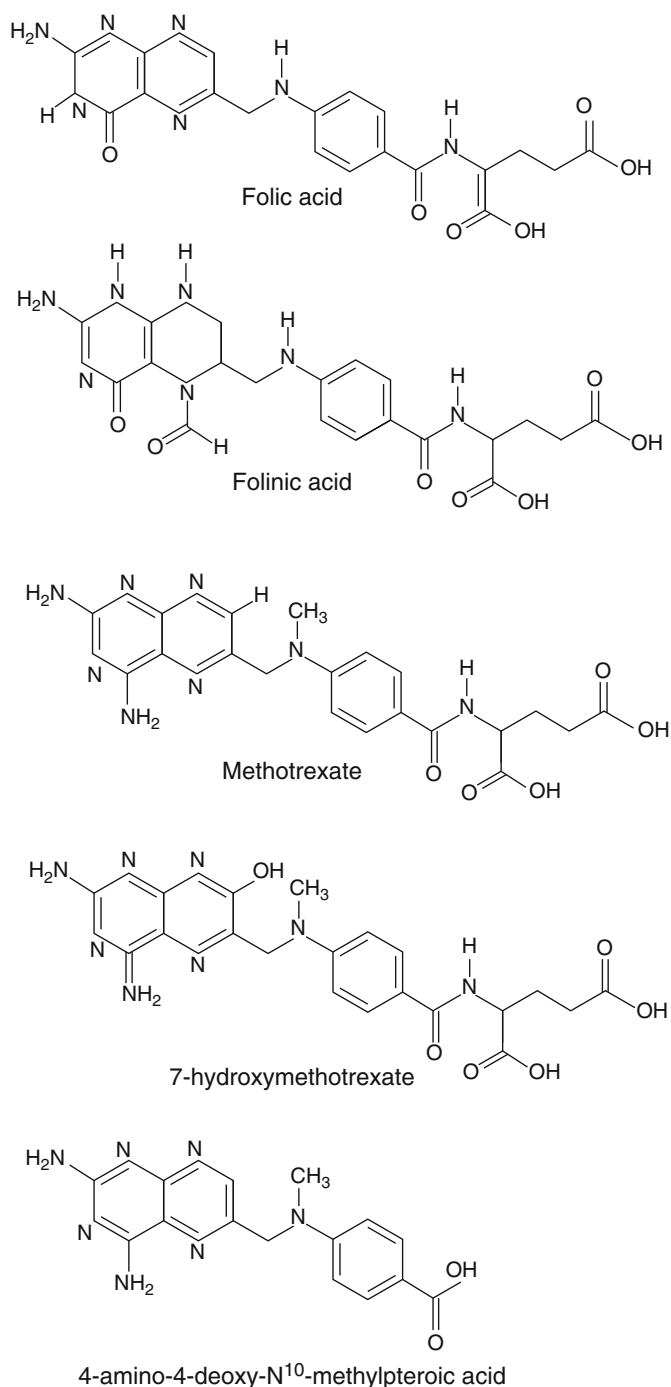
The pharmacokinetics of methotrexate is characterized by striking interpatient variability.

Absorption: The reduced folate carrier protein (RFC1) actively transports methotrexate. This is a cell surface transmembrane protein and a bidirectional transporter of reduced folates and methotrexate. It is highly expressed in the colon, kidney, brain, thymus, and spleen and moderately in the small intestine, liver, bone marrow, lung, and testes. Several ATP-binding cassette (ABC) transporters (e.g., ABCB1, ABCC1, ABCB2, ABCG2) are located on the apical side of various epithelial and endothelial cells, hepatocytes, kidneys, and in lymphocytes. They are responsible to

efflux carrier-mediated transport of methotrexate. All these transporters are subjected to pharmacogenetic variability [13, 14]. Oral methotrexate doses of less than 30 mg are absorbed rapidly and almost completely. Intestinal absorption is active and saturable; therefore, high doses should be given parenterally in order to achieve effective plasma concentrations [15]. Bioavailabilities of 90% and 50% were reported after oral doses of less than 30 mg/m² and 30–80 mg/m², respectively [16]; a plateau was reached at doses of 25–50 mg [17]. Another study showed bioavailability to be significantly lower following doses higher than 40 mg/m² compared with lower doses, 17.5% versus 42%, respectively [18]. However, variable bioavailabilities of 23–95% were reported in children treated with oral methotrexate doses of less than 28.1 mg/m² [19]. Oral doses of 80 mg/m² or higher are incompletely absorbed resulting in plasma concentrations less than one-tenth of that seen after IV administration [16, 17, 20, 21]. The mean oral bioavailability of methotrexate in pediatric patients with inflammatory bowel disease was 84 ± 38%. Interpatient variability was similar between subcutaneous and oral administration. This finding is similar to that found in other disease states [22]. Bioavailability was substantially higher after intramuscular administration than oral and less variable [18].

Peak plasma concentrations after oral doses of less than 20 mg/m² are 0.3–2.2 µmol/L at 1.5–2.5 h [20, 21]. In pediatric patients, oral doses of 6.3–30 mg/m² resulted in a significant interindividual variability in peak concentrations (0.27–1.1 µmol/L) and time to peak (1–5 h) [19, 23]. Treatment with 50–250 mg/kg methotrexate as a 6-h infusion was associated with peak levels between 100 and 1,000 µmol/L [24]. Methotrexate doses of 12 g/m² IV resulted in a C_{max} of >1,000 µmol/L in 96% of patients [25]. In another study of patients with HD-MTX (300 mg/m² to 12 g/m²), plasma methotrexate concentrations at 24 and 48 h after the start of infusion were 0.66 µmol/L and 0.12 µmol/L, respectively; 7-hydroxy-methotrexate (the main active and toxic metabolite) concentrations were 2.52 µmol/L and 0.72 µmol/L, respectively [26].

Fig. 1 Molecular structure of folic acid, folinic acid, methotrexate, and its main metabolites



Distribution: The protein binding of methotrexate is 50–70%, primarily to albumin [16]. Distribution half-life is 0.75 h [27]. Initial volume of distribution is 0.18 L/kg, and

the steady-state volume of distribution is 0.4–0.8 L/kg [28–30]. A population kinetic study found a volume of distribution of the central compartment of 23 L; the volumes of

the first and second peripheral compartments were 185 and 5.34 L, respectively [26].

Elimination: Methotrexate is eliminated mainly in its unchanged form through the kidneys by glomerular filtration together with tubular reabsorption and secretion (50–90% within 48 h, mostly within 8–12 h) [20, 21, 26]. It was suggested that tubular reabsorption and secretion are also saturable [31, 32]. Inadequate hydration, low urine flow and pH, and concomitant nephrotoxic drugs can affect renal clearance of methotrexate resulting in toxicity. A small amount of unchanged methotrexate (less than 10%) undergoes biliary excretion and enterohepatic circulation [33].

Metabolism becomes more important in HD-MTX. Methotrexate undergoes liver and intracellular metabolism; it is also partially metabolized by intestinal flora after oral administration. Hepatic aldehyde oxidase metabolizes about 10% of the methotrexate dose via hydroxylation to 7-hydroxy-methotrexate. This metabolite possesses 1/100–1/200 of the inhibitory dihydrofolate reductase (DHFR) activity of methotrexate [31, 32, 34–36]. Within 12–24 h of the start of HD-MTX, the plasma concentration of 7-hydroxy-methotrexate exceeds that of methotrexate. Both methotrexate and 7-hydroxy-methotrexate undergo intracellular polyglutamation by Folypolyglutamyl synthase, causing its retention and leading to amplified cytotoxicity [6, 37, 38]. Methotrexate is also metabolized to 2,4-diamino- N^{10} -methylpteroic acid (DAMPA), an inactive metabolite (less than 5% of dose). It is believed that DAMPA is formed from hydrolysis of methotrexate excreted into the intestinal tract by bacterial carboxypeptidase. Eventually, DAMPA is reabsorbed, accounting for less than 5% of the total methotrexate dose excreted in urine [6, 20, 38–41].

Population pharmacokinetics showed methotrexate and 7-hydroxy-methotrexate clearances to be 147.5 and 33.3 mL/min, respectively [26]. The range of methotrexate clearance reported was 99.1–156.7 mL/min [42, 43]. A threefold variation in plasma methotrexate concentrations was found after a dose of 1 g/m² IV, suggesting patient variability in elimination [44]. Methotrexate clearance

was significantly lower in infants less than 6 months old compared with infants 7–12 months old, 89 ± 32 mL/min/m² and 111 ± 40 mL/min/m², respectively [45].

Plasma methotrexate concentrations fell in a bi-exponential curve corresponding to elimination half-lives of 2 and 10.4 h [24]. Other studies suggested a triphasic disappearance of methotrexate from plasma following intravenous administration. The initial (distribution) half-life was 0.75 ± 0.11 h, second half-lives were 2.06 ± 0.16 , 3.49 ± 0.55 , and 2.0–3.4 h (representing mainly renal clearance), and terminal half-life was 10.4 ± 1.8 h (representing tissue redistribution) [16]. Another study also showed that a linear three-compartment model with first order elimination from the central compartment best described methotrexate concentration-time data. 7-hydroxy-methotrexate followed a linear two-compartment model with first order elimination from the central compartment [26]. In osteosarcoma patients on HD-MTX, non-compartmental analysis and population pharmacokinetic modeling showed that median methotrexate late elimination half-life was 4.02 h [42]. Elimination half-life after oral administration was 4–6 h [19, 20]. In children on weekly LD-MTX, median elimination half-life was 1.7 h [46].

The main pharmacokinetic characteristics of methotrexate are summarized in Table 2.

Cerebrospinal fluid (CSF) concentrations after HD-MTX are about 1–10% of the corresponding plasma concentrations. CSF concentrations between 0.1 and >10 μ mol/L were measured after a 24-h infusion of 500 mg/m² and a 7.5 g/m² IV bolus, respectively [47–50]. Methotrexate is pumped out of the CSF by ABC transporters [20].

Ascites or effusions may serve as a reservoir from which methotrexate can redistribute. The concentrations of methotrexate in third space collections are usually 10% of the plasma concentrations. The volume and consistency of these fluids can affect the elimination of methotrexate from such spaces, resulting in much higher levels and prolonged cytotoxic plasma concentrations. Methotrexate doses higher than 250 mg/m² are

Table 2 Pharmacokinetic parameters of methotrexate

Pharmacokinetic parameter	
Systemic oral bioavailability	17.5–95% Variable and dose dependent Highest if $<30 \text{ mg/m}^2$, lowest if $>80 \text{ mg/m}^2$
C _{max} oral (6.3–30 mg/m^2)	0.27–1.1 $\mu\text{mol/L}$
T _{max} oral (6.3–30 mg/m^2)	1–5 h
C _{max} HD-MTX (IV 12 g/m^2)	$>1,000 \mu\text{mol/L}$
C _{max} HD-MTX (IV 50–250 mg/kg)	100–1,000 $\mu\text{mol/L}$
Protein binding	50–70%
Volume of distribution, steady state	0.4–0.8 L/kg
Clearance	99–157 mL/min
Renal elimination	50–90% within 48 h
Elimination half-life, terminal (HD-MTX)	10.4 h

more likely to be associated with these effects [51–53].

Pharmacokinetic Drug–Drug Interactions

In patients on HD-MTX (300 mg/m^2 to 12 g/m^2), population pharmacokinetics showed that concurrent use of benzimidazoles (e.g., omeprazole, lansoprazole) caused a significant 3.03 (range 2.19–4.19) and 2.1 (range 1.5–2.95) increases in plasma methotrexate concentrations at 24 and 48 h, respectively; methotrexate clearance significantly decreased by 27% [26]. Decreased elimination of methotrexate by benzimidazoles may due to inhibition of methotrexate transport by the drug transporter ABCG2 (BCRP) [54].

Prior administration of nonsteroidal anti-inflammatory drugs (e.g., diclofenac, ibuprofen) increased plasma methotrexate concentrations by 1.26 (range 0.84–1.91) and 1.34 (range 0.84–2.13) at 24 and 48 h, respectively; plasma clearance decreased by 16%. Similar changes

were reported for 7-hydroxy-methotrexate; all changes were significant [26]. Nonsteroidal anti-inflammatory drugs exert their interaction with methotrexate via decreased renal blood flow.

The main mechanisms of pharmacokinetic drug interaction include decreased renal tubular secretion (e.g., by piperacillin/tazobactam, salicylates, probenecid, trimethoprim–sulfamethoxazole, ciprofloxacin), protein binding displacement (e.g., by trimethoprim–sulfamethoxazole), and reduced glomerular filtration [26, 55, 56].

Therapeutic Drug Monitoring

Early studies showed that plasma methotrexate concentrations of 0.9 $\mu\text{mol/L}$ or higher 48 h after the start of high-dose infusion (50–250 mg/kg) were associated with myelosuppression and mucositis [24]. Therefore, plasma methotrexate concentrations and serum creatinine should be determined during HD-MTX therapy in order to identify patients at risk and guide administration of high-dose folinic acid rescue, enzymatic cleavage with glucaridase, and enhanced elimination. It is important to measure plasma methotrexate concentrations at the time intervals dictated by the HD-MTX protocol used. It is usually recommended to monitor plasma methotrexate concentrations 24, 48, and 72 h after the start of a 4-h HD-MTX infusion, aiming to reach target concentrations of ≤ 5 –10, ≤ 1 , and $\leq 0.1 \mu\text{mol/L}$, respectively [6, 57, 58]. If a 24-h infusion is administered, it is recommended to determine plasma methotrexate concentrations at 42 and 66 h after the start of the infusion; target concentrations are <0.5 –1 and $<0.1 \mu\text{mol/L}$, respectively [58].

It was suggested to continue folinic acid until plasma methotrexate concentrations are less than 0.01 $\mu\text{mol/L}$, the methotrexate threshold for in vivo inhibition of DNA synthesis in bone marrow and gastrointestinal epithelium [24, 59]. More recent studies suggest that concentrations of less than 0.05–0.1 $\mu\text{mol/L}$ allow discontinuation of folinic acid [6].

Pathophysiology

Methotrexate is a folate antagonist. Therefore, its mechanisms of action and toxicity are better understood by knowing the metabolic pathways of folic acid (Fig. 2).

Folate is transported into the cells where it is converted to tetrahydrofolate (FH₄). It participates in a series of metabolic reactions necessary for pyrimidine and purine syntheses, involving the enzymes dihydrofolate reductase (DHFR), methionine synthase (MS), thymidylate synthase (TS), aminoimidazole carboxamide

ribonucleotide transformylase (AICRT), and glycinamide ribonucleotide transformylase (GARFT). Folates undergo polyglutamation inside the cell, which increases their intracellular store due to reduced efflux and increased uptake [6, 26, 60–63].

The main intracellular sites of action of methotrexate and folinic acid are shown in Fig. 3.

Methotrexate is actively transported into cells via the reduced folate carrier (RFC1, SLC19A1). When methotrexate extracellular concentrations exceed 20 μmol/L, passive diffusion across the cell membrane takes place. ATP-binding cassette

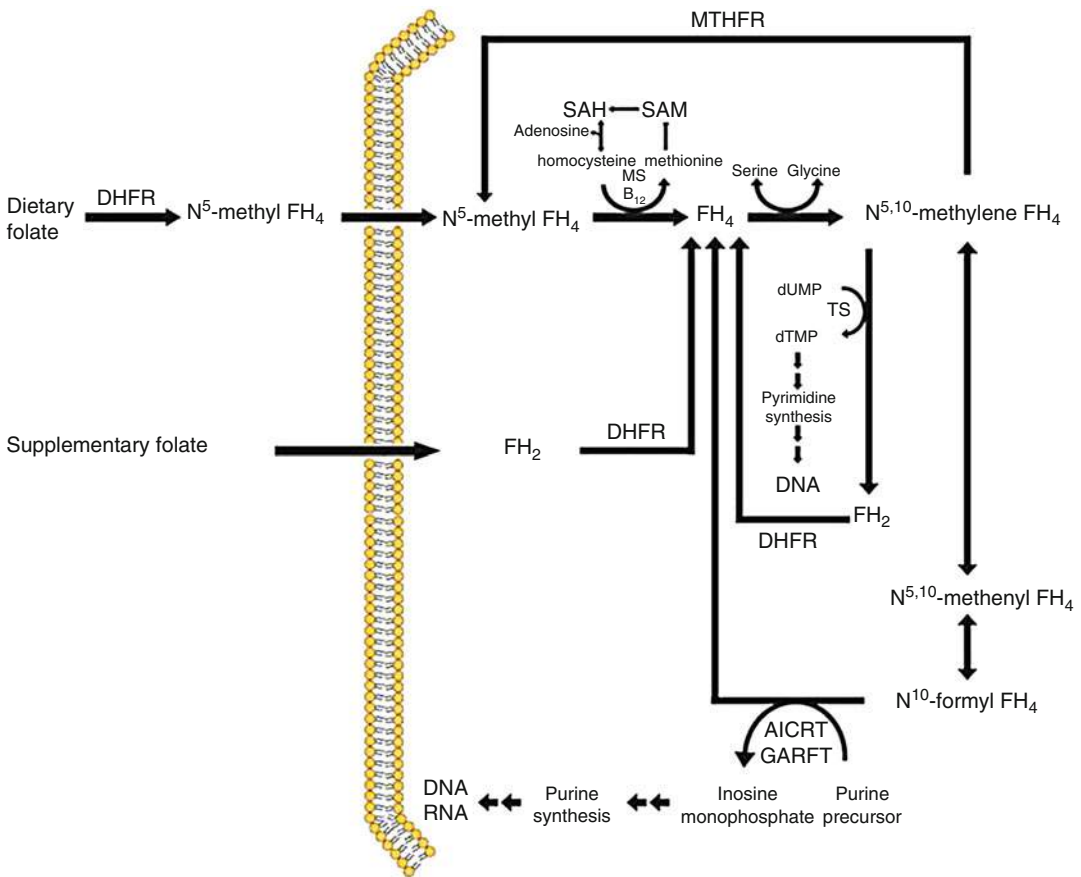


Fig. 2 Metabolic pathways of folate AICRT – 5-aminoimidazole-4-carboxamide ribonucleotide transformylase; DHFR – dihydrofolate reductase; dTMP – deoxythymidine monophosphate; dUMP – deoxyuridine monophosphate; FH₂- dihydrofolate; FH₄- tetrahydrofolate;

GARFT – glycinamide ribonucleotide transformylase; MS – methionine synthetase; MTHFR – methylene tetrahydrofolate reductase; SAH – S-adenosylhomocysteine; SAM – S-adenosylmethionine; TS – thymidylate synthetase

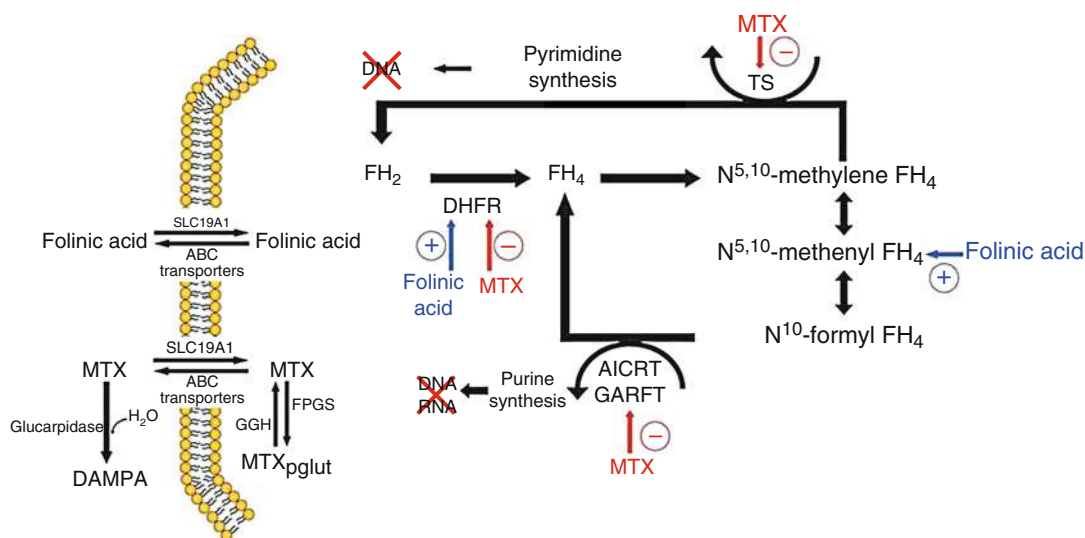


Fig. 3 Intracellular sites of action of methotrexate and folinic acid. ABC – ATP binding cassette; AICRT – aminoimidazole carboxamide ribonucleotide transformylase; DHFR – dihydrofolate reductase; GARFT – glycinamide ribonucleotide transformylase; GGH – glutamyl hydrolase; FH_2 – dihydrofolate;

FH_4 – tetrahydrofolate; FPGS – folypolyglutamyl synthetase; DAMPA – 2,4-diamino-N-methylptericoic acid; MTX – methotrexate; MTXpglu – methotrexate polyglutamate; SLC19A1 – reduced folate carrier (RFC); TS – thymidylate synthetase; Folic acid – N^5 -formyl tetrahydrofolate (Leucovorin)

(ABC) transporters (mainly ABCC1-4, ABCG2) pump methotrexate out of the cells. Intracellular methotrexate (as well as folate) undergoes polyglutamation to an active form (methotrexate polyglutamate; MTXpglut) which is retained in the cells for prolonged periods of time. Polyglutamation increases the affinity of methotrexate for vulnerable enzymes. The longer the polyglutamated tail (>5 glutamic acid residues) is, the diffusion out of cells is slower, and the affinity to the inhibited enzymes is stronger. Hydrolysis by γ -glutamyl hydrolase (GGH) reverses polyglutamation of methotrexate. This results in cellular efflux of methotrexate and short-chain MTXpglut.

Three enzymes are inhibited by methotrexate and MTXpglut:

1. DHFR. The binding of methotrexate to DHFR is stoichiometric and competitive; 95% inhibition is required to stop FH_4 synthesis. This will result in FH_4 depletion and decreased synthesis of thymidylic acid and inosine monophosphate involved in pyrimidine and purine synthesis,

respectively. The reduced concentrations of FH_4 and N^5 -methyl FH_4 resulting from inhibition of DHFR also cause accumulation of homocysteine and its metabolites and excitatory amino acids [excitatory agonists of N -methyl-D-aspartate (NMDA) receptors]. The decreased supply of methionine eventually results in reduced synthesis of neuronal myelin sheath.

2. Thymidylate synthase. The inhibition of thymidylate results in reduced pyrimidine synthesis.
3. AICRT and GARFT. Purine synthesis diminishes due to inhibition of these enzymes.

The net result is blockade of DNA, RNA, and protein synthesis through both direct enzyme inhibition and depletion of FH_4 [20, 59, 62, 64–77].

The severity and type of methotrexate cytotoxicity depend on both concentration and duration of exposure. Brief exposure to high concentrations (mmol/L for minutes or hours) may be tolerated, but may also lead to acute renal, liver, and

central nervous system (CNS) toxicity. Low concentrations for a prolonged period (e.g., 0.05–0.1 $\mu\text{mol/L}$ for 24–48 h) can result in life-threatening toxicity, including bone marrow and gastrointestinal effects [6, 26, 59]. Polyglutamation occurs when cells are exposed to methotrexate concentrations of $\geq 2 \mu\text{mol/L}$ for ≥ 6 h, explaining the greater incidence and severity of toxicity associated with HD-MTX [78, 79]. Following HD-MTX, 7-hydroxy-methotrexate is formed; it has about 1/100–1/200 of the DHFR inhibitory activity of methotrexate [31, 32, 34–36]. 7-hydroxy-methotrexate is also polyglutamated; this form retains in the cells for prolonged periods of time, resulting in enhanced toxicity [6, 37, 38].

Supplemental folate is reduced intracellularly to FH_4 by DHFR. Methotrexate-induced inhibition of DHFR explains why supplemental folate cannot be used as an antidote for methotrexate toxicity. Folic acid was found to decrease kidney reabsorption of methotrexate in an experimental study [80].

The mechanism of action of folinic acid is discussed in the “[Treatment](#)” section. The clinical pharmacology of folinic acid is discussed in ► [Chap. 149, “Folic and Folinic Acids.”](#)

Mechanism of Methotrexate-Induced Nephrotoxicity

Methotrexate is highly eliminated via the kidneys. It is a weak acid with a pH of 4.8–5.5, meaning that it is poorly soluble in an acidic environment. HD-MTX can produce renal methotrexate concentrations above its solubility, 2 $\mu\text{mol/L}$ at urine pH of 5.5. Its metabolites, 7-hydroxy-methotrexate and DAMPA, are six- to tenfold less soluble at neutral or acidic pH, respectively. 7-hydroxy-methotrexate can also compete with methotrexate on tubular secretion. Therefore, in acidic urine, methotrexate and metabolites will precipitate in the renal tubules, causing a nonoliguric, usually reversible, renal failure. Increasing the urine pH from 5 to 7 will increase methotrexate solubility by 23-fold, 7-hydroxy-methotrexate by 12, and DAMPA by 17. Maintaining an alkaline urine

(pH > 7) before, during, and after HD-MTX together with adequate hydration and urine flow can reduce the risk of methotrexate-induced renal failure and its consequences [6, 12, 16, 39, 81–86]. Renal failure significantly decreases methotrexate clearance. The resulting sustained increased plasma methotrexate concentration leads to enhanced toxicity and reduced efficacy of folinic acid.

Mechanism of Methotrexate-Induced Neurotoxicity

Methotrexate-induced neurotoxicity can be acute, subacute, or chronic and develop after systemic, intrathecal (IT), or combined administration. Both methotrexate and its polyglutamated metabolites are involved in this toxicity. Several mechanisms were proposed for methotrexate-induced neurotoxicity:

1. Inhibition of DHFR (via depletion of reduced folate)
2. Accumulation of homocysteine (toxic to vascular endothelium) and its metabolites (increased excitatory amino acids – NMDA receptor agonists)
3. Decreased synthesis of myelin sheath (due to depletion of S-adenosylmethionine and accumulation of S-adenosylhomocysteine)
4. Accumulation of adenosine (dilates cerebral blood vessels, alters release of neurotransmitters, and slows neuronal discharge)
5. Acute arachnoiditis (reported only after IT administration) [75, 76, 87]

Pharmacogenetics

All metabolic pathways of folates and methotrexate are subjected to genetic polymorphisms. This is reflected in the variable clinical response to methotrexate and its toxicity. The following include examples of genetic polymorphisms that were suggested to be associated with methotrexate toxicity [13, 20].

Methotrexate Transport

Reduced Folate Carrier Protein (RFC1)

Methotrexate is transported intracellularly via the RFC1 encoded by *SLC19A1* gene located on chromosome 21. AA homozygous patients have decreased cellular influx of methotrexate leading to high plasma concentration. In children receiving HD-MTX, the A allele was shown to be associated with liver, gastrointestinal, and skin toxicity, and the G allele with hyperbilirubinemia and vomiting. Some studies suggested that *SLC19A1* polymorphism was not associated with high plasma methotrexate concentrations. Studies in rheumatoid arthritis patients showed inconsistent results on the association between *SLC19A1* 80G > A polymorphism and methotrexate toxicity [88–94].

ATP-Binding Cassette (ABC) Transporters

P-glycoprotein (multidrug resistance protein 1; MDR1) is encoded by the *ABCB1* gene. The highly polymorphic ABC transporters mediate methotrexate efflux. *MDR1* C3435T was found to increase the risk for methotrexate toxicity. However, overall conflicting results exist on the association between single nucleotide polymorphisms (SNPs) of this gene and methotrexate toxicity [88, 95, 96].

Multidrug resistance-associated protein 1 (MRP1) is encoded by the *ABCC1*, also participating in methotrexate efflux. Several studies could not demonstrate an association with SNPs on this gene and methotrexate toxicity [95, 97].

Multidrug resistance-associated protein 2 (MRP2) is encoded by *ABCC2* gene. Some variants of *ABCC2* may affect methotrexate and 7-hydroxy-methotrexate. Data on the association with toxicity are inconsistent [95, 97]. Multidrug resistance efflux transporter ABC subfamily G member 2 (breast cancer resistance protein – BCRP) is expressed by *ABCG2* gene. This gene is involved in the transport of methotrexate and MTXpglut. Some SNPs were reported to be related to overall toxicity of methotrexate [97].

Polyglutamation of Methotrexate

Folypolyglutamate Synthetase (FPGS)

FPGS catalyzes sequential additions of glutamate residues to methotrexate, causing its intracellular retention and enhanced toxicity. SNPs on the FPGS gene encodes for polymorphisms of this enzyme. Several alleles were related to increased risk for methotrexate toxicity, especially in the presence of low activity SNPs in *gamma-glutamyl hydrolase* (*GGH*) gene [93, 98].

Gamma-Glutamyl Hydrolase (GGH)

GGH catalyzes removal of glutamic acid residues from MTXpglut, enabling efflux of methotrexate by transporters. Several SNPs in the *GGH* gene may affect polyglutamation. The presence of *GGH*-354GG was associated with myelosuppression, and *GGH*-401CC with gastrointestinal and CNS side effects in rheumatoid arthritis patients. *GGH*-401CT and TT genotypes were found to increase the risk of severe leukopenia and thrombocytopenia in children with ALL treated with HD-MTX. Other SNPs were not found to be related to methotrexate toxicity [93, 98–101].

Methotrexate-Induced Enzyme Inhibition

Dihydrofolate Reductase (DHFR)

DHFR is one of the main enzymes inhibited by methotrexate. Polymorphisms in the *DHFR* gene can be associated with an increased relapse rate in children with ALL treated with HD-MTX [102]. DHFR polymorphism was associated with hepatotoxicity in adults with ALL [103]. Conflicting results were reported on the association between *DHFR* polymorphisms and methotrexate toxicity [93, 101, 104].

Methylenetetrahydrofolate Reductase (MTHFR)

MTHFR is responsible for the conversion of $N^{5,10}$ -methylene FH₄ to N^5 -methyl FH₄, during which homocysteine is re-methylated to

methionine. Its gene, *MTHFR*, is essential for the response to methotrexate. The data on the effects of *MTHFR* polymorphisms on the activity of *MTHFR* and the response to methotrexate and its toxicity are inconsistent [88, 89, 96, 103, 105–109].

Thymidylate Synthase (TS)

TS is a major enzyme in pyrimidine synthesis. Some genetic polymorphisms in the TS gene (*TYMS*) were not associated with the response to methotrexate or with its toxicity [110].

5-Aminoimidazole-4-Carboxamide Ribonucleotide Transformylase (AICRT)

This enzyme is involved in de novo purine synthesis and is encoded by the *ATIC* gene. Polymorphisms on the *ATIC* 347G allele were shown by several studies to be associated with toxicity, e.g., gastrointestinal [107, 111, 112], but not by others.

Methionine Synthase (MS)

The conversion of homocysteine to methionine is catalyzed by MS (methyltransferase; *MTR* gene) in a process requiring B₁₂; N⁵-methyl FH₄ is converted to FH₄ at the same time. Polymorphism on the allele *MTR* 2756GG was reported to increase the risk of MTX-induced accelerated rheumatoid nodulosis [113]. Toxicity associated with other alleles has not been confirmed.

Methionine Synthase Reductase (MTRR)

MTRR activates cobalamin-dependent methionine synthase that converts homocysteine to methionine. It maintains adequate levels of methylcobalamin required for this reaction. Polymorphism of *MTRR* 66A > G allele is associated with an increased frequency of HD-MTX-induced mucositis [114].

Toxic Doses and Concentrations

Methotrexate toxicity depends on both concentration and duration of exposure. Concentrations of 0.05–0.1 µmol/L for more than 24–48 h can result

in gastrointestinal and hematological toxicity. Millimolar (mmol/L) concentrations for minutes to hours can cause renal, liver, and CNS adverse effects [20].

High-Dose Methotrexate (HD-MTX)

HD-MTX is usually defined as IV dose of >500 mg/m², range 30 mg/m² to >12 g/m². Very high doses, up to 33.6 g/m², were used together with folinic acid in childhood ALL requiring CNS preventive therapy [6, 115]. Some clinicians consider doses of 50–500 mg/m² as intermediate dose. It is generally considered that plasma methotrexate concentrations of 700 – >1,000 µmol/L and ≥1,500 µmol/L at the end of the 6-h infusion are associated with treatment success and a worse long-term outcome, respectively. Methotrexate blood concentrations measured every 24 h for 72 h after the start of the infusion are useful for detecting delayed elimination and guide dosing of folinic acid. The following plasma methotrexate concentrations define its delayed elimination and are predictive of toxicity: ≥5–10 µmol/L at 24 h, ≥1 µmol/L at 48 h, and ≥0.1 µmol/L at 48 h. These concentrations require increased dosing of folinic acid until methotrexate concentration is less than 0.05–0.1 µmol/L [6, 25]. It should be emphasized that a rise in serum creatinine of 50% and higher within 24 h after the beginning of HD-MTX (5–8 g/m²) has a sensitivity and specificity of 0.32 and 0.99, respectively, to predict delayed elimination of methotrexate [116]. A pilot matched case-control study of 11 children and 17 controls with ALL and osteosarcoma evaluated the association between plasma methotrexate concentrations and oral mucositis WHO Grade II (painful ulceration; can eat). The results showed concentrations of ≥1 µmol/L at 42 h or ≥0.2 µmol/L at 66 h after the start of HD-MTX to be associated with an odds ratio of 4.3 and 8.2, respectively, for developing oral mucositis compared with lower concentrations [117].

Low-Dose Methotrexate (LD-MTX) and Associated Medication Errors

Methotrexate oral doses of 5–25 mg/week are used to treat nonmalignant diseases (e.g., psoriasis, rheumatoid arthritis). These therapeutic doses can be associated with adverse reactions involving bone marrow, kidney, liver, intestine, skin, lungs, and mucous membranes. In general, plasma concentrations of methotrexate used for nonmalignant indications are expected to be less than 0.01 $\mu\text{mol/L}$ [17].

A retrospective study evaluated data of 28 patients aged 33–88 years admitted due to methotrexate poisoning associated with LD-MTX. Mean methotrexate dose was 10.5 ± 4.2 mg/week (range 5–20). Iatrogenic errors were made in three (10.7%) patients, daily instead of weekly dose. Seven (25%) patients died. No correlation was found between plasma methotrexate concentrations and toxicity or survival. However, it is unclear when samples were drawn relative to last dose [7].

In a series of four patients, methotrexate poisoning caused by iatrogenic errors (10–20 mg daily instead of weekly) resulted in fatalities after 5–9 days [8]. In another series of fatal iatrogenic errors, doses administered were 10 mg/day for 23 days, 20 mg/week for 3 weeks, 100 mg during 8 days, 10 mg/day for 9 days, and 15 mg/day for 6 days. Methotrexate concentrations were 0.25, 0.2, and ≤ 0.1 $\mu\text{mol/L}$, 1, 7, and 2 days after the last methotrexate dose, respectively [118]. Published cases reported survival after iatrogenic dosing errors ranging from similar doses (e.g., 60 mg weekly for 2 weeks, 2.5 mg daily for more than 6 days, 10 mg for 4 days) to much higher (i.e., 2.5 g IM) [119–122].

Unintentional Overdose

A retrospective poison center chart review identified 11 patients who unintentionally ingested methotrexate, including children; lowest age was 20 months. The most common formulation ingested was 2.5 mg tablet. Ten patients were observed at home, one at the emergency

department, all with excellent outcome [9]. No data were provided on individual dose taken, methotrexate concentrations, kidney function, and liver enzymes. Pediatric case reports described no effect or transient elevation of liver enzymes after alleged doses of 25–250 mg methotrexate. Methotrexate concentrations were 0.67 $\mu\text{mol/L}$ in one case. Folinic acid was withheld or delayed [10, 123–125]. Unintentional single oral overdose of methotrexate is usually associated with low to moderate plasma concentrations for a limited time, explaining the favorable outcome of these cases [10].

Intentional Overdose

Two self-harm attempts were reported in a retrospective poison center chart review and one pediatric. Concomitant ingestions included ibuprofen and acetaminophen. Patients were asymptomatic, without hepatic or bone marrow toxicity at 48 h post ingestion. Plasma methotrexate concentrations were 0.09 and 0.47 $\mu\text{mol/L}$, much lower than the concentration considered therapeutic [9]. The exact doses taken in these cases are unclear. Saturable intestinal absorption could limit the toxicity of acute high oral methotrexate dose.

Clinical Presentation

The toxicity profile of methotrexate varies markedly according to dose, frequency and duration of administration, route of exposure, and patient characteristics (e.g., kidney function and concomitant drugs). For example, neurotoxicity and nephrotoxicity are more common and severe in HD-MTX, whereas hematologic toxicity is more common in patients on LD-MTX who do not receive folinic acid rescue. Most of our knowledge about methotrexate toxicity comes from the adverse effects reported in HD-MTX, LD-MTX, and medication errors. The toxicity of acute overdose can be extrapolated from that knowledge.

The following is a discussion of methotrexate toxic effects according to the type of exposure:

HD-MTX, LD-MTX, medication errors, and acute overdose.

High-Dose Methotrexate

HD-MTX regimens involve the infusion of highly toxic and potentially lethal doses and require adequate patient preparation and folinic acid rescue to reduce or prevent methotrexate toxicity. Meticulous patient selection, monitoring, and intervention plan are required. In a retrospective study of patients treated with HD-MTX before 1977, there were 6% methotrexate-related deaths; 80% were attributed to severe myelosuppression resulting in either sepsis or hemorrhage and 20% to renal failure [4]. With current protocols, mortality is rare, but severe toxicity still occurs, especially in patients with delayed methotrexate clearance due to renal impairment, drug interactions, and genetic predisposition and in the elderly. The following is a discussion of the toxicity associated with HD-MTX.

Gastrointestinal: Oral mucositis occurs in up to 72% of HD-MTX treated [126–128]. It has serious consequences, including pain, route of entry for infections, and inadequate nutrition. Although mild to moderate in most cases, it may be severe in the setting of delayed methotrexate elimination and its prolonged exposure [85, 129]. Nausea, vomiting, and diarrhea can also be severe in this setting. Vomiting during the course HD-MTX infusion was one of the variables associated with high-risk plasma methotrexate concentrations and toxicity [57, 117].

Nephrotoxicity: Methotrexate administered in high doses can damage the kidneys by precipitation in renal tubules (especially if urine is acidic) or by direct toxic effect. Methotrexate-induced renal dysfunction is usually nonoliguric and reversible. It can cause delayed elimination of methotrexate resulting in sustained elevation in plasma methotrexate concentrations and increased systemic toxicity. Concurrent administration of nephrotoxic agents (e.g., IV contrast agents) and drugs interfering with methotrexate excretion (e.g., probenecid, salicylates, sulfisoxazole, penicillins, and nonsteroidal anti-

inflammatory agents) can also increase methotrexate plasma concentrations and toxicity [6, 55]. Even with current protocols of hydration, urinary alkalization and folinic acid rescue, significant morbidity and mortality due to methotrexate renal dysfunction still occur. A review of 20 clinical trials on patients with osteosarcoma between 1980 and 2002 found that the median incidence of renal toxicity was 1.5% (range, 0.0–12.4%): 1.8% developed Grade II or higher nephrotoxicity and 0.6% developed Grade III or IV nephrotoxicity. Mortality among nephrotoxic patients was 4.4%, 0.08% in all patients on HD-MTX [12]. The incidence is probably higher in patients outside clinical trials and in older patients [79]. In 48% of patients with a median age of 72 years (78% aged 50 years or older) who received HD-MTX (8 g/m²), serum creatinine doubled [130].

Hepatotoxicity: Acute transient elevation in the serum transaminases occurs in most patients treated with HD-MTX [79, 127, 128]. In a cohort of 97 osteosarcoma patients (376 HD-MTX courses, 8–12 g/m²), 81% of the patients experienced elevated ALT levels; AST and GGT were often elevated too. These enzyme abnormalities were always reversible and generally asymptomatic [128]. Increased bilirubin (less than threefold) was less frequent [127]. No reports were found on long-term hepatic complications such as fibrosis or cirrhosis.

Hematologic toxicity: Myelosuppression is a major risk of prolonged exposure to high plasma methotrexate concentrations [24]. The onset of leukopenia is between days 3 and 10 (median 6 days), with a nadir between days 5 and 15 (median 8 days). The onset of thrombocytopenia is between days 4 and 12 (median 9 days) with a nadir between days 9 and 14 (median 11 days) [131]. Infections and bleeding due to bone marrow suppression can be life-threatening [85, 129].

Neurotoxicity: Neurotoxicity may develop following IV high-dose or intrathecal (IT) administration of methotrexate. Toxicity of IT methotrexate is discussed below.

Methotrexate neurotoxicity can cause acute, subacute, and long-term effects [132, 133]; others divide it into acute and chronic [134, 135].

Acute or subacute encephalopathy generally develops within hours to days after methotrexate administration and is usually transient. Its manifestations include headache, nausea, vomiting, lethargy, fatigue, altered mental status, somnolence, confusion, blurred vision, speech disorders, ataxia, hemiparesis, choreoathetosis, seizures, and affective disturbances. The term “stroke-like syndrome” is often used to describe some of these effects [132, 133, 135].

In pediatric osteosarcoma patients, acute/subacute neurologic deficits, including hemiplegia, speech disorders, convulsions, and rapidly ascending paralysis, occurred in up to 15% of the patients. The average interval between the methotrexate course and the onset of the neurologic disturbance was 6 days (range, several hours to 20 days) [136]. Among pediatric ALL patients receiving IV and/or IT methotrexate, clinical acute/subacute encephalopathy developed in 0.8–3.8% of the patients [133–135]. The higher incidence of acute encephalopathy in osteosarcoma patients may be due to the higher doses of methotrexate used. It should be noted that acute/subacute methotrexate neurotoxicity was transient in most pediatric cancer patients. Clinical symptoms of methotrexate-induced neurotoxicity are often associated with leukoencephalopathy, evident as white matter hyperintensities on T2-weighted and fluid-attenuated inversion recovery magnetic resonance imaging (MRI) [133]. Leukoencephalopathy occurred following IV high-dose or IT methotrexate and their combination, with or without cranial irradiation. Although leukoencephalopathy is low grade in most patients, fatal diffuse necrotizing leukoencephalopathy has been reported [133, 137]. Leukoencephalopathy can also develop in asymptomatic children receiving methotrexate. In a study on 369 pediatric ALL patients treated with combined IV high-dose and IT methotrexate, 3.8% developed clinical neurotoxicity. Leukoencephalopathy was found in 20.6% of asymptomatic patients and in all symptomatic patients, persisting at the end of therapy in 74% of asymptomatic patients and 58% of symptomatic patients [133].

Chronic encephalopathy develops slowly, even months to years following HD-MTX therapy. It may progress and can permanently impair neuropsychological function. It is often associated with HD-MTX, inadequate folinic acid rescue, and prior cranial irradiation. The characteristic syndrome is leukoencephalopathy presenting with confusion, somnolence or irritability, impaired vision and speech, seizures, ataxia, and dementia; quadriparesis, coma, and death may occur [132, 134, 135]. Leukoencephalopathy involves mainly the white matter, mostly the periventricular region and the centrum semiovale. It is characterized by demyelination, multifocal white matter necrosis, astrocytosis, and axonal damage. Intracerebral calcifications, cerebral atrophy, and mineralizing microangiopathy were also reported [132]. Stabilization or partial recovery of the leukoencephalopathy was reported, mainly in children [132]. In addition, concerns were also raised about late neurocognitive effects of IT and HD-MTX [138].

Dermatologic: Dermatologic toxicity may range from mild transient erythematous eruptions to frank exfoliative dermatitis [73, 139, 140]. About 14% of patients on HD-MTX with minimal folinic acid rescue developed a patchy erythematous macular rash [141]. Alopecia, to some degree, may occur.

Ophthalmologic: Transient conjunctivitis was infrequently (4.2%) reported. It seemed not to be related to the occurrence of rash or stomatitis [73, 141] (Table 3).

Low-Dose Methotrexate

Prolonged use of low oral doses of methotrexate for systemic inflammatory diseases is considered relatively safe. However, toxicity can limit this treatment, and severe toxicity can occur under certain circumstances.

Folic or folinic acid supplementation reduces the incidence of gastrointestinal and hepatic adverse reactions. The effect on hematologic toxicity is not well defined due its low incidence [142, 143]. The following includes a discussion of LD-MTX toxicity according to organ systems.

Table 3 Main clinical manifestations of methotrexate toxicity (for the manifestations of intrathecal overdose, please see the relevant section)

	Acute methotrexate overdose	Low-dose methotrexate	Medication errors associated with low-dose methotrexate	High-dose methotrexate
Gastrointestinal	Abdominal pain, throat irritation, nausea, diarrhea	Stomatitis, nausea, vomiting, loss of appetite and weight, diarrhea, abdominal pain, dyspepsia, ulcer, bleeding	Mucositis, diarrhea	Mucositis, nausea, vomiting, diarrhea
Hematological		Myelosuppression	Pancytopenia	Myelosuppression
Neurological	Headache, dizziness/vertigo	Headache, dizziness, mood disorders, memory impairment, sleep disturbances, leukoencephalopathy (rare)		Acute and chronic encephalopathy, leukoencephalopathy
Hepatic	Minor impairment of liver enzymes	Liver enzyme elevation, hepatic fibrosis or cirrhosis	Abnormal liver enzymes	Liver enzyme abnormalities
Renal		Renal impairment (rare)		Renal failure
Lung		Interstitial pneumonitis Less frequent: noncardiogenic pulmonary edema, pleuritis, pleural effusion, progressing rheumatoid pulmonary nodules		
Dermatologic	rash	Eruptions, alopecia, photosensitivity, vasculitis, Stevens–Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, exfoliative dermatitis, ulceration/necrosis	Erosive dermatitis, erythema	Erythematous macular rash progressing to bullous formation, alopecia
Cardiovascular	Chest pain, tachycardia			
Infection		Increased risk (suspected)	Pneumonia, sepsis	

Gastrointestinal: This is the most common system involved. Manifestations occur in about 30% of patients, including stomatitis, nausea, vomiting, loss of appetite and weight, diarrhea, constipation, abdominal pain, dyspepsia, ulcer, and gastrointestinal bleeding [144, 145].

Hepatotoxicity: Liver enzyme elevation is the second most common adverse effect of methotrexate [144]. A literature systematic review found a pooled cumulative incidence of 31% in methotrexate-associated liver enzyme abnormalities in the first 3 years of methotrexate use. No dose adjustment was required in most of the patients (67%); dose reduction or temporary discontinuation and to a lesser extent permanent

withdrawal of the drug were required in the rest of the patients [146]. In a meta-analysis of randomized controlled trials, methotrexate was associated with minor and major liver enzyme impairment but not with liver failure, cirrhosis, or death. The study duration (24–105 weeks) could have been too short to detect long-term methotrexate-induced severe liver toxicity [147]. Methotrexate-induced severe hepatic fibrosis or cirrhosis is uncommon but of major concern; the contribution of methotrexate as an independent risk factor has not been well established [146]. Suggested risk factors for hepatotoxicity in patients on LD-MTX include psoriatic arthritis, combination of methotrexate dose

higher than 10 mg/week and leflunomide [148], obesity, untreated hypercholesterolemia, pre-methotrexate elevated aspartate and alanine aminotransferases (AST, ALT), coadministration of a biologic agent, lack of folic acid supplementation [149], methotrexate cumulative dose higher than 3 g, alcohol use, diabetes mellitus, and hepatitis [150, 151].

Hematologic toxicity: Myelosuppression is a possible adverse effect of LD-MTX and can be associated with severe outcome. According to pooled results from 21 prospective studies, cytopenia of one cell line occurred in about 5% of the patients receiving LD-MTX up to 3 years [144]. Pancytopenia is less frequent (1.4%), and neutropenia can be associated with fatal infections [7, 152]. Elevated mean corpuscular volume (MCV) was suggested as a predictor of hematologic toxicity due to folate depletion [153].

Infections: LD-MTX was associated with increased risk of infections in some but not all studies [154, 155]. Case reports suggested an association with opportunistic infections. However, cause and effect relationship could not be established, and increased disease severity, comorbidities, and concomitant glucocorticoid use could have exposed these patients to opportunistic infections [154, 156].

Neurotoxicity: CNS toxicity is infrequent due to low penetration of methotrexate through the blood–brain barrier. It is usually mild, including headache, dizziness and mood disorders, memory impairment, and sleep disturbances [145, 157]. Nevertheless, rare cases of leukoencephalopathy have been reported [158, 159].

Nephrotoxicity: Renal insufficiency due to LD-MTX rarely occurs, if at all. Uncontrolled studies found a slight decrease in creatinine clearance in methotrexate-treated rheumatoid arthritis patients [160, 161]. Renal impairment can decrease methotrexate clearance, possibly increasing the risk of myelosuppression and other methotrexate-related toxicities. Methotrexate should be used under rigorous monitoring in patients with renal disease and avoided in patients with end-stage renal disease [162].

Pulmonary toxicity: The most frequent form of methotrexate-induced pulmonary toxicity is

interstitial pneumonitis. It has been estimated to occur in up to 50% of patients on LD-MTX, with fatality of 17%. It was suggested that the etiology is immunologic, as repletion of folate stores does not reduce its risk, but this is not proven. Clinical manifestations include dyspnea, dry cough, fever, chills, fatigue, auscultatory crackles, and hypoxemia; eosinophilia and interstitial lung opacities progressing to patchy acinar consolidation are common [163]. It may occur any time during treatment, seems to be more common in the elderly, and it is not always reversible after discontinuation of methotrexate.

Other less frequent or even rare forms of methotrexate pulmonary toxicity include noncardiogenic pulmonary edema, pleuritis, pleural effusion, and progressing rheumatoid pulmonary nodules [164, 165].

Dermatologic: Reported skin reactions include cutaneous eruptions, alopecia, photosensitivity, skin vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and ulceration/skin necrosis [13, 144, 151, 166]. Drug interactions and genetic predisposition may be involved in the development of severe adverse skin reactions [151].

Lymphoproliferative disorders: Methotrexate is suspected to increase the risk for lymphoproliferative diseases. Cause and effect relationship is hard to establish as rheumatoid arthritis by itself can be associated with an increased frequency of lymphoproliferative diseases [13].

Medication Errors of LD-MTX

Methotrexate toxicity can occur due to daily administration of the weekly dose or using the wrong strength tablets. Although toxicity could be mild, severe outcome was reported, even after relatively minor errors. Toxic effects reported include mucositis, pancytopenia (could be severe), diarrhea, abnormal liver enzymes, pneumonia, sepsis, multi-organ failure, and death [7, 8, 118, 119, 167, 168]. Plasma methotrexate concentrations were not different between fatal and nonfatal cases in a small retrospective study, but

these data are limited. Mortality occurred when methotrexate concentrations on admission were below 0.1 $\mu\text{mol/L}$ [7].

Acute Oral Overdose

There are few detailed reports of acute oral overdose. Most patients had favorable outcomes. The toxicity of high oral dose may be limited due to the saturable absorption and low bioavailability of methotrexate. Lack of effects or minor impairment of liver enzymes was reported in unintentional pediatric exposures treated with folinic acid [10, 124]. No effects were reported in a prospective study of 12 patients, of whom nine were adult intentional ingestions (methotrexate dose 40–1,000 mg, highest plasma methotrexate concentration 2.08 $\mu\text{mol/L}$). Some of the patients were treated with folinic acid [169]. In a retrospective poison center study evaluating 63 adult patients (88% acute overdoses, 79% unintentional), 68% were asymptomatic. The rest of the patients were mildly symptomatic, including abdominal pain, oral and throat irritation, nausea, diarrhea, headache, chest pain, tachycardia, dizziness/vertigo, and rash; 14.3% of all patients were treated with folinic acid. Hospital medical records were not available for review [170]. It is difficult to draw conclusions from these reports and series because of the limited data on dose, duration of treatment with folinic acid, and follow-up.

Diagnosis

The evaluation of patients possibly poisoned by methotrexate should include the following considerations: type and extent of overdose, clinical manifestations, risk factors, laboratory assessment (especially renal function), treatment already given, and methotrexate concentrations in relation to exposure time axis.

1. Extent of overdose: Details to be obtained include type of exposure [acute (intentional or

unintentional), subacute (e.g., medication error), chronic (LD-MTX), HD-MTX, intrathecal], cumulative dose, duration of exposure, time elapsed from last dose, and route of exposure. Folate supplementation should be assessed.

2. Clinical manifestations: Special emphasis should be given to the presence of nausea, vomiting, oral mucositis, low urine output, and myelosuppression [57, 117].
3. Identification of risk factors: Renal impairment and drug–drug interaction (e.g., benzimidazoles, nonsteroidal anti-inflammatory drugs, trimethoprim–sulfamethoxazole, other anticancer drugs, disease-modifying antirheumatic drugs). The estimated frequency of high-risk methotrexate concentrations increased from 12% to 19%, 32%, and 47% in the presence of one, two, or three risk factors (increased methotrexate AUC, low urine pH, emesis), respectively [7, 20, 57, 171, 172]. Inconclusive data exist on the association between toxicity and age, gender, and BMI [13].
4. Laboratory assessment: Mainly renal function, liver enzymes, complete blood count (neutropenia, thrombocytopenia) [117].
5. Treatment already given: This refers mainly to hydration, urinary alkalinization, and the use of folinic acid. Delay of 24–48 h in the administration of folinic acid from the beginning of HD-MTX may result in severe irreversible toxicity.
6. Determination of plasma methotrexate concentration: Methotrexate concentrations can indicate severity and guide the need and aggressiveness of hydration, urinary alkalinization, and antidotal treatment with folinic acid and glucarpidase. It is recommended to draw serial blood samples, e.g., on admission and 12, 24, 48, and 72 h after exposure. Timing can be adjusted according to the circumstances of exposure, clinical manifestations, and initial concentration. It should be noted that when plasma methotrexate concentrations are increasing or very high, the concentrations of folinic acid required for preventing toxicity (mainly myelosuppression) should be considerably higher.

Plasma methotrexate is routinely monitored by autoanalyzers using immunochemical assays. Cross-reactivity with methotrexate metabolites (mainly 7-hydroxy-methotrexate and DAMPA) can result in overestimation of the concentration. The longer the time elapsed from the administration, the higher the overestimation becomes. In addition, overestimation was higher in enzyme-multiplied immunoassay (EMIT) than in fluorescence polarization immunoassay (FPIA), compared with high-performance liquid chromatography (HPLC) reference (31% and 3% in 66-h samples, respectively) [173, 174]. Coadministration of folate and trimethoprim can diminish assay specificity [175]. It is recommended using HPLC assay after administration of glucarpidase due to the increased production of DAMPA [58, 176]. Attention should be drawn to the units expressing the results, as they may be a source of confusion (e.g., $\mu\text{mol/L}$, 10^{-7} M). We suggest using $\mu\text{mol/L}$, the most commonly used unit.

Treatment

The mainstays of treating methotrexate poisoning include supportive measures, timely gastrointestinal decontamination, adequate hydration, urinary alkalinization, antidotes (folinic acid and glucarpidase), extracorporeal elimination, and possibly gastrointestinal decontamination (Table 4). The following includes a discussion of each treatment modality.

Criteria for ICU Admission in Methotrexate Toxicity

1. Acute renal failure
2. Hemodynamic instability
3. Respiratory failure requiring ventilatory support
4. Sepsis
5. Active bleeding
6. Severe neurologic impairment (coma, seizures)
7. Intrathecal overdose

Criteria for ICU Discharge in Methotrexate Toxicity

1. Hemodynamic stability
2. No requirement for ventilatory support
3. No active bleeding
4. Resolution of sepsis
5. No further deterioration or improvement of neurologic impairment

Supportive Measures

Antiemetics, nutritional support, infection control, cardiovascular and respiratory support, and seizure control are indicated as required.

Methotrexate-induced myelosuppression should be treated using blood products, as necessary. Severe neutropenia can be treated with granulocyte colony-stimulating factor (G-CSF) such as filgrastim, sargramostim, and pegfilgrastim.

Gastrointestinal Decontamination

In patients with acute ingestion of potentially toxic or lethal dose, timely administration of activated charcoal should be considered if administered early after the overdose. Multiple-dose activated charcoal does not appear to be useful as methotrexate tablets are not known to form concretions, and there is no evidence it can increase the clearance of methotrexate [177]. One study showed smaller AUC when multiple-dose activated charcoal was given after a 6-h infusion of 1 g/m^2 methotrexate. Interruption of enterohepatic circulation was proposed as a mechanism for this observation. However, the number of patients was very small (7 treated, 8 controls), doses were separated by unusually long periods, and there is no evidence it can affect the outcome of overdosed patients [178].

There is no role for gastrointestinal decontamination in chronic overdoses (e.g., medication errors) as methotrexate is rapidly absorbed. The administration of activated charcoal has not been

Table 4 Suggested management approach of methotrexate overdose^a (for the management of intrathecal overdose, please see the relevant section)

	Acute unintentional overdose	Acute intentional overdose	Medication error associated with low-dose methotrexate	High-dose methotrexate
Gastrointestinal decontamination	Timely activated charcoal Consider gastric lavage	Timely activated charcoal Consider gastric lavage	Not relevant	Not relevant
Hydration and urine alkalinization	Usually unnecessary	Consider according to methotrexate dose and renal function Maintain adequate urine output and urine pH > 7	Begin; maintain adequate urine output and urine pH > 7 Reconsider according to dose, toxicity, and renal function Plasma methotrexate concentration has limited usefulness	Routinely performed Maintain adequate urine output and urine pH > 7 Continue until plasma methotrexate concentration < 0.01 µmol/L Note: protocols may vary; use institution protocol
Folinic acid >50 mg should be given IV; in children, consider if >25 mg	Begin with 12–15 mg/m ² every 6 h if methotrexate dose >50 mg/m ² in adults or 15 mg/m ² in children. Alternatively, use dose of folinic acid equal to the methotrexate dose. Continue until plasma methotrexate concentration < 0.01 µmol/L Reconsider according to plasma methotrexate concentration and renal function	Begin with 12–15 mg/m ² every 6 h; higher dose can be considered in large ingestion. Continue until plasma methotrexate concentration < 0.01 µmol/L Reconsider according to plasma methotrexate concentration and renal function	Begin with 12–15 mg/m ² every 6 h Consider modifying dose and interval according to cumulative methotrexate dose, duration of exposure, toxicity, and renal function Plasma methotrexate concentration has limited usefulness Continue until clinical improvement, especially bone marrow recovery	Routinely administered, e.g., 12–15 mg/m ² every 6 h beginning 24–36 h after the start of the methotrexate infusion Dose should be adjusted to methotrexate dose, scheduled plasma methotrexate concentrations, and toxicity Escalating dose should be considered according to scheduled methotrexate concentrations Continue until plasma methotrexate concentration < 0.05–0.1 µmol/L Note: protocols may vary; use institution protocol
Glucarpidase	Use has not been reported, usually unnecessary	Use has not been reported, usually unnecessary	Use has not been reported Consider according to methotrexate dose, toxicity, plasma methotrexate concentration, and renal function	FDA approved indication: plasma methotrexate concentration ≥ 1 µmol/L, and renal impairment Consider in HD-MTX-induced renal dysfunction and sustained elevated

(continued)

Table 4 (continued)

	Acute unintentional overdose	Acute intentional overdose	Medication error associated with low-dose methotrexate	High-dose methotrexate
				plasma methotrexate concentrations, e.g., >50 $\mu\text{mol/L}$ at 24 h or >5–10 $\mu\text{mol/L}$ at 42 h after start of methotrexate infusion Dose: 50 units/kg as IV bolus over 5 min. Consider second dose according to plasma methotrexate concentration
Extracorporeal elimination	Use has not been reported, usually unnecessary	Use has not been reported, usually unnecessary	Usually not required Consider according to toxicity, plasma methotrexate concentration, and renal function See HD-MTX scenario for preferred methods	Consider according to plasma methotrexate concentration, renal function, and availability of glucarpidase Most effective method: charcoal hemoperfusion and hemodialysis or high-flux hemodialysis Single most effective method: high-flux hemodialysis Note: protocols may vary; use institution protocol Caution: rebound in plasma methotrexate concentrations

^aSupportive measures: antiemetics, nutritional support, infection control, cardiovascular and respiratory support, seizure control, granulocyte colony-stimulating factor

shown to alter the outcome following methotrexate overdose.

Hydration and Urinary Alkalinization

Adequate hydration and maintaining urine output together with urinary alkalinization are essential in order to prevent renal toxicity due to methotrexate, i.e., replacement of fluid losses and avoiding tubular precipitation of methotrexate [179–181]. In a multivariate analysis, low urine

pH was one of the most important covariates of high-risk methotrexate concentrations. A more aggressive hydration and alkalinization regimen for subsequent courses reduced the frequency of high-risk methotrexate concentrations and toxicity [57].

Most HD-MTX treatment protocols recommend at least 2.5–3.5 L/m²/day of crystalloids. One protocol recommends IV infusion of 3 L/m²/day or more, in order to achieve urine output of at least 100 mL/h. When delayed elimination is suspected (vomiting, diarrhea, marked increase in

serum creatinine, or high-risk methotrexate concentration), hydration rate should be increased.

Urine pH should be maintained above 7 until methotrexate plasma concentration decreases to less than 0.1 $\mu\text{mol/L}$ (Grade II recommendation). In our institution, urine alkalinization is started by adding 50 mEq of sodium bicarbonate and 1 g (13.4 mEq) KCl to 1 l of dextrose 5%; higher concentrations may be required. Other clinicians have used higher doses such as 44–100 mEq of sodium bicarbonate in 1 l of 5% dextrose in 0.25% normal saline or 88–150 mEq in 1 l of 5% dextrose at 2–3 ml/kg/h (adults: 150–200 ml/h) [182]. Urine pH should be closely monitored, and the amount of bicarbonate modified in order to achieve the desired target of >7 . Serum pH and electrolytes, especially potassium and calcium, should be measured serially in order to avoid excessive alkalemia and electrolyte abnormalities. Hypokalemia and fluid depletion prevent effective urinary alkalinization [6, 73, 182].

In patients with osteosarcoma treated with HD-MTX, urinary alkalinization (even without forced hydration) was found to be a safe and reliable method to avoid precipitation of methotrexate and its metabolites in the renal tubules and prevented nephrotoxicity. Methotrexate dose was 8–12 g/m²; alkalinization protocol included 500 mL 8.4% sodium bicarbonate (500 mEq) over 1 h prior to HD-MTX followed by a similar dose once daily for three more days, together with KCl supplementation; target urine pH was >7.5 [86].

Drugs and Antidotes

Folinic Acid

Folinic acid (*N*⁵-formyl FH₄; Leucovorin) is the primary antidote for patients exposed to an overdose of methotrexate or to HD-MTX as part of their chemotherapy (Grade I recommendation) [183–185]. The aim of administration of folinic acid during HD-MTX treatment is to salvage normal cells and is termed Leucovorin rescue. Folinic acid rescue enables the administration of otherwise highly toxic and even lethal doses of methotrexate with an acceptable toxicity profile. The

two most important elements affecting methotrexate cytotoxicity in any tissue are drug concentration and duration of exposure. Folinic acid rescue usually begins 24–42 h and up to 48 after the start of methotrexate infusion [186, 187]. Longer delay in folinic acid administration may be associated with irreversible toxicity. In cases of delayed elimination of methotrexate, highly toxic concentrations develop even following appropriate methotrexate dosage, hydration, and alkalinization. In these cases, folinic acid doses should be intensified according to methotrexate plasma concentrations. It should be remembered that the salvage effect of folinic acid depends on both plasma methotrexate and folinic acid concentrations, but it is limited at very high methotrexate concentrations [188].

In patients with methotrexate overdose other than HD-MTX or IT regimens (i.e., acute single intentional or unintentional overdose, medication error), it is unclear when folinic acid should be administered. One approach is to promptly initiate folinic acid and reconsider it according to clinical manifestations, kidney function, blood count, and plasma methotrexate concentration [189]. This approach is based on the toxicity of methotrexate, safety of folinic acid, and its inefficacy after methotrexate-induced DNA damage has occurred.

Pharmacokinetics: Folinic acid is a racemic mixture of the active L-isomer and the inactive D-isomer. An IV preparation of the L-isomer, levofolinic acid, is also available. The bioavailability process of orally administered folinic acid is saturable and stereoselective. The absorption of the L-isomer is approximately five times higher than that of the D-isomer. The bioavailability of the L-isomer was found to be 97% at an oral dose of 25 mg and decreased to 75% and 37% at 50 mg and 100 mg doses, respectively [190]. Adult patients who require more than 50 mg folinic acid should receive the drug intravenously. After IV administration, the serum half-lives of the active L-isomer and its active metabolite *N*⁵-methyl FH₄ were 31.6 ± 1.1 min and 227 ± 20 min, respectively. The half-life of the inactive D-isomer was 451 ± 24 min [190]. The carrier-mediated transport process of

methotrexate is shared with reduced folates such as folinic acid (Fig. 3); thus, high extracellular concentrations of methotrexate can impair intracellular transport of folinic acid [188, 191].

Folinic acid is extensively metabolized intracellularly to $N^{5,10}$ -methenyl FH_4 and subsequently to N^{10} -formyl FH_4 and $N^{5,10}$ -methylene FH_4 [192].

Mechanism of action (Fig. 3): Folinic acid is a reduced, biologically active form of folic acid. It can serve as a precursor for several other reduced forms of folic acid ($N^{5,10}$ -methenyl FH_4 , N^{10} -formyl FH_4 , $N^{5,10}$ -methylene FH_4 , N^5 -methyl FH_4) that function as cofactors, providing one-carbon groups necessary for many intracellular metabolic reactions, including DNA synthesis. The mechanisms suggested for rescue of host tissue from methotrexate toxicity by folinic acid are:

1. Competitive interaction with methotrexate on their shared membrane transport carrier (reduced folate carrier – RFC), thus limiting methotrexate entry into the cell
2. Provision of reduced folate cofactors, thereby circumventing the block at the DHFR level and allowing for continued DNA synthesis
3. Direct competition of cellular folinic acid derivatives with methotrexate the level of DHFR. This promotes the net dissociation of underivatized methotrexate from DHFR (DHFR reactivation)
4. Decreased polyglutamation of methotrexate arising from competition at the level of folypolyglutamate synthetase [192–196].

The mechanism of selective rescue of normal cells but not malignant cells is incompletely understood. The two main mechanisms suggested for this selective rescue are: (1) reduced transport rate of folinic acid into transport-resistant tumor cells and (2) differential methotrexate metabolism leading to higher and sustained intracellular concentrations of methotrexate polyglutamate derivatives in tumor cells. This will result in a lesser competition of folinic acid on DHFR and its impaired reactivation [195, 197].

The protective effect of folinic acid depends on both the timing of administration and concentration of both methotrexate and folinic acid. Folinic acid must be administered before methotrexate-induced DNA damage had occurred, i.e., 24–36 h from initiating HD-MTX. In an in vitro study, toxicity of 0.1 $\mu\text{mol/L}$ methotrexate was completely reversed by equimolar concentrations of folinic acid. Higher methotrexate concentrations required relatively more folinic acid plateauing at high concentration; 10 $\mu\text{mol/L}$ but not 100 $\mu\text{mol/L}$ methotrexate was rescued by 1,000 $\mu\text{mol/L}$ folinic acid. Higher concentrations of folinic acid resulted in the formation of a precipitate in the medium [188].

Dose: The dose and duration of folinic acid should be determined according to the dose of methotrexate administered and the clinical scenario.

Mode of administration: Folinic acid can be administered orally, intravenously, or intramuscularly. Doses higher than 50 mg should be administered parenterally due to saturable absorption kinetics [198]. Some clinicians suggest that in children, doses of folinic acid higher than 25 mg be given parenterally. The infusion should be administered over 15–30 min, but not faster than 160 mg/min in adults due to its calcium content [199]. In neonates, a benzyl alcohol-free preparation should be used.

Levofolinic acid, the active L-isomer of folinic acid, is available for IV use. It should be dosed at half the dose of the racemate folinic acid.

HD-MTX regimens: Folinic acid rescue is routinely administered as part of chemotherapy regimens that include methotrexate doses of 1,000 mg/m^2 or higher. Some protocols use folinic acid in lower doses [6, 186, 200–202]. Folinic acid infusion is usually initiated within 24–36 h of the start of the methotrexate infusion. The dose and frequency of folinic acid rescue have been developed empirically and differ according to the HD-MTX regimen used [79]. The usual initial folinic acid dose is 12–15 mg/m^2 every 6 h. Serial monitoring of plasma methotrexate concentrations at 24, 48, and 72 h after the beginning of methotrexate infusion is required, and folinic acid dose is adjusted accordingly [6, 187, 198]. Other

regimens use higher initial loading dose of folinic acid and shorter intervals, especially in very high methotrexate dose, e.g., 200 mg/m² folinic acid in 33 g/m² methotrexate dose [203]. In case of delayed methotrexate elimination, folinic acid dose and duration should be increased [6]. There are several protocols for folinic acid dose escalation according to plasma methotrexate concentration following HD-MTX; two examples are presented herein:

1. Twenty-four hours after the start of the HD-MTX infusion, 10 mg folinic acid is given orally every 6 h if plasma methotrexate concentration is ≤ 10 $\mu\text{mol/L}$. If the concentrations at this time point are 10–20, 20–30, or 30–50 $\mu\text{mol/L}$, the adjusted dose of folinic acid will be 20, 30, or 50 mg orally every 6 h, respectively; concentration of ≥ 50 $\mu\text{mol/L}$ should be treated with 1 g IV folinic acid over 24 h. Concentration of ≥ 1 $\mu\text{mol/L}$ at 48 h may require further dose escalation [198]
2. Folinic acid is administered at 42 h after the start of methotrexate infusion in a dose of 30 mg/m²; at 48 and 54 h, a 15 mg/m² dose is given at each time point. If plasma methotrexate concentrations at 42 or 48 h are higher than expected (>1 and >0.4 $\mu\text{mol/L}$, respectively), folinic acid dose adjustments and methotrexate measurements are continued every 6 h, as follows: If methotrexate concentrations are >1 –2, >2 –3, >3 –4, or >4 –5 $\mu\text{mol/L}$, folinic acid dose will be 30, 45, 60, or 75 mg/m², respectively. If concentration is >5 $\mu\text{mol/L}$, folinic acid should be administered IV according to the formula: dose (mg) = plasma methotrexate concentration ($\mu\text{mol/L}$) \times body weight (kg) [202]. Folinic acid should be continued until plasma methotrexate concentration falls below 0.05–0.1 $\mu\text{mol/L}$. Overzealous dosing of folinic acid was suspected to compromise antitumor efficacy [186, 204, 205]. However, methotrexate-induced damage may not be reversible beyond 42–48 h of continuous exposure [15, 187].

Controversy exists regarding the efficacy of folinic acid in patients with methotrexate

concentrations above 100 $\mu\text{mol/L}$ [15, 188]. However, successful treatment with high-dose folinic acid (up to 10 g/day) was reported in a series of 13 patients with methotrexate concentration higher than 100 $\mu\text{mol/L}$ (range, 102–940 $\mu\text{mol/L}$) at 24 h after HD-MTX. Although all patients recovered, significant neutropenia occurred in 61%, thrombocytopenia in 53%, stomatitis in 46%, and diarrhea in 30% of them [206]. In patients with very high plasma methotrexate concentrations, addition of glucarpidase or extracorporeal elimination should be strongly considered.

Patients with ascites, gastrointestinal obstruction, or pleural effusion may require prolonged monitoring (beyond 72–96 h) and folinic acid treatment (up to weeks) because of prolonged elevated plasma methotrexate concentrations [51, 207, 208].

Medication errors of LD-MTX: Even few days of repeated low-dose methotrexate can cause severe and even fatal toxicity. These patients should be immediately treated with folinic acid and closely monitored. It should be noted that methotrexate plasma concentrations may not predict the risk, but the data for that is limited [7]. There are no evidence-based recommendations on how to adjust folinic acid dose according to plasma methotrexate concentrations in these patients. One approach is to use the same dose administered in HD-MTX chemotherapy, e.g., 12–15 mg/m² every 6 h. This dosage regimen can be modified according to the cumulative dose ingested, duration of exposure, toxicity, renal function, and perhaps plasma methotrexate concentration. It should be remembered that patients with myelosuppression might require prolonged dosing because of persistent intracellular methotrexate stores.

Acute oral overdose (intentional or unintentional): There are no evidence-based recommendations for folinic acid dose in acute oral overdose. Methotrexate toxicity may be limited due to saturable absorption and low bioavailability of large oral doses. In addition, there may be interpatient variability in tolerance to the toxic effects of methotrexate [131]. Acute single doses

of less than 50 mg/m² methotrexate in adults (single-dose regimen for ectopic pregnancy) and 15 mg/m² (range 10–25 mg/m²) in children (doses used in juvenile rheumatoid arthritis and uveitis) usually do not require folinic acid rescue. Lower thresholds can be considered in high-risk patients (i.e., renal impairment, drug interactions, and elderly patients) [209–211]. A small case series published as an abstract found no toxicity in acute oral overdose of methotrexate and suggested folinic acid can be safely withheld for ingestions of less than 500 mg in adults [169]. However, some of these patients were treated with folinic acid. One approach is to treat immediately acute oral doses of methotrexate above 50 mg/m² with folinic acid until plasma methotrexate concentrations are available.

It is usually recommended to administer folinic acid in a dose equal to the methotrexate dose [189]. Dose of 12–15 mg/m² folinic acid used in many HD-MTX cancer chemotherapy regimens should be sufficient in most cases of acute oral methotrexate exposure. Higher dose can be considered in cases of a large overdose and when delayed elimination is expected (e.g., renal impairment, drug interactions, elderly patients). We recommend monitoring plasma methotrexate concentrations within 24 h and adjusting folinic acid dose accordingly. Folinic acid should be continued until serum methotrexate concentration is below 0.01 µmol/L and preferably undetectable. In contrast with HD-MTX cancer chemotherapy, there is no “tolerable toxicity” in this case.

Folinic acid and glucarpidase interaction: Folinic acid is a substrate for glucarpidase, and they should not be administered concomitantly within 2–4 h prior or after glucarpidase. Since plasma methotrexate concentrations measured by immunoassay are not reliable during glucarpidase treatment, they cannot be used for adjusting the dose of folinic acid. The dose used prior to glucarpidase should be continued for 48 h after glucarpidase. Folinic acid should be continued thereafter according to plasma methotrexate concentrations and according to institution protocol [58, 212].

Adverse effects: Folinic acid is considered generally safe. Adverse effects include allergic or

anaphylactoid reactions. Seizures were reported in some patients who concomitantly received fluoropyrimidines and folinic acid [213].

Folinic acid should not be given intrathecally; see the section on Intrathecal Toxicity of Methotrexate.

Glucarpidase

Glucarpidase (carboxypeptidase G₂, Voraxaze) is an enzyme that rapidly metabolizes circulating methotrexate into two inactive metabolites: glutamate and 2,4-diamino-*N*¹⁰-methylpteroic acid (DAMPA). It has been used in methotrexate-induced toxicity since 1993 and gained US Food and Drug Administration (FDA) approval for treating toxic plasma methotrexate concentrations (greater than 1 µmol/L) in patients with delayed methotrexate clearance due to impaired renal function in 2012 [214].

Pharmacology and mechanism of action: Glucarpidase is a genetically engineered form of the bacterial enzyme carboxypeptidase G₂, produced by recombinant DNA technology in *Pseudomonas* species strain RS-16. It is a 390-amino acid homodimer protein with a molecular weight of 83 kDa. Each potency unit corresponds to enzymatic cleavage of 1 µmol/L of methotrexate per minute at 37 °C [212]. Glucarpidase hydrolyzes the carboxyl terminal residue of folic acid and its analogs forming inactive metabolites, glutamate and DAMPA. Glucarpidase effectively reduces plasma methotrexate concentrations; it does not penetrate intracellularly.

Pharmacokinetics: In subjects with normal renal function, the mean C_{max} was 3.1 µg/mL, mean t_{1/2} 9.0 ± 3.18 h, and mean AUC_{0–∞} 23.4 µg·h/mL. The steady-state V_d was 58 ± 18.08 mL/kg. Similar values were found in patients with severe renal impairment (creatinine clearance < 30 mL/min). In renally impaired subjects, the mean C_{max} for glucarpidase was 2.9 µg/mL, mean t_{1/2} 10.0 ± 2.06 h, and mean AUC_{0–∞} 24.5 µg·h/mL. The steady-state V_d was 67.9 ± 29.64 mL/kg [215].

Clinical efficacy: Several clinical trials studied the use of methotrexate in patients with delayed methotrexate elimination and methotrexate-induced nephrotoxicity. The criteria for delayed

elimination and nephrotoxicity were not uniform. In three studies, the median and range of methotrexate baseline concentration were 11.93 $\mu\text{mol/L}$ (range 0.52–901), 56 $\mu\text{mol/L}$ (range 1–1,187), and 28.2 $\mu\text{mol/L}$ (range 0.37–849). The mean reduction in plasma methotrexate concentration 15 min post administration was 97–98.7% [85, 129, 216]. A small rebound in methotrexate concentrations occurred in some patients [85, 216]. In a pooled analysis of efficacy data from four single-arm clinical trials from 1993 to 2007, 169 patients who had documented methotrexate plasma concentration measurement by high-performance liquid chromatography (HPLC) were studied. Rapid and sustained clinically important reduction (RSCIR) in plasma methotrexate concentration (defined as values $\leq 1 \mu\text{mol/L}$ in all post-glucarpidase determinations) was achieved in 59% of 140 patients with pre-glucarpidase methotrexate concentrations greater than 1 $\mu\text{mol/L}$. Patients who had a pre-glucarpidase methotrexate concentration of $\geq 50 \mu\text{mol/L}$ were less likely to achieve RSCIR compared with patients who had concentrations of $< 50 \mu\text{mol/L}$. However, the percent reduction of methotrexate concentrations was larger in patients with higher pre-glucarpidase methotrexate concentrations. Ninety-eight percent (44/45) of patients with pre-glucarpidase methotrexate concentrations of $\geq 50 \mu\text{mol/L}$ had 95% decrease at the first post-glucarpidase measurement, compared with 83% (92/111) of patients with pre-glucarpidase concentrations of $< 50 \mu\text{mol/L}$ [58]. In most of the cases, a second and third dose of glucarpidase did not result in an additional marked decrease in methotrexate concentration [85, 129, 216].

While glucarpidase was clearly safe and effective in reducing methotrexate concentrations within minutes of administration, it was difficult to assess its effect on renal recovery and survival due to the lack of a control group [85, 129, 216]. Varying degrees of renal dysfunction and different definitions for recovery from HD-MTX-induced renal dysfunction limit the assessment of retrospective studies comparing the efficacy of supportive treatment (including hemodialysis) and glucarpidase. In a retrospective study of

young osteosarcoma patients with HD-MTX methotrexate-induced nephrotoxicity, the median time to renal recovery was 16 days in patients on supportive care (including dialysis-based methods in some patients). In glucarpidase-treated patients, renal recovery (serum creatinine within normal values) occurred at a median of 22 days [12]. The mortality rates found in three studies on patients with delayed methotrexate elimination and methotrexate-induced nephrotoxicity treated with glucarpidase were 6.1% [85], 6% [216], and 23% [129]. One study on HD-MTX patients using multiple regression analysis model identified associations between several parameters and the development of methotrexate Grades IV and V toxicity. The parameters identified were the presence of pre-glucarpidase Grade IV nephrotoxicity, inadequate folinic acid rescue within the first 3 days after HD-MTX, diuretic use, and administration of glucarpidase more than 96 h after start of HD-MTX [216].

Safety: Glucarpidase is generally well tolerated. Main adverse events reported (about 2% of patients) include paresthesias (and related events such as burning, tingling, formication), flushing (including feeling hot, erythema), and nausea/vomiting. Less frequent adverse events (about 1%) included headache and hypotension; blurred vision, diarrhea, hypersensitivity, hypertension, rash, throat irritation/tightness, and tremor were reported in less than 1% of patients [12, 58, 212].

Anti-glucarpidase antibodies were detected in some clinical studies. In most cases it did not decrease glucarpidase activity [129, 216].

Dose and administration: Glucarpidase dose approved by the FDA for the treatment of toxic methotrexate concentration ($\geq 1 \mu\text{mol/L}$) is 50 units/kg. This dose should be administered as an IV bolus over 5 min; each vial contains 1,000 units as a lyophilized powder [58, 212]. Some studies used a second similar dose, but criteria varied, e.g., plasma methotrexate concentration of > 0.1 or $\geq 1 \mu\text{mol/L}$ more than 24 h after dose 1 and 48 h after dose 1 if pre-glucarpidase plasma methotrexate of $> 100 \mu\text{mol/L}$ [83, 129, 216]. No dose adjustment is recommended for patients with renal impairment.

The use of glucarpidase is often limited by its high cost. Glucarpidase dosages of less than 50 units/kg administered due to shortage of supply or capping the dose at a full vial size were reported to be efficacious in several cases and a retrospective study [129, 217–219]. In the retrospective study, 42% and 58% of the patients received glucarpidase doses of less than and equal or higher than 50 units/kg, respectively. The median reduction in plasma methotrexate concentrations was 99.4% in both groups (range 98–100% and 77–100%, respectively). Time to recovery of serum creatinine was not related to glucarpidase dose in multivariate analysis [219].

During glucarpidase treatment, supportive care including IV hydration, urinary alkalinization, and folinic acid rescue should be continued. Folinic acid is also a substrate for glucarpidase and can compete with methotrexate on binding to glucarpidase. Folinic acid should not be administered for 2 h before and after glucarpidase [58, 212].

Monitoring methotrexate after administration of glucarpidase: DAMPA, the inactive metabolite of methotrexate formed after glucarpidase, cross-reacts with methotrexate resulting in falsely elevated methotrexate concentrations when using immunoassays. Therefore, methotrexate concentrations should be measured during the 48 h following administration of glucarpidase only by a chromatographic method [174, 220, 221].

Current role in therapy: Glucarpidase is highly effective and safe in lowering plasma methotrexate concentration within minutes of its administration. It can decrease the need for dialysis-based methods and hence their complications. Its delayed administration, especially when cytotoxicity has already ensued, can reduce its efficacy. Glucarpidase (IV 50 units/kg) is FDA approved for treating toxic plasma methotrexate concentrations ($\geq 1 \mu\text{mol/L}$) in patients with delayed methotrexate clearance due to impaired renal function. It is suggested to consider glucarpidase in patients with HD-MTX-induced renal dysfunction (e.g., a 1.5- to 2-fold or greater increase in serum creatinine above baseline) and sustained elevated

plasma methotrexate concentrations (e.g., $>50 \mu\text{mol/L}$ at 24 h or $>5\text{--}10 \mu\text{mol/L}$ at 42–48 h after infusion) [6, 58, 222].

It should be noted that glucarpidase could handle methotrexate burden in the intravascular compartment, not intracellular or in the urinary collecting system [223].

More data are required in order to establish its efficacy in reducing severe morbidity and mortality compared with best supportive treatment, folinic acid, and elimination enhancement by dialysis-based methods.

There are no reports on the use of glucarpidase in methotrexate medication errors and intentional or unintentional overdoses.

The role of glucarpidase in intrathecal methotrexate overdose is elaborated in section “[Intrathecal Toxicity of Methotrexate](#).”

Standard supportive care, including folinic acid, must be continued following administration of glucarpidase.

Other Suggested Drugs

Dextromethorphan and aminophylline: These drugs were suggested for the treatment of methotrexate neurotoxicity. For detailed discussion, see section “[Intrathecal Toxicity of Methotrexate](#).”

Thymidine: Thymidine, an endogenous nucleoside, was used as an investigational rescue agent. It can be directly converted to thymidine monophosphate by the salvage enzyme thymidine kinase and circumvent the blockade of the de novo pyrimidine pathway by methotrexate. It was used in combination with folinic acid [81] and glucarpidase [83]. Its development was discontinued [6].

Extracorporeal Elimination

Methotrexate is a small molecule (454 kDa), about 50% protein bound, with volume of distribution of 0.4–0.9 L/kg, making it suitable though not an ideal candidate for removal by hemodialysis [224]. In a literature review on the efficacy of dialysis-based methods for removal of

methotrexate, the methods most frequently used were hemodialysis, high-flux hemodialysis, and charcoal hemoperfusion or charcoal hemofiltration [12]. Peritoneal dialysis alone resulted in a minimal decrease in methotrexate concentrations. The most effective extracorporeal removal methods were charcoal hemoperfusion in combination with hemodialysis or with high-flux hemodialysis. As a single method, high-flux hemodialysis resulted in the greatest decrease in plasma methotrexate concentrations (median 75.7%; range 42%–94%) within the shortest period of time (median 4 h; range 4–12 h) [12]. In a case series of patients with chronic and acute renal failure (three each), mean plasma clearance of methotrexate was 92.1 ± 10.3 mL/min (range 59–126.6 mL/min). One patient who was on chronic hemodialysis prior to HD-methotrexate therapy underwent 6 h of high-flux hemodialysis daily and reached a target methotrexate concentration (<0.3 $\mu\text{mol/L}$) in 5.6 ± 0.3 days, without signs of methotrexate toxicity [225]. Methotrexate dialysis clearances of 198–258 mL/min per 1.73 m² during high-flux hemodialysis were reported [226]. A major limitation of dialysis-based methods is a marked rebound in plasma methotrexate concentrations due to redistribution. Increases in post-dialysis plasma methotrexate concentrations by 10–221% of the post-procedure values and to 90–100% of the pre-procedure levels were reported [12]. This implies that prolonged course of repeated hemodialysis is required, up to 12 sessions during several days in one case report [227]. Early initiation of dialysis-based method after detection of acute exposure and before tissue distribution is completed, could be more effective in removing excess methotrexate. The time window for early removal is limited to a few hours as methotrexate distribution half-life is 0.75 h [228].

Continuous renal replacement modalities such as continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF) are now widely used in the management of acute kidney injury and extracellular fluid volume expansion in hemodynamically unstable patients. These techniques

are logistically easier to accomplish as they are often used in intensive care units without mobilizing experienced dialysis unit staff. However, its efficacy in treating poisoning is limited by its relatively lower clearance rate compared with hemodialysis [228]. The use of continuous renal replacement modalities to enhance elimination of methotrexate was reported in several cases [229, 230]. In one of them, several methods [CVVHD, single pass albumin dialysis (SPAD), CVVHDF, and glucarpidase] were used over 12 days in a pediatric patient who received 14.4 g for osteosarcoma and developed severe methotrexate toxicity. Methotrexate transmembrane clearance rates in this patient were 28–34.5 mL/min and 64.4 mL/min during CVVHD and CVVHDF, respectively. Compared with standard CVVHD, SPAD insignificantly increased methotrexate removal. The calculated overall amount of methotrexate removed over 97 h using these different removal methods was 2.18 g. The largest quantity of methotrexate was removed early in the course of treatment, when its plasma concentrations were the highest [229]. In another case, CVVH was used in combination with charcoal hemoperfusion. The contribution of hemoperfusion to the decline in plasma methotrexate concentrations was insignificant [231].

In clinically stable patients, frequent intermittent high-flux hemodialysis is probably the single most effective method for extracorporeal elimination of methotrexate. In unstable patients who cannot tolerate intermittent hemodialysis, continuous removal modalities can be considered. It is conceivable that high-flux hemodialysis followed by continuous removal method might achieve two goals, rapid elimination and prevention of rebound; this is yet to be proven.

Other treatments including urinary alkalization and folinic acid should be continued during extracorporeal treatments. As folinic acid is probably eliminated by extracorporeal removal techniques, supplementary doses should be given.

Glucarpidase rapidly metabolizes methotrexate to inactive metabolite (DAMPA), which may obviate the need for extracorporeal removal. Both

treatments can be combined, not simultaneously, as part of the supportive treatment of renal failure.

Intrathecal Toxicity of Methotrexate

IV and IT methotrexate are widely used for the treatment or prophylaxis of CNS involvement (leptomeningeal tumor spread) of leukemia (e.g., ALL), lymphoma, and osteosarcoma. This treatment has replaced cranial radiotherapy and substantially reduced ALL relapse [232–234]. The reasons for IT overdose of methotrexate include preparation errors such as wrong strength vial (e.g., 500 mg vial instead of 50 mg one) and administration errors (e.g., giving the higher IV dose IT) [232, 233, 235]. Contamination with other chemotherapeutic agents (e.g., vincristine) was also reported [236]. Accidental IT methotrexate overdose is rare but can be severe and fatal, depending on the dose and promptness and quality of treatment given [237].

Toxic IT Methotrexate Dose and Concentration

The clinical manifestations of IT overdose of methotrexate are usually dose dependent. They correlate with the total amount of methotrexate administered and its concentration in the CNS [238]. In some patients, toxicity can develop shortly after the first IT dose (inadvertent large overdose), and in some after few doses, even if in the therapeutic range [239]. Overlap exists between doses that were associated or not associated with neurotoxicity.

The usual IT methotrexate dose ranges between 5 and 12 mg in children [76, 239], up to 15 mg in adults [87, 233, 237], at 2–5-day intervals. Overdose of less than 100 mg or 15-fold of the therapeutic dose is believed to be relatively well tolerated, usually with treatment [240–243]. However, a 125 mg IT dose (tenfold error) in 3- and 4-year-old children resulted in generalized convulsions 3 h after administration, both completely recovered [235]. IT methotrexate overdose was defined in one study as >100 mg

[233]. A 1996 literature survey concluded that IT overdoses of <100 mg need less intervention, 100–500 mg can be treated with a variety of approaches, and >500 mg would not respond to any intervention [244]. However, some reports are in disagreement with this conclusion; survival was reported after IT overdoses of 625 mg and 1,200 mg treated with multimodalities [237, 245]. In addition, the use of IT glucarpidase can change the outcome of >500 mg IT methotrexate overdoses, as discussed later on.

IT injection of 12 mg/m² methotrexate resulted in a 100-fold variation in CSF drug concentrations. In patients treated with IT 6.25 mg or 12.5 mg/m² methotrexate, peak CSF concentrations ranged between 0.6 and 22 µmol/L. These concentrations were achieved 4–8 h after injection and decreased exponentially thereafter. Intraventricular instillations of 6.25 mg/m² via Ommaya reservoir were associated with less variability and were more reliably distributed in the CSF than after lumbar administration. Peak ventricular concentrations achieved were 200 µmol/L and declined exponentially over 48 h [246, 247].

In IT therapeutic dose (12 mg/m²), CSF methotrexate concentrations declined in a biphasic manner with half-lives of 4.5 and 14 h, approximately parallel to the plasma disappearance curve [248]. An earlier study of the same group showed that in patients treated with IT 12–15 mg/m² methotrexate, mean CSF concentrations in the neurotoxic group were 13.8 (range 1.5–100) times higher compared with the asymptomatic group. Methotrexate CSF half-life in some neurotoxic patients was similar to that found in the asymptomatic group (12–18 days) and much longer in others (48 days) [249]. In a 7-year-old boy, CSF methotrexate concentrations were 100-fold higher after an overdose of 54 times the intended dose (650 mg instead of 12 mg), and half-life doubled. The authors suggested that saturation or destruction of the transport mechanisms may have caused prolongation of the half-life [243]. CSF methotrexate concentration reached a peak of 1,250 µmol/L 9 h after an IT overdose of 1,200 mg. Plasma concentration at 7 h after the overdose was 10 µmol/L [237]. Methotrexate CSF concentration was 5.2 µmol/L at 23 h post IT overdose of

170 mg/m² (instead of 12 mg/m²) in a 2-year-old child. The only clinical manifestation was a mild headache. Methotrexate CSF elimination half-life was 8 h [241]. Earlier study found prolonged methotrexate CSF concentrations greater than 0.01 µmol/L during and after apparent neurotoxicity in patients treated with IT methotrexate [249]. It should be noted that DNA synthesis (determined as deoxyuridine incorporation into DNA) recovered to 50% of pretreatment level in mice bone marrow and intestinal epithelium only after plasma methotrexate concentration fell below 0.01 and 0.005 µmol/L, respectively [59].

Mechanisms of IT Methotrexate Toxicity

The mechanisms of methotrexate neurotoxicity are probably multifactorial; they were discussed earlier. Other mechanisms may be involved in the neurotoxicity of IT methotrexate.

Chemical preservatives, degradation products, and vehicle-induced alterations in CSF pH and osmolarity were proposed but not proven as causative [249].

The direct contact of methotrexate and its excipients with nervous tissue can be toxic and fatal due to focal tissue necrosis. This can happen after an uneventful IT injection, but also after inadvertent injection of methotrexate intraparenchymally [250, 251].

Another important factor that may play a role in methotrexate neurotoxicity after IT administration is the volume injected into the lumbar sac. The injected volume and pressure may affect distribution within the subarachnoid space and ventricular system, but this is difficult to assess. In addition, extradural and subdural leakage may occur [250].

Elevated CSF methotrexate concentrations seem to be associated with neurotoxicity after IT administration, especially in the presence of prolonged exposure. Elevated concentrations can result from high dose relative to CSF volume or impaired elimination from the CSF. Older age and the presence of meningeal leukemia were suggested to predispose to increased CSF

methotrexate concentrations and its neurotoxicity [249]. The contribution of cranial irradiation cannot be excluded.

The role of homocysteine (direct toxin to vascular endothelium) and its metabolites (excitatory amino acids, NMDA receptor agonists) should be emphasized. Hyperhomocysteinemia is a risk factor for neurodegeneration [75, 236, 252]. Elevated blood homocysteine concentrations can be associated with endothelial cell injury and cerebrovascular infarcts, explaining focal neurological deficits and seizures [250].

Adenosine also plays a role in methotrexate-induced neurotoxicity, as discussed earlier, mainly due to dilation of cerebral blood vessels, slowing release of neurotransmitters at presynaptic junctions, modifying postsynaptic response, and slowing neuronal discharge rates [253].

Several biochemical changes in the CSF were reported to be associated with IT methotrexate and HD-MTX. A study of 29 children with ALL, median age 4 years (range 2–17 years), found significantly reduced CSF concentrations of *N*⁵-methyl FH₄ and S-adenosylmethionine (SAM) in patients not receiving folinic acid rescue and in two with neurotoxicity (subacute in both). In patients, receiving rescue, CSF *N*⁵-methyl FH₄ and SAM were in the normal range. S-adenosylhomocysteine (SAH) concentrations were slightly low, but they could be quantified only in 23% of the patients [75]. This study supports other studies showing low CSF *N*⁵-methyl FH₄ and SAM in patients receiving HD-MTX or intraventricular methotrexate together with elevated homocysteine [254, 255] and in a rodent model [256]. Low CSF SAM was reported to be associated with demyelination in patients with leukoencephalopathy [257, 258]. High CSF adenosine concentrations were found in patients treated with methotrexate compared with control subjects, when toxicity was absent or mild [259].

Clinical Manifestations of IT Methotrexate Toxicity

Neurotoxicity after IT methotrexate is more common and severe than after IV or oral

administration [76]. Leukoencephalopathy was reported in 40% and less than 10% of patients treated with IT and IV methotrexate, respectively [87].

Methotrexate-induced neurotoxicity can be manifested in three main forms: acute, subacute, and chronic. Following therapeutic IT administration, these three forms are characterized by the following:

1. Acute chemical arachnoiditis including headache, back pain, confusion, nausea, vomiting, dizziness, nuchal rigidity, fever, and seizures; usually reversible but can be fatal
2. Ascending myelopathy manifested with leg pain, sensory alterations, neurogenic bladder, intestinal ileus, stroke-like episodes (e.g., hemiparesis, dysphasia, stupor); usually reversible, can be severe
3. Leukoencephalopathy usually manifested by confusion, irritability, tremor, ataxia, progressive personality changes, dementia, focal neurological signs, and seizures can be irreversible and fatal. Combined IV and IT methotrexate and cranial irradiation put the patient at a greater risk for delayed chronic leukoencephalopathy [16, 75, 76, 243, 249, 250].

A retrospective study of 18 pediatric patients, mostly with ALL, 17 received only IT methotrexate, reported the following clinical manifestations: headache, slurred speech, dizziness, disorientation, confusion, agitation, weakness, ataxia, numbness, dysarthria, aphasia, dysphagia, behavioral disorders, somnolence, mental status changes, impaired sensorium hemiparesis, incontinence, and convulsions. These manifestations appeared 2–12 days after last methotrexate dose, thus considered as subacute toxicity [76]. In another study on accidental IT methotrexate overdose, five of seven patients developed acute severe toxicity within 1 h after the overdose. Clinical manifestations included seizures, coma, apnea, hypotension, tachycardia, hypertension, confusion, severe headache, intense back pain, nausea, and vomiting [233]. Case reports supported these findings [87, 237, 239, 260, 261]. Adult respiratory distress syndrome (ARDS) was reported in one case [237].

Intraparenchymal injection can result in acute elevation in intracranial pressure, massive brain edema, cystic defect, monoparesis, and permanent neurological deficit [250, 251].

Ancillary Tests

Electroencephalogram (EEG): A tenfold IT methotrexate error was associated with a disturbed background rhythm shown as a slow activation increase and paroxysmal activation in the right temporal region [232]. An EEG done in a 22-year-old patient with behavioral and speech disturbances after a cumulative IT methotrexate dose of 62.5 mg showed excessive bilateral slow-wave activity suggestive of diffuse cerebral dysfunctions [260].

Magnetic resonance imaging: White matter changes can be found in MRI imaging before overt clinical neurotoxicity, reflecting demyelination, necrosis, and angiopathy [250]. MRI findings after IT methotrexate with subacute toxicity included ischemic lesions in the white matter characterized as supraventricular infarcts and demyelination [75]. In one patient, serial MRIs with diffusion-weighted imaging showed recurrent areas of restricted diffusion within cerebral hemispheric white matter, which correlated chronologically with the IT administration of methotrexate and severity of the clinical manifestations [239]. In another case, diffuse symmetric bilateral hyperintense T2 signal abnormality within the white matter was reported [87].

Some studies suggest that up to 40% of patients may develop MRI or CT changes indicative of methotrexate-induced leukoencephalopathy, although clinical neurotoxicity may not be seen [87].

Management of IT Methotrexate Overdose and Toxicity

There is limited data on IT methotrexate overdose and no well-established guidelines for treating this medical emergency. It is emphasized that prompt recognition of the overdose and immediate

adequate multimodality treatment are critical to improve short- and long-term outcomes. Treatment strategies of IT methotrexate overdose and toxicity include removal of CSF fluid with or without exchange, systemic folinic acid, systemic and IT corticosteroids (preferably dexamethasone), IT glucarpidase, and combined treatments [232, 233, 237, 262]. The use of aminophylline and dextromethorphan was also suggested.

CSF drainage/exchange: This treatment modality was reported in a series of patients and several cases, including asymptomatic high-dose incidents. Lumbar puncture is used for this purpose; ventriculolumbar perfusion should be considered in continued or worsening neurotoxicity [233]. In a series of seven pediatric and adult patients receiving an IT overdose of 155–600 mg (median 364 mg) methotrexate, four underwent CSF exchange, mainly with warm saline. This procedure removed 32–58% of the dose. The patients also received IT glucarpidase after the exchange and IV folinic acid and dexamethasone [233]. Lumbar CSF exchange was performed in a 34-year-old male after an inadvertent administration of 1,200 mg methotrexate IT. The procedure lasted 48 h during which 200 mL of CSF were exchanged with warm normal saline. Methotrexate CSF concentrations decreased from 1,250 to 47 $\mu\text{mol/L}$. At the end of the exchange, 2 mg folinic acid and 2 mg dexamethasone were injected IT. The patient was also treated with IV folinic acid for 72 h and IV mannitol to reduce intracranial pressure [237]. Removing IT methotrexate using lumbar drainage is expected to be successful if done within a short time after injection, as it reaches the basal cisterns within an hour. In large overdoses and late recognition of the error, ventriculolumbar perfusion should be considered [263, 264]. A 6-year-old boy received 600 mg IT methotrexate instead of the intended 12 mg dose and rapidly developed severe acute neurotoxicity. He was successfully treated with rapid lumbar CSF drainage of 15 mL CSF 2 h after the overdose followed by ventriculolumbar perfusion with 240 mL warmed normal saline. Within 8.5 h of administration, 90% of the drug was removed. IT 2,000 U glucarpidase was also

administered; the patient fully recovered [265]. The use of IT glucarpidase after lumbar CSF drainage while administering systemic corticosteroids and folinic acid may preclude the need for ventriculolumbar perfusion [233, 266]. Future studies may indicate whether IT glucarpidase may obviate the need for ventriculolumbar perfusion [262].

Technical considerations of CSF drainage/exchange:

- (a) CSF drainage. This is done using lumbar puncture. CSF volume reported to be removed is 10–70 mL [244, 262, 264–266]. According to a pharmacokinetic model, early CSF drainage is predicted to remove larger doses of methotrexate, and smaller volumes can be used. For example, drainage of 20–40 mL CSF within 15, 30, and 60 min will remove 94%, 72–89%, and 40–79% of the injected methotrexate dose, respectively; larger volume will remove a greater dose. Ten mL CSF drained at these time points will result in removal of 54%, 36%, and 20% of IT injected methotrexate dose, respectively [264]. Therefore, remove larger CSF volumes if longer time has elapsed from the IT overdose. The first CSF fluid removed is usually yellow, becoming clearer later on [232].
- (b) CSF exchange. CSF is exchanged with warm normal saline via a lumbar or ventricular catheter. Exchanged volumes via lumbar catheter reported were 20 mL, total volume of 210–250 mL [242]; 3 mL every 15 min, total volume 72 mL [232]; 200 mL over 48 h [237]; and 240 mL over 2 h [266]. Volumes exchanged via ventricular exchange were 80–250 mL during 3 h [266]. Ventricular exchange requires the presence of a neurosurgeon.
- (c) Ventriculolumbar perfusion. This is done by ventriculostomy and lumbar drainage and depends on the availability of neurosurgeons. One study suggested using this procedure in >10-fold overdose, unless large volume of CSF can be removed by lumbar drainage within 15 min of the overdose [266]. Another study suggested it in overdose of >100 mg

or >7-fold the intended dose [264]. Preservative-free warm normal saline is administered through the ventriculostomy, and an equal amount of CSF is removed through the lumbar side. Volumes used were 130 mL over 1.5 h and 240–250 mL over 3–4 h [265, 266].

Corticosteroids: Dexamethasone is the preferred corticosteroid due to its better penetrance of the blood–brain barrier; it can be given IV, IT, or by both routes. Pediatric IV dexamethasone dose reported was 0.15 mg/kg every 6 h, four doses [232].

The IV dose of dexamethasone used in most reports is 4 mg every 4–6 h. The reported range was 0.15 mg/kg to 4 mg/m² and up to 20 mg/m²/day in three divided doses. Duration of treatment ranged between 1 and 3 days; longer treatments were also reported [232, 233, 235, 261, 262, 264, 265].

IT dexamethasone was administered in a case of a large IT methotrexate overdose (1,200 mg). Five 2 mg doses of dexamethasone were given IT during lumbar CSF exchange, and an additional one at the end, together with IT 2 mg folinic acid. Although the patient recovered from the overdose, it is unclear what were the contributions of IT dexamethasone and folinic acid. The rationales for the IT dexamethasone in this case were persistent elevated CSF methotrexate concentration (47 μ mol/L), relieving arachnoiditis and preventing adhesions [237].

Folinic acid: Folinic acid should be given only IV, not IT because of increased risk for seizures and death [244].

The dose used in one case series was 100 mg every 6 h, four doses [233]. However, a broad range of doses were used: 12 mg every 12 h, 15 mg/kg every 3–6 h, 30 mg/kg every 6 h, 100 mg every 3 h, 40 mg/m² every 6 h (in children), 100 mg/m² every 3 h, and 200 mg/m² every 3 h. Some reports also used a loading dose of 1,000–1,200 mg [232, 235, 237, 244, 261, 262, 264, 265]. Duration of treatment ranged between 12 h and several days. The use of lower doses of folinic acid may be considered in smaller overdose (e.g., 50 mg every 3–6 h in < 100 mg methotrexate overdose).

Another report used IV 1,200 mg folinic acid followed by 15 mg every 6 h for 72 days, concomitantly with lumbar CSF exchange. In this report, 2 mg folinic acid were also administered IT after the exchange; no neurotoxic adverse effects of folinic acid were recorded. Its role in the recovery from the overdose is unclear [237].

In a pediatric case, 300 mg (instead of 12 mg) IT methotrexate was followed by headache, coma, and seizures after 90 min. Treatment included 100 mg IV levogyrum folinic acid (equivalent to double dose of the racemic mixture of folinic acid) every 3 h for 24 h and then every 6 h for 24 more hours. The patient regained consciousness and remained in normal neurological status [261].

An 11-year-old boy was treated with three doses of IT 50 mg folinic acid each over 24 h after an IT 20 mg methotrexate overdose (a dose not expected to be lethal or to cause severe neurotoxicity). Shortly after completion of the folinic acid treatment, he developed seizures and fatal multi-organ failure [244]. Folinic acid was found to be associated with seizures in cancer patients [213].

If glucarpidase is administered IT, it is suggested to continue folinic acid for at least 48 h after it. Glucarpidase hydrolyzes folinic acid, and the continued administration can ensure adequate repletion of reduced folate stores [262].

Glucarpidase: In an animal study using nontoxic and toxic doses of IT methotrexate, IT glucarpidase caused a dramatic and very rapid decrease in methotrexate CSF concentrations; all animals survived without neurotoxicity [267]. IT glucarpidase was administered to seven pediatric and adult patients with accidental overdose of IT methotrexate (median dose 364 mg). Four of them received it after CSF exchange. Median CSF methotrexate concentrations before IT glucarpidase were 264 μ mol/L and 8,050 μ mol/L in patients who underwent prior CSF exchange and those who did not, respectively. Glucarpidase was given via either lumbar, ventriculostomy, Ommaya reservoir, and lumbar and ventriculostomy routes, at a median of 5 h (range 3–9 h) after the IT overdose. Following this treatment, CSF methotrexate concentrations decreased by more than 98% within 2 h. Five patients fully

recovered, and two were left with memory impairment. IT glucarpidase was well tolerated; no antibodies to glucarpidase were detected. It should be noted that these patients also received IV folinic acid and dexamethasone. The authors of this study concluded that although the contribution of glucarpidase to the favorable outcome of the patients cannot be precisely determined, the rapidity in which it decreased CSF methotrexate concentrations and its lack of toxicity suggest it is beneficial in this form of overdose [233]. A single dose of 2,000 U IT glucarpidase was administered after CSF lumbar drainage and ventriculolumbar perfusion to a 6-year-old boy with IT methotrexate overdose (600 mg instead of 12 mg). It resulted in a further 150-fold decrease in CSF methotrexate concentration; the patient fully recovered [265]. A literature review concluded that IT glucarpidase caused a nearly 2-log reduction in CSF methotrexate concentrations in patients receiving 155–600 mg methotrexate IT; neurologic outcome was excellent.

The usual IT glucarpidase dose is 2,000 U reconstituted in 12 mL normal saline and administered over 5 min [233, 262, 265].

Dextromethorphan: Dextromethorphan is the methylated D-isomer of levorphanol, acting centrally in the medulla oblongata to suppress cough. Unlike the L-isomer, it has little analgesic and minimal addictive properties. It is a noncompetitive NMDA receptor antagonist [268]. Its use was reported in a retrospective study of 18 children (mean age 11.2 years) with subacute methotrexate toxicity; 16 received it IT as a 12 mg dose. Dextromethorphan dose ranged between 1 and 3 mg/kg/bid to 2.5 mg/kg/qd for 1–20 days; 12 (66.6%) patients were treated for 4 days. Symptomatic improvement was noted in all of patients within 0.2–43 h and 15 (83.3%) within 12 h. Time to resolution after initial onset ranged between 2 h and 20 days, 13 (72.2%) within 7 days, two (11.1%) had long-term sequelae (ataxia, left-sided weakness) [76]. Although this study is a retrospective non-placebo-controlled one, its results suggest dextromethorphan be considered for the treatment of methotrexate neurotoxicity, especially after IT administration.

Aminophylline: Aminophylline, a methylxanthine competitive adenosine antagonist, was suggested to be used in methotrexate neurotoxicity. According to one case series, 2.5 mg/kg IV aminophylline as a 45–60 min infusion reversed subacute neurotoxicity after HD-MTX in four out of six pediatric patients (3–16 years old). Response was observed after or during the infusion. These patients received IV methotrexate, not IT [259]. A later publication reported on a 20-year-old patient treated with 15 mg IT methotrexate together with other chemotherapeutic agents who developed rapid consciousness deterioration, diminished verbal output, and behavioral changes. She was treated with 145 mg aminophylline daily for 7 days together with IV folinic acid, with gradual cognitive and behavioral improvement over the next 6 months [87]. A 16-year-old patient with subacute neurotoxicity after 12 mg IT methotrexate was treated with 5 mg/kg aminophylline every 6 h and folinic acid. He improved clinically and radiologically over 7–10 days. However, neurotoxicity recurred after re-administration of IT methotrexate, in spite of prophylactic aminophylline and folinic acid [239]. The contribution of aminophylline to the recovery is unclear. Although aminophylline use was not reported after IT methotrexate, biologic plausibility and some beneficial effects reported suggest it may be used also in severe or large IT methotrexate overdose.

Suggested Treatment Recommendations for IT Methotrexate Overdose

No controlled studies evaluated the efficacy and safety of the available treatments of IT methotrexate overdose, and no well-established guidelines exist. The following suggested approach relies on case series, case reports, and approaches recommended by other clinicians; it should not be considered evidence based.

Early recognition of the overdose and the prompt use of multimodality treatments are the two main principles critical for reducing short- and long-term outcomes and death.

1. *Prevention.* This is certainly the best treatment modality; attention should be drawn to the dose

prescribed for IT administration, dose prepared, and route of administration (IT instead of IV). It is suggested to keep the methotrexate vials used and review the whole process of drug administration, before and immediately after the IT injection.

2. *Supportive treatment.* This includes hydration and maintaining adequate urine output, urinary alkalization, and seizure control.
3. *Clinical evaluation.* Determine time elapsed from IT injection; assess clinical manifestations of neurotoxicity, severity, and time to onset; obtain kidney function tests, plasma, and if possible also CSF methotrexate concentrations; consider EEG, CT, or MRI.
4. *Determination of the dose administered.* Three dose ranges were reported according to severity of neurotoxicity and outcome: less than 100 mg, 100–500 mg, and higher than 500 mg.
5. *Principles of treatment according to the methotrexate dose injected IT:*

- (a) *<100 mg dose.* Immediate CSF drainage, IV folinic acid (15–50 mg), and dexamethasone (2–4 mg in adults, 0.15 mg/kg in children), every 6 h, four doses of each; continue according to clinical manifestations.
- (b) *100–500 mg dose.* Immediate CSF drainage and exchange (lumbar, ventricular if delayed diagnosis). Consider ventriculolumbar perfusion if high methotrexate dose or prolonged time elapsed from the IT overdose (e.g., several hours) due to the rapid distribution of methotrexate throughout the CSF. Administer IV folinic acid (40 mg/m² or 100 mg), and dexamethasone (4 mg in adults, 0.15 mg/kg in children), every 6 h, four doses of each; continue according to clinical manifestations. Consider IT 2 mg dexamethasone and IT 2,000 U glucarpidase after the drainage/exchange/perfusion.
- (c) *>500 mg dose.* Immediate CSF drainage and exchange. Urgently proceed to ventriculolumbar perfusion, IV folinic acid (40 mg/m² or 100 mg), and dexamethasone (4 mg in adults, 0.15 mg/kg in

children), every 6 h, four doses of each; continue according to clinical manifestations. Administer IT 2,000 U glucarpidase after the drainage/exchange/perfusion, and consider IT injection of 2 mg dexamethasone. Consider dextromethorphan (1–3 mg/kg/bid for 4 days) and IV aminophylline (2.5 mg/kg daily for up to 7 days).

- (d) *Monitoring CSF methotrexate concentrations.* CSF methotrexate concentrations 24 h after IT glucarpidase administered for IT overdose were $\leq 0.65 \mu\text{mol/L}$, similar to the concentrations found after therapeutic dose of IT methotrexate [233]. This may be considered as a desired target concentration, until which treatments should be continued. Methotrexate is hydrolyzed in the CSF to DAMPA which cross-reacts with methotrexate in immunoassays. It can result in falsely elevated concentration of methotrexate, and an HPLC assay is preferred in these circumstances [233, 262].

Reproductive Toxicity and Lactation

Methotrexate is an abortifacient. A 50 mg/m² dose is used for a nonsurgical termination of ectopic pregnancy. It is also a human teratogen, causing a characteristic pattern of malformations including (but not limited to) the skull, limb, other skeletal, and craniofacial and growth restriction, termed methotrexate embryopathy. Adverse pregnancy outcomes seem to be dose and gestational time dependent. A critical period for exposure of 6–8 weeks after fertilization and a critical dose of 10 mg/week were suggested based on a limited number of observations [269]. However, other small studies reported on malformations after exposure in earlier stage of pregnancy [270] and lower doses (7.5 mg) [271]. Most cases of congenital defects were observed after a failed attempt of pregnancy termination [272]. The teratogenic potential of methotrexate in dosage

typically used for the treatment of rheumatoid arthritis remains uncertain. There are reports on healthy babies born after exposure to LD-MTX during the first few weeks of gestation, before pregnancy was diagnosed [273]. A prospective cohort study found that postconception exposure to LD-MTX (≤ 30 mg/week) was associated with a higher rate of spontaneous abortions (42.5%; adjusted hazard ratio 2.1, 95% CI 1.2–3.2 using disease-matched controls) and major birth defects (6.6%; statistically higher than 2.9% in healthy controls, insignificant from 3.6% in the disease-matched controls). Preconception exposures were not different from the control group. None of the malformations were clearly consistent with methotrexate embryopathy [274].

Male reproduction: The effect of methotrexate on male fertility is not well determined. Azospermia or oligospermia was documented in patients after HD-MTX, but since the chemotherapy regimens included other drugs and sometimes radiotherapy, it is difficult to determine the role of methotrexate. Chronic LD-MTX was reported to have no effect in several case reports and studies and reversible sterility by others [275]. Paternal LD-MTX was not found to be associated with adverse pregnancy outcome in an observational cohort study of 113 pregnancies [276].

Lactation: Data from a case report suggest low levels in breast milk following a daily 15 mg/m² oral dose for choriocarcinoma, milk plasma ratio of 0.08 [277]. The author of another case report believes that parenteral weekly doses of methotrexate can be used in lactating women with active rheumatoid arthritis [278]. This approach is not widely accepted. Breastfeeding during HD-MTX is contraindicated.

According to an international panel of rheumatologists, methotrexate should not be used by women and men for at least 3 months before planned pregnancy and should not be used during pregnancy or breastfeeding [279]. According to the manufacturer, pregnancy should be avoided during and for a minimum of 3 months after therapy for male patients and during and for at least one ovulatory cycle after therapy for female patients [33].

Body Surface Area Calculation

Calculating body surface area (BSA) is required for determining methotrexate and folinic acid doses. Several formulas exist for this purpose; Mosteller formula is a common and simple one:

$$BSA (m^2) = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}} \quad [280].$$
 Online calculators and nomograms (e.g., West nomogram [281]) can be easily found on the Web.

Key Points in Methotrexate Toxicity

1. Methotrexate is used to treat a variety of malignant and nonmalignant illnesses.
2. Methotrexate poisoning can occur in the following settings: high dose for cancer chemotherapy, low-dose and its associated medication errors, acute overdose (intentional/unintentional), and intrathecal overdose.
3. Medication errors associated with low-dose or intrathecal methotrexate can be severe and even fatal.
4. Toxicity includes myelosuppression, renal impairment, gastrointestinal disturbances (e.g., mucositis), and hepatic enzyme abnormalities.
5. Treatment principles: hydration, urine alkalization, folinic acid, glucarpidase, and extracorporeal elimination.
6. Folinic acid must be administered before methotrexate-induced DNA damage had occurred; delay may be associated with irreversible toxicity.
7. Glucarpidase should be used in severe toxicity determined by plasma methotrexate concentrations and renal function.
8. In medication error of LD-MTX and acute overdose, folinic acid should be initiated as soon as possible, before obtaining plasma methotrexate concentration.
9. Intrathecal overdose requires prompt identification, CSF drainage/exchange or ventriculolumbar perfusion, and systemic folinic acid and dexamethasone; intrathecal glucarpidase can be used in severe overdose.
10. Methotrexate is a known human teratogen.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse class of compounds that share anti-inflammatory, analgesic, and antipyretic properties. Both therapeutic and adverse effects of NSAIDs are primarily due to cyclooxygenase (COX) inhibition. There are different types of COX, denoted as COX-1, COX-2, and COX-3 (which is considered a variant of COX-1) [1].

NSAIDs are commonly utilized and comprise up to 2.5% of all prescription dollars spent, globally. A National Health Interview Survey in 2010 revealed that 12.8% of adults in the United States were taking NSAIDs at least three times a week for 3 months, which represented a more than 40% increase in use since 2005. Further, telephone surveys reveal that 26% of users of over-the-counter NSAIDs take more than the recommended dose [2]. These factors explain the finding that adverse effects from NSAIDs are among the most common drug side effects reported in the United States and worldwide [3]. In 2005, the US Food and Drug Administration released a statement stressing “the importance of using the lowest effective dose for the shortest duration possible if treatment with a NSAID is warranted for an individual patient” [2]. This thought is echoed throughout current literature.

Despite the significant number of reports of toxicity from chronic use and overuse, intentional acute overdosage of NSAIDs is rarely life-threatening and death from acute NSAID overdose is quite rare.

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Biochemistry and Clinical Pharmacology

Metabolism of phospholipids by the enzyme phospholipase A₂ produces arachidonic acid, a 20 carbon unsaturated fatty acid which is embedded in cellular membranes. During inflammatory processes, arachidonic acid is converted into prostaglandins and thromboxanes. This conversion is mediated by COX, lipoxygenase, and cytochrome P450 enzymes. Nonsteroidal anti-inflammatory drugs prevent the substrate arachidonic acid from binding to the active site of COX enzymes (Fig. 1).

Pathophysiology of Toxic Effects

In general, the COX-1 isoform performs house-keeping functions, such as gastric mucosal protection. Due to its function in maintaining homeostasis, COX-1 is found in high concentrations in many cells and tissues, including endothelial cells, platelets, renal collecting tubules, and the gastrointestinal (GI) tract. Conversely, COX-2 is inducible by mediators of inflammation, such as tumor necrosis factor and cytokines. Nonsteroidal anti-inflammatory drugs can downregulate COX-2 pathways, thereby inhibiting inflammation. These differences in COX isoenzymes has led to classifying various NSAIDs by strength of inhibition of each isoenzyme, with nonselective NSAIDs inhibiting both COX-1 and COX-2 enzymes and selective NSAIDs inhibiting COX-2 more than COX-1 enzyme. Despite these classifications, both COX-1 and COX-2 are expressed in many tissues and there is overlap in COX-1 and COX-2 function. For instance, COX-2 derived prostaglandins play a role in maintenance of GI mucosal integrity and COX-1 derived prostaglandins contribute to inflammation [1, 4–7]. Further, we are discovering that there is significant similarity in the clinical toxicity produced by nonselective and selective NSAIDs. It appears that dose may be more important than laboratory-defined COX selectivity. At higher doses, COX selectivity blurs [1].

While some continue to classify by COX selectivity (“nonselective” if the NSAID inhibits both COX-1 and COX-2 well and “selective” if it

primarily inhibits COX-2; selective is also sometimes denoted as COXIB), others prefer to classify NSAIDs by chemical composition (See Tables 1 and 2). Most reviews include both classifications and both can be useful clinically; however, NSAIDs classified as selective do not always share common adverse effect profiles with each other, even at therapeutic doses. For instance, regardless of selectivity, GI side effects may occur with most NSAIDs, particularly in the lower GI tract [1]. The same is true for adverse cardiovascular effects, especially at high doses [1]. Some propose that solubility and partition coefficients, pH, and pKa may determine the distribution of various NSAIDs into various body tissues, contributing to differing toxic effects from different NSAIDs. Table 3 lists pharmacokinetic parameters of some NSAIDs. Others have suggested that NSAIDs target Ca⁺⁺ induced K⁺ channels but differ in their ability to affect the channels and produce toxicity [1]. Still others suggest that differential transport of NSAIDs with transporters such as the organic anion transporting polypeptide 2A1 (OATP2A1) may account for varying toxicity of various NSAIDs [1].

Clinical Presentation and Life-Threatening Complications

Adverse effects and clinical toxicity may occur from: drug-drug interactions (Table 4), acute allergic reactions, chronic use and overuse, and acute overdosage. While the focus of this textbook is acute overdose and associated toxicity, drug-drug interactions and chronic toxicity are so common with NSAIDs due to the prevalence of their use that these adverse effects are discussed. Allergic reactions are less common, but can be life-threatening, and are also discussed.

Acute Allergic Reactions

Nonsteroidal anti-inflammatory drug hypersensitivity reactions have been reported with diclofenac, ibuprofen, naproxen, ketoprofen, phenylbutazone, and oxyphenbutazone [17].

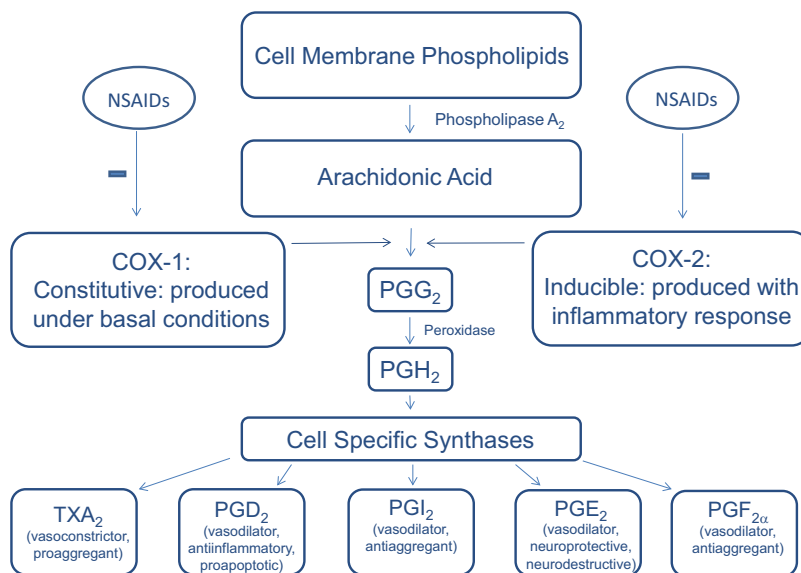


Fig. 1 Actions of NSAIDs. In normally functioning cells, phospholipase converts phospholipids in the cell membrane into arachidonic acid, which begins the arachidonic acid cascade. Arachidonic acid is further converted to PGG₂ by COX enzymes. PGG₂ is then converted to PGH₂ by peroxidase. Under normal circumstances, the action of COX enzymes on arachidonic acid eventually produce prostaglandins D₂, E₂, F_{2α} (PGD₂, PGE₂, PGF₂), prostacyclins (PGI₂), and thromboxane A₂ (TXA₂), needed for gastrointestinal mucosal protection, maintenance of renal perfusion, and regulation of platelet aggregation. NSAIDs

limit the production of PGG₂ by inhibiting COX enzymes, which subsequently results in less PGH₂. Since NSAIDs reduce the amount of PGH₂ that can be acted upon by cell specific synthases to produce prostaglandins (PGD₂, PGE₂, PGF₂), prostacyclins (PGI₂), and thromboxanes (TXA₂), many cell functions are altered. The reduced production of prostaglandins, prostacyclins, and thromboxanes can affect vasoconstriction/vasodilation, platelet aggregation, neuroprotection, neurodestruction (e.g., apoptosis), inflammatory responses, and carcinogenesis

Acetaminophen and salicylates, which are discussed in other chapters, have also been associated with hypersensitivity reactions. Nonsteroidal anti-inflammatory drugs are amongst the most likely drugs to induce anaphylaxis. Single oral administration of a NSAID may result in anaphylaxis. Nonsteroidal anti-inflammatory drug-induced anaphylaxis is likely due to an IgE-mediated response, may occur rapidly, and may be life-threatening [17–19]. Retrospective analysis of an allergy service in the Netherlands found that 17% of hospitalizations were related to NSAID hypersensitivity, 30% of which were secondary to diclofenac. The most common reaction was anaphylaxis, in this hospitalized group [18]. Of note, nonallergic drug hypersensitivities, commonly called pseudoallergic or idiosyncratic reactions, may result from NSAID use as well.

Topical NSAID application, such as topical ketoprofen use, may produce contact and photocontact allergic reactions as well as anaphylaxis [17, 19].

Adverse Effects and Clinical Toxicity Due to Chronic Use

Generally, higher doses, longer duration of use, and comorbidities of the patient are associated with increased risk of adverse drug effects from NSAIDs. Additionally, genetic susceptibility may contribute to variable toxicity. The major adverse effects of NSAIDs involve the GI, renal, and cardiovascular systems; however, other systems may also be affected [1]. These adverse effects will be discussed systematically.

Table 1 Classification by chemical structure^a

Chemical class	Examples of drugs: generic name (brand name)
Acetic acids	Bromfenac (Duract[®]) – a benzene acetic acid; withdrawn from US market due to severe hepatotoxicity, resulting in death and transplantation [8–10] Diclofenac (Voltaren[®], Cataflam[®]) – a phenylacetic acid; associated with DILI [10] Etodolac (Lodine[®], Lodine XL[®]) – an indole acetic acid Indomethacin (Indocin[®]) – an indole acetic acid Sulindac (Clinoril[®]) – an indene acetic acid Tolmetin (Tolectin[®]) – a heteroaryl acetic acid
Butanones (Ketones)	Nabumetone (Relafen[®]) – a prodrug
Diarylheterocyclics (also, COXIBs or COX-2 selective inhibitors)	Rofecoxib (Vioxx[®]) – a furanone; a sulfone; withdrawn from US and other markets due to risk of myocardial and cerebral infarctions Celecoxib (Celebrex[®]) – a sulfonamide derivative; a pyrazole; occasional DILI [10] Valdecoxib (Bextra[®]) – a isoxazole; a sulfonamide derivative; withdrawn from US and other markets Paracoxib (Dynastat[®]) – injectable prodrug of valdecoxib; not on US market Etoricoxib (Arcoxia[®]) – a bipyridine; a sulfone; not on US market Lumiracoxib (Prexige[®]) – a phenylacetic acid; never on US market; analog of diclofenac; highly COX-2 sensitive; associated with liver toxicity (severe hepatic necrosis, requiring transplantation or resulting in death) [9–12]
Fenamic acids (anthranilic acids)	Meclofenamic acid (Meclomen[®]) Mefenamic acid (Ponstel[®])
Oxicams (enolic acids)	Meloxicam (Mobic[®]) Piroxicam (Feldene[®])
Propionic acid derivatives	Fenoprofen (Nalfon[®]) Flurbiprofen (Ansaid[®]) Ibuprofen (Motrin[®]) – occasional DILI [10] Ketoprofen (Orudis[®]) Naproxen (Naprosyn[®]) Oxaprozin (Daypro[®]) Suprofen (Suprol[®]) – off US and other markets
Pyrazolones	Oxyphenbutazone Phenylbutazone
Pyrrolo-pyrroles	Ketorolac (Toradol[®]) – a carboxylic acid; banned from many European markets; significant gastrointestinal toxicity
Salicylates (discussed in a separate chapter)	Acetyl salicylic acid (Aspirin[®]) Sulfasalazine (Azulfidine[®]) Diflusal (Dolobid[®])
Sulphonanilides	Nimesulide (never on US market; severe hepatotoxicity) [10]

Key: *DILI* drug-induced liver injury, *US* United States, *COX* cyclooxygenase

^aThis table is a composite of many works [1, 4, 10, 13]. Of note, there is some variation in classification by chemical structure amongst different authors. The brand names given are examples of those used in the United States. These may differ in other countries

Neurological and Neurovascular Effects from Chronic Exposure

Cerebrovascular accidents: There is controversy regarding the risk of stroke with NSAID use [1, 15]. Studies are historical and contradictory. For instance, one retrospective cohort study revealed an increased risk of stroke among users of rofecoxib and valdecoxib but not diclofenac, ibuprofen, naproxen, and indomethacin; however, another retrospective cohort study revealed both

nonselective (naproxen, indomethacin, piroxicam, meloxicam, diclofenac) and selective (celecoxib and rofecoxib) NSAIDs were associated with increased risk of stroke. In the later study, ibuprofen was the only NSAID that did not increase the risk of stroke [1]. Most clinical trials suggest an association of increased thromboembolic events with NSAID use, regardless of COX-2 selectivity. In general, meloxicam appears to present less risk than rofecoxib and celecoxib

Table 2 Classification by COX-1 and COX-2 isoform selectivity^a

COX 1 selective (Low COX-2 inhibition: COX-1 inhibition ratios; lowest listed at top)	Unselective (Progressing from more COX 1 selective to more COX-2 selective)	COX 2 selective ^b (High COX-2 inhibition: COX-1 inhibition ratios; highest listed at top)
Ketorolac ^c	Meclofenamate	Etodolac
Flurbiprofen	Sulindac	Celecoxib
Ketoprofen	Naproxen	Meloxicam
Indomethacin	Piroxicam	
Tolmetin	Ibuprofen	
Aspirin (Acetylsalicylic acid)	Acetaminophen	
Nabumetone	Sodium salicylate	
Fenoprofen	Diffunisal	

This table was generated from multiple sources [1, 4, 5, 13]

Key: COX cyclooxygenase

^aNote: COX 1 selective and unselective are generally called “nonselective” and COX 2 selective is generally referred to as “selective” or “COXIB”

^bOthers that are typically classified as COX-2 selective but that are not available on the US market include: rofecoxib (thrombotic disease), nimesulide (liver toxicity), valdecoxib (thrombotic disease), lumiracoxib (liver toxicity), etoricoxib, and paracoxib

^cOff the market in France, Germany, and some other countries for bleeding complications, primarily perioperatively, and for renal failure, especially in the elderly or those with impaired renal function. Ketorolac has a higher relative risk of GI bleeding than most NSAIDs

Table 3 Pharmacokinetics of some NSAIDs^a

NSAID	Bioavailability (%)	Half-life (h) (therapeutic; may differ in overdose) ^b	Volume of distribution (L/kg, unless otherwise stated)	Clearance (L/h; unless otherwise stated)	Primarily renally eliminated (Y/N)	Peak (h) (therapeutic; may differ in overdose)	Protein binding (%)
Celecoxib	Solution: 64–88 Capsule: 22–40	6–12	400 L	27.7	N (hepatic metabolism; inhibits CYP2D6)	2–4	97
Diclofenac	50–60 (first-pass effect)	1–2	0.1–0.2	21.0	Y	2–3	99
Ibuprofen	>80	2–4	0.15	3–3.5	Y	0.5	99
Ketoprofen	90	2	0.1	6.9	Y	1–2	99
Meloxicam	89	15–20	10 L	0.4–0.5	half	4–10	99
Naproxen	95	12–17	0.16	0.13 ml/min/kg	Y	1	99

Many sources were used to develop this table [7, 13, 14]

^aGenerally, most NSAIDs are acidic, have high bioavailability, and are highly protein bound. Most are metabolized by the liver. Some (such as, naproxen, ibuprofen, and ketoprofen) are also glucuronidated by renal enzymes [1]

^bWhile NSAIDs (excluding Aspirin) reversibly inhibit the COX enzyme, drugs with long half-lives, such as piroxicam with its half-life of 30–86 h, will appear to irreversibly inhibit COX enzyme. Further, in overdose half-lives of all NSAIDs may be prolonged. Aspirin irreversibly inhibits COX enzyme; thus, new COX enzyme must be made to restore function

and most studies indicate that ibuprofen does not present a significant stroke risk [1].

Aseptic meningitis: Aseptic meningitis generally presents with fever, headache, photophobia, and meningeal signs (e.g., neck stiffness). Less

commonly, confusion, lethargy, and seizures are seen. Aseptic meningitis is a rare complication of NSAID use, but NSAIDs are the most common cause of drug-induced aseptic meningitis. Aseptic meningitis has been reported following

Table 4 Drug-drug interactions producing toxicity and critical illness

Drug or drug class that interacts with NSAIDs	Effect	Some specific interactions
Angiotensin-converting enzyme inhibitors ^a	Increase risk of renal compromise, hyperkalemia, and hypertension	Indomethacin (and probably other NSAIDs) inhibits the antihypertensive response of captopril; however, sulindac has a small opposing effect of the antihypertensive efficacy of captopril and enalapril
Angiotensin inhibitors	Increased risk of renal compromise and hyperkalemia	
Anticoagulants	GI side effects (e.g., bleeding)	NSAIDs can produce hypoprothrombinemia, but the effect is variable and dependent on the specific NSAID COX-2 selective agents can have platelet-aggregating effects and compete with warfarin for albumin binding sites NSAIDs increase the incidence of bleeding in patients receiving heparin therapy
Antidiabetic agents (Sulfonylureas and insulin)	Increased risk of hypoglycemia	Phenylbutazone enhances the hypoglycemic response of antidiabetic agents
Beta-blockers	Increased risk of hypertension	NSAIDs (indomethacin, flurbiprofen, piroxicam) reduce the antihypertensive effects of beta-blockers Sulindac is less likely to interfere with beta-blockers Calcium channel blockers have lesser interactions with NSAIDs than do beta-blockers
Corticosteroids	GI side effects (e.g., ulceration, bleeding)	
Cyclosporine	Increased risk of cyclosporine toxicity (nephrotoxicity)	Sulindac increased cyclosporine concentrations and serum creatinine (2- to 3-fold) within 3 days Indomethacin increases nephrotoxicity in animals Mefenamic acid increases serum creatinine and cyclosporine concentrations within 1 day
Diuretics	Increased risk of renal compromise and hypertension	Concomitant administration of indomethacin, diclofenac, or ibuprofen with triamterene has produced hyperkalemia Indomethacin may inhibit the formation of prostaglandins, which protect against drug-induced nephrotoxicity
Ethanol	Increased risk of GI bleeding	A two- to threefold increase in incidence of minor gastric bleeding has been reported with co-ingestion of ethanol and NSAIDs
Hydralazine	Increased risk of hypertension	Indomethacin increases blood pressure through inhibition of prostaglandin synthesis
Lithium	Increased risk of lithium toxicity	NSAIDs (including COXIBs) increase serum lithium levels to varying degrees (12–448%), depending on the NSAID Elevations in lithium levels may occur in as few as 3 days Diclofenac, ibuprofen, indomethacin, ketorolac, mefenamic acid, naproxen, phenylbutazone, and piroxicam reportedly interfere with renal prostaglandins that are involved in the excretion of lithium

(continued)

Table 4 (continued)

Drug or drug class that interacts with NSAIDs	Effect	Some specific interactions
Methotrexate	Increased risk of methotrexate toxicity (hematologic toxicity)	NSAIDs may increase methotrexate levels Toxicity is generally seen at higher (antineoplastic) doses of methotrexate and less commonly with lower doses Diclofenac prior to high-dose methotrexate therapy has resulted in serious methotrexate toxicity Flurbiprofen, co-administered with low-dose methotrexate, has reportedly produced neutropenia, thrombocytopenia, and GI bleeding Ibuprofen decreases the renal clearance of methotrexate by 50% and doubles the methotrexate area under the curve Death has occurred with concomitant use of indomethacin, ketoprofen, naproxen, and phenylbutazone
Serotonin reuptake inhibitors (SSRIs)	Increase adverse GI effects (e.g., GIB)	SSRIs increase bleeding risk by inhibiting platelet adhesion and function Conversely, tricyclic antidepressants do not appear to increase GI risks as much

This table was generated from many sources [1, 4, 15, 16]

Key: *GIB* gastrointestinal bleed, *COXIBs* COX-2 selective

^aIncreases in blood pressure with NSAIDs are most pronounced when co-administered with angiotensin II receptor blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEIs) and lowest with calcium channel blockers and loop diuretics [16]

therapeutic doses of ibuprofen, naproxen, sulindac, piroxicam, diclofenac, ketoprofen, and tolmetin. It occurs most commonly in women with systemic lupus erythematosus. The cause may be direct chemical irritation of the meninges by the NSAID but may also involve a hypersensitivity reaction. Laboratory findings include pleocytosis, primarily neutrophils, in the CSF, with associated elevations of protein; however, the cultures will be negative for infectious agents [20–22]. The differential diagnosis should include medication overuse headache, a refractory, chronic headache that resolves following cessation of the NSAID.

Hearing loss: Transient and persistent sensorineural hearing loss have been reported to occur after therapeutic doses of ketorolac [23, 24].

Pulmonary Effects from Chronic Exposure

Asthma: There is nearly complete cross-reactivity between aspirin-induced asthma and nonselective NSAID-induced asthma. Selective NSAIDs do not often appear to exacerbate asthma, although

there are a few case reports of cross-reactivity with aspirin-induced asthma [15, 16, 18]. Patients with nasal polyps, a marker of arachidonic acid metabolism abnormalities, are more likely to experience NSAID-exacerbated respiratory disease. Genetic susceptibility contributes to this risk [18].

Cardiovascular Effects from Chronic Exposure

Myocardial infarction: Once it was discovered that rofecoxib increased the risk of serious cardiovascular events (e.g., myocardial infarctions, congestive heart failure, and cardiac failure events), the cardiovascular risks of other NSAIDs were investigated. Meta-analyses revealed that other NSAIDs are associated with adverse cardiovascular events, such as myocardial infarction. This risk appears to be dose dependent, but some agents are more strongly associated with cardiovascular events. Low-dose ibuprofen has cardioprotective effects, similar to aspirin; however, high-dose ibuprofen increases cardiovascular risks [1, 15]. Diclofenac use presents a 40–60% higher relative risk of serious

cardiovascular events, compared to no NSAID use. This risk appears to be at least equivalent to rofecoxib, which has been withdrawn from the US market [1, 6, 15]. Despite this, diclofenac is the most commonly used NSAID worldwide [1]. Etoricoxib, which is not available in the United States, also appears to increase the risk of adverse cardiovascular events. Conversely, celecoxib and etodolac (both selective NSAIDs), and naproxen (a nonselective NSAID), have very low risks of adverse cardiovascular events [1, 6]. Patient factors, such as previous myocardial infarction, contribute to the risk of myocardial infarction, especially when taking higher doses of NSAIDs [1].

Dysrhythmias: Multiple studies indicate an increased risk of atrial fibrillation associated with NSAID use, especially long-term use [1].

Gastrointestinal Effects from Chronic Exposure

Dose- and duration-dependent adverse effects range from mild (dyspepsia, nausea) to severe (duodenal ulcers, gastrointestinal bleeding and stricture of the lumen, occasionally complicated by obstruction and perforation) [2]. In general, the most severe adverse effects involve the distal (lower) GI tract, while the more mild effects are more proximal (upper GI tract). Patients taking NSAIDs have a relative risk of 4.7 for upper GI bleeding and perforation, compared with nonusers; however, this risk varies depending on the agent [2] (See Table 5). Enteric-coated and sustained release products may decrease upper GI symptoms; however, these preparations increase the risk of distal GI toxicity, which is more serious [1].

Some measures can be taken to limit the GI toxicity induced by NSAIDs. Patient risk factors, such as advanced age; previous GI injury; and concurrent therapy with anticoagulants, aspirin,

corticosteroids, and selective serotonin reuptake inhibitors (SSRIs) also contribute to toxicity; therefore, other agents should be considered [2]. When topical, rather than oral, NSAIDs can be utilized, this should be done to limit the GI side effects [1]. Protective strategies, such as the co-administration of misoprostol, are recommended to limit GI toxicity (Grade I evidence) [2]. Modeling suggests that a proton pump inhibitor may reduce upper GI adverse effects [15]. Meta-analysis of nine randomized clinical trials comparing celecoxib with nonselective NSAIDs found less GI side effects associated with celecoxib [1]. However, this data cannot be extrapolated to other selective NSAIDs, as rofecoxib does not appear to provide this advantage [1].

Hepatic Effects from Chronic Exposure

NSAIDs (when acetaminophen is included) are third, following antibiotics and anticonvulsants, as causes of drug-induced liver injury (DILI) [10]. Up to 10% of cases of DILI are felt to be attributable to NSAIDs and nearly all NSAIDs have been implicated in causing liver injury [9, 12] (Table 6). A higher incidence of DILI has been described with diclofenac and sulindac compared to other NSAIDs. Most DILI caused by NSAIDs is minor; rarely, severe hepatotoxicity develops, occasionally resulting in death or the need for liver transplantation [10]. Nonsteroidal anti-inflammatory drug-induced liver diseases include: acute hepatitis, cholestasis (ibuprofen), cholestatic hepatitis (sulindac), chronic hepatitis (diclofenac), granulomatous hepatitis (phenylbutazone), and acute liver failure (bromfenac, lumiracoxib; neither are on US market) [12].

A genetic predisposition to DILI has been noted with diclofenac and lumiracoxib (not on US market) [10]. Lumiracoxib is structurally similar to diclofenac. The hepatotoxicity is generally idiosyncratic [10]. However, nongenetic risk factors are involved in NSAID-induced DILI as well, including use of other hepatotoxic drugs and chronic liver disease [10]. The hepatotoxicity of both diclofenac and lumiracoxib can be delayed for 1–3 months and has been associated with hepatotoxic metabolites and glutathione adduct

Table 5 Relative risk of GI bleeding with NSAIDs [7]

Low risk:	Ibuprofen (RR = 2.23)
Moderate risk:	Diclofenac (RR = 3.61)
	Naproxen (RR = 4.46)
	Indomethacin (RR = 5.12)
High risk:	Ketorolac (RR = 14.54)

RR Relative risk

Table 6 NSAID-induced liver injury

NSAID	Type of liver injury seen	% of reported NSAID-induced hepatotoxicity ^b
Diclofenac	Hepatocellular injury	34.1%
Ibuprofen ^a	Hepatocellular injury (some cases may occur with hepatitis C) Cholestasis Vanishing bile duct syndrome	14.6%
Sulindac	Cholestatic Hepatocellular injury Mixed pattern Generalized hypersensitivity reactions (associated with most of the fatal cases)	12.4%
Naproxen	Hepatocellular injury Cholestasis Rarely, immune-allergic hypersensitivity reactions Cross-hepatotoxicity with fenoprofen	11.1%
Piroxicam	Cholestatic jaundice Hepatocellular injury Rarely, hypersensitivity (rash, fever, eosinophilia)	9.3%

Note: While this table is unique, much of the data is derived from the text, graphs, and tables found in the article by Unzueta A, et al. [10]

^aIbuprofen has one of the best hepatotoxic safety profiles of the NSAIDs; however, because it is one of the most frequently used NSAIDs, it is responsible for a significant number of cases

^bAcetylsalicylic acid is responsible for 12% of reported NSAID-induced hepatotoxicity; acetaminophen-induced hepatotoxicity was not included in the data used to populate this table

formation, with glutathione depletion, oxidative stress, and mitochondrial injury [12, 25]. With lumiracoxib use, severe hepatocellular necrosis associated with positive auto-antibodies (antinuclear antibodies) has resulted in the need for transplantation and in death [9, 12].

Renal Effects from Chronic Exposure

Kidney injury: It is estimated that 2.5 million people in the United States experience NSAID-mediated renal disease annually [5]. Acute and chronic renal failure, with an associated reduction in glomerular perfusion and filtration rate, are seen [1]. Understanding blood flow to the kidney helps elucidate this disease process (See Fig. 2). Prostaglandins normally dilate the afferent arteriole bringing blood to the glomerulus. Nonsteroidal anti-inflammatory drugs limit prostaglandin production, producing vasoconstriction of the afferent arteriole, thereby limiting blood flow to the glomerulus [1, 26].

Risk factors for NSAID-mediated renal disease include: high doses, concomitant use of medications that alter renal autoregulation, age greater than 65 years, male gender, intravascular volume depletion, cardiovascular disease, diabetes, and pre-existing chronic renal disease [1, 5, 15]. Nonsteroidal anti-inflammatory drugs may produce renal papillary necrosis, acute interstitial nephritis (AIN), and the nephrotic syndrome. Renal papillary necrosis may result from medullary ischemic injury [1, 5]. The nephrotic syndrome is characteristic, with edema, oliguria, foamy urine, hematuria, and proteinuria. Acute interstitial nephritis is generally reversible [1, 5, 26]. Chronic renal failure (CRF) secondary to NSAIDs is rare but may occur secondary to interstitial nephritis or papillary necrosis [1]. While regular doses of NSAIDs are unlikely to produce CRF, high doses of NSAIDs increase the risk significantly [1].

Electrolyte abnormalities: Generally, all NSAIDs are associated with sodium retention, edema, and weight gain, regardless of COX selectivity. Hyponatremia is the most common electrolyte abnormality seen with NSAID use. Hyperkalemia, likely secondary to potassium retention, also occurs, regardless of COX selectivity; however, hypokalemia may also occur [1, 5, 27]. Hypocalcemia, hypomagnesemia, and hypophosphatemia are also reported [27]. Renal tubular acidosis, type 4, with associated electrolyte abnormalities may be seen [5].

Hypertension: Hypertension may worsen in previously hypertensive patients once placed on NSAIDs. In one study, rofecoxib was associated

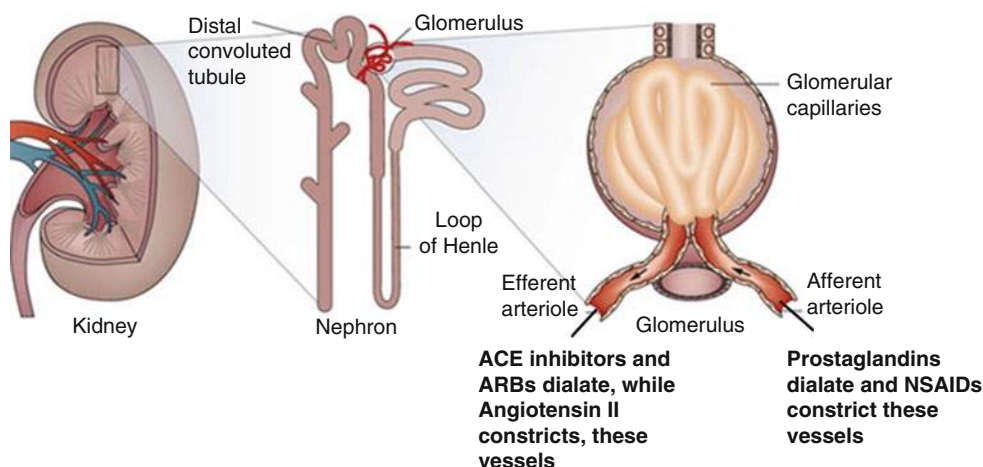


Fig. 2 NSAID effects on the kidney. The afferent arteriole normally dilates in response to prostaglandins; this results in an increased GFR. NSAIDs inhibit this effect by reducing the production of prostaglandins. This produces relative vasoconstriction of the afferent arteriole and decreases GFR. Conversely, angiotensin II normally constricts the efferent arteriole to increase GFR. However, ACE inhibitors inhibit this effect and produce a relative dilation of the efferent arteriole; this decreases GFR.

Administration of ARBs also leads to vasodilation of the efferent system. By acting at different sites to reduce GFR, NSAIDs (afferent vasoconstriction) and ACE inhibitors/ARBs (efferent vasodilation) can significantly limit GFR when administered concomitantly. This explains the increased risk of renal insufficiency and failure seen when these agents are used together [5]. *GFR* glomerular filtration rate, *ACE* angiotensin-converting-enzyme, *ARBs* angiotensin II receptor blockers

with worsening hypertension, while celecoxib was associated with a lower risk, revealing that this adverse effect is independent of COX selectivity, although this is not uniformly found in all studies [1]. The mean increase in systolic blood pressure is 2–3 mmHg, but it can be much greater, especially if the patient is co-ingesting angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, or diuretics [15]. This effect has been demonstrated in randomized controlled trials.

Immunologic Effects from Chronic Exposure

NSAIDs (with acetylsalicylic acid included) are the most frequent drugs involved in hypersensitivity drug reactions. Hypersensitivity may be mediated by immunoglobulin E (IgE), by T cells, or by activation of pathways that release vasoactive mediators (histamine, prostaglandins, sulfidopeptide leukotrienes) [17, 18]. Immunologic disease includes NSAID-induced respiratory disease (e.g., anaphylaxis, which is discussed above),

cutaneous disease (e.g., delayed fixed drug eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis), renal disease (e.g., nephritis, which is discussed above), and hepatic disease (which is discussed above) [9, 17, 18]. A multisystem hypersensitivity syndrome characterized by fever, rash, hepatic injury, and lymphadenopathy has been reported as well [28].

Both nonselective and selective (e.g., valdecoxib) NSAIDs may produce serious skin reactions [12]. The most frequent dermal reactions are exanthemas that are maculopapular and are commonly due to ibuprofen or naproxen. Contact dermatitis and photosensitivity may occur, generally triggered by ketoprofen and diclofenac. Severe reactions such as toxic epidermal necrolysis or Stevens-Johnson syndrome have been only rarely reported with NSAID use; these syndromes can prove fatal [15, 17, 18]. Chronic propionic acid-NSAID use has also produced pseudoporphyria, with bullous photosensitivity and similarities to porphyria cutanea tarda [29].

Hematopoietic Effects from Chronic Exposure

Phenylbutazone can produce serious blood dyscrasias, including aplastic anemia, agranulocytosis, and thrombocytopenia [30]. Phenylbutazone is sometimes referred to as “bute” and has been taken illicitly by jockeys and other racetrack workers [30]. Oxyphenbutazone, a metabolite of phenylbutazone, can produce similar toxicity.

Adverse Effects and Clinical Toxicity Due to Acute Overdosage

NSAIDs are generally well tolerated in overdose, with acute poisonings most commonly producing minimal morbidity and very rarely death. However, large overdosage may produce toxic encephalopathy, seizures, respiratory failure, cardiovascular arrest, renal failure, and hepatic injury. In the United States, ibuprofen is one of the most frequently ingested NSAIDs in acute overdose. Several deaths have been reported [27]. Lodise et al. report of a 51-year-old man who presented after intentional, isolated ibuprofen ingestion, confirmed by gas chromatography/mass spectrometry (GC/MS). The patient presented with coma, hypotension, metabolic acidosis, and respiratory depression. Despite vigorous supportive care, he died 4 h after arrival to the ED. Postmortem examination revealed edema of the brain, heart, and lungs, with unspecified myocardial injury. Postmortem ibuprofen concentrations were approximately 25 times greater than therapeutic concentrations [27]. Naproxen is also commonly ingested. Al-Abri et al. report of a 28-year-old man who ingested 70 g of naproxen and ethanol. He was drowsy, tachycardic, and developed metabolic acidosis that was treated with continuous venovenous hemofiltration (CVVH). He had recurrent seizures and respiratory failure requiring intubation. His naproxen concentration was approximately 40 times greater than therapeutic concentrations [31].

While many NSAIDs share a similar clinical appearance in overdose, there are notable distinctions. Clinical findings of acute NSAID overdoses found in the literature are summarized in Table 7,

and the unique features of different classes of agents are further delineated in the footnotes of Table 7 and in the discussion that follows.

Some important points to remember when caring for patients with large overdoses of NSAIDs, reviewed by system, include:

Neurologic: Acute psychosis and auditory hallucinations have been reported with overdosage of indomethacin, diclofenac, sulindac, and mefenamic acid [4]. Seizures, including status epilepticus, may occur, especially after overdosage of mefenamic acid [4, 32]. A retrospective review of single-agent exposures resulting in seizures from 1997 to 2010 in Switzerland revealed that mefenamic acid was the most prevalent cause of drug-induced seizures; however, due to its current infrequent use, this is not likely the case now [45]. Nystagmus, diplopia, miosis, and blurred vision have also been reported following overdosage of NSAIDs [4, 32]. The pupils may be fixed in miosis, but this should not be utilized as a prognosticator, since patients with this finding have made full neurological recoveries [56].

Pulmonary: Pulmonary edema and respiratory distress syndrome (ARDS) in conjunction with multiple organ failure have occurred in overdose [4, 50].

Renal: A profound, anion-gap, metabolic acidosis can occur with massive overdoses, occasionally with pH less than 7 [48, 49].

Complications of overdosage: Complications of toxic encephalopathy and hypotension may occur and occasionally prove fatal. These can include: aspiration pneumonia, respiratory failure, rhabdomyolysis, ischemia, and sepsis [27, 56, 61]. Rarely, dysrhythmias, such as ventricular fibrillation, and cardiac arrest have been reported [27]. Ischemic necrosis of the extremities may ensue [36].

Diagnosis of Acute Overdose

Blood studies: Symptomatic patients warrant the following basic blood studies: complete blood count, electrolytes, renal function tests, and liver

Table 7 Reported clinical findings with acute NSAID overdose^a

NSAID	Clinical findings in overdose
General NSAID overdose [4, 32–35]	<p><i>Neurological</i>: headache, dizziness, toxic encephalopathy (irritability, agitation, or coma), seizures, blurred vision</p> <p><i>HEENT</i>: tinnitus</p> <p><i>Pulmonary</i>: hyperventilation, respiratory alkalosis (rarely respiratory failure)</p> <p><i>Cardiovascular</i>: mild hypotension and tachycardia (rarely cardiovascular collapse or dysrhythmias)</p> <p><i>Gastrointestinal</i>: GI distress (nausea, vomiting, diarrhea, abdominal pain), rarely GI bleeding, rarely pancreatitis</p> <p><i>Hepatic</i>: hepatic injury, generally mild</p> <p><i>Renal</i>: sodium and water retention, rarely acute renal failure, hematuria, proteinuria</p> <p><i>Heme</i>: hypoprothrombinemia (prolonged prothrombin time), rarely: neutropenia, aplastic anemia, agranulocytosis, leukocytosis, thrombocytopenia</p>
Acetic acids (diclofenac, etodolac, indomethacin, sulindac) [33, 36–40]	<p><i>Neurological</i>: headache, dizziness, toxic encephalopathy (disorientation, irritability, agitation, hallucinations, coma), quadriplegia with interspersed choreiform movements (rare), extensor reflexes on plantar stimulation (rare), fixed gaze (without doll's eye movements; rare)</p> <p><i>HEENT</i>: tinnitus</p> <p><i>Pulmonary</i>: respiratory arrest (rare)</p> <p><i>GI</i>: GI distress (vomiting, abdominal pain); colonic perforation (with diclofenac; rare)</p> <p><i>Hepatic</i>: falsely elevated bilirubin (due to the phenolic metabolites of etodolac); hyperbilirubinemia (with normal liver enzymes in patient with sulindac overdose)</p> <p><i>Renal</i>: acute kidney injury, proteinuria, hematuria, renal failure (anuria)</p> <p><i>Hematopoietic</i>: hypoprothrombinemia, bone marrow aplasia and cytopenias, granulocytosis (transient, with acute sulindac overdose)</p> <p><i>Integument</i>: skin necrosis (ischemic)</p>
Diarythetereocyclics (celecoxib) [41]	<p><i>Neurological</i>: drowsiness, irritability, agitation</p> <p><i>GI</i>: GI distress, abdominal pain</p> <p><i>Integument</i>: rash</p>
Fenamic acids (flufenamic acid, meclofenamic acid, mefenamic acid, tolfenamic acid) [26, 32, 42–45]	<p><i>Neurological</i>: toxic encephalopathy (agitation, coma) seizures,^b dyskinesia, muscle twitching, hyperreflexia, extensor plantar response, miosis</p> <p><i>Cardiovascular</i>: cardiopulmonary arrest (rare)</p> <p><i>GI</i>: GI distress (vomiting, diarrhea)</p> <p><i>Renal</i>: acute renal failure</p> <p><i>Hematopoietic</i>: hypoprothrombinemia</p>
Propionic acid derivatives^c (fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin) [27, 31–33, 46–60]	<p><i>Neurological</i>: dizziness, headache, drowsiness, toxic encephalopathy (agitation, coma), seizures (rare; may be recurrent), muscle twitching (rare), nystagmus (rare), diplopia (rare), blurred vision, miosis, unreactive pupils (rare; with eventual full neurological recovery), ataxia, vertigo</p> <p><i>HEENT</i>: tinnitus, decreased hearing</p> <p><i>Pulmonary</i>: hyperventilation (respiratory alkalosis with metabolic acidosis; generally, less severe than is seen with salicylate), respiratory depression (rarely, respiratory arrest)</p> <p><i>Cardiovascular</i>: tachycardia, bradycardia (rare), hypotension, congestive heart failure (rare), dysrhythmias (rare), cardiac arrest (ventricular tachycardia/fibrillation; very rare)</p> <p><i>GI</i>: GI distress (nausea, vomiting, abdominal pain, hematemesis); pancreatitis (rare)</p> <p><i>Hepatic</i>: liver failure (very rare); hyperbilirubinemia^d</p> <p><i>Renal</i>: hematuria and proteinuria; polyuria; acute renal insufficiency; acute renal failure (tubular necrosis, nephritic syndrome); metabolic acidosis (common, though generally mild; however, may be severe in large overdosage); hyperkalemia; hypokalemia; hyponatremia; hyponatremia</p> <p><i>Hematopoietic</i>: hypoprothrombinemia, thrombocytopenia</p> <p><i>Metabolic/endocrine</i>: hypothermia (rare, but more often than hyperthermia);^e adrenal insufficiency</p>

(continued)

Table 7 (continued)

NSAID	Clinical findings in overdose
Pyrazolones (oxyphenbutazone, ^f phenylbutazone ^f) [30, 33, 61]	<i>Neurological</i> : toxic encephalopathy (irritability, agitation, coma), seizures (may include status epilepticus) <i>Cardiovascular</i> : tachycardia, hypotension, cardiovascular collapse <i>Pulmonary</i> : respiratory depression and failure, respiratory alkalosis, pulmonary edema <i>GI</i> : GI irritation, ulceration and GIB <i>Hepatic</i> : hepatic injury (hepatocellular, cholestasis) <i>Renal</i> : hematuria, acute renal failure (may require weeks of hemodialysis), electrolyte and fluid imbalances, metabolic acidosis (may be profound) <i>Endocrine</i> : Hyperglycemia, acutely <i>Hematopoietic</i> : acute leukocytosis (granulocytosis) ^g hypoprothrombinemia, thrombocytopenia, hypocellularity of bone marrow (if biopsied)
Sulfonanilides (nimesulide) [62]	Metabolic/endocrine: hypothermia ^c ; hypoglycemia ^h

^aTable 7 comprises primarily data from case reports, case series, and retrospective reviews. Often, only severe or unusual cases are reported in the literature

^bMefenamic acid is more likely to produce seizures, compared with other NSAIDs, with >1/3 of patients overdosing on mefenamic acid having seizures [32]

^cGenerally, dose of >400 mg/kg of ibuprofen are required to produce significant toxicity [32]

^dBilirubin may be falsely elevated due to NSAID metabolites that interfere with the assays for bilirubin [63, 64]

^eNSAIDs are known to uncouple oxidative phosphorylation in laboratory studies, so one would expect to see hyperthermia, but this is not generally seen clinically. In severe overdose, hypothermia following coma is more commonly reported than hyperthermia. Hypothermia has also been reported with nimesulide, even at therapeutic doses, in young children

^fTend to be more toxic than most other NSAIDs; Phenylbutazone is used in veterinary medicine and by equine racetrack workers; oxyphenbutazone is a metabolite of phenylbutazone [30, 33]

^gBone marrow dyscrasias are more characteristic of chronic use

^hBoth hypoglycemia and hypothermia may occur after a single therapeutic dose, as well

function tests. Bilirubin may be falsely elevated after overdosage of some NSAIDs [38].

In the older literature, many acute NSAID overdose cases occurred with significant co-ingestion of salicylate, and in the reported fatalities involving NSAIDs, significant salicylate toxicity was often noted; therefore, it is important to assess for concomitant salicylism [33]. Similarly, acetaminophen levels and liver function tests should be assessed to assess for concomitant acetaminophen toxicity (See chapters on Salicylate and Acetaminophen). Diflunisal, a salicylic acid derivative, cross-reacts with some salicylate assays and may produce a false positive for salicylate. Laboratory studies for NSAID concentrations are not generally available and are not likely to be of clinical utility in the acute management. Further, the once advocated nomogram to assess severity of ibuprofen toxicity, based on ibuprofen concentrations, is not useful [4].

Urine studies: Urinalysis may reveal proteinuria and hematuria. Phenylbutazone toxicity has been associated with red-discoloration of the urine, due to a rubazonic acid metabolite [65]. Generally, rapid urine drug screens (enzyme-linked immunoassays) are of limited value. Further, many rapid urine drug screens may produce false positive cannabinoid screens after the use of NSAIDs. If a patient is critically ill, GC/MS may be helpful at detecting co-ingestants as well as NSAIDs.

Imaging studies: Computed tomography (CT) may be useful in the patient with altered mental status of uncertain etiology but is not uniformly necessary for patients known to have overdosed on NSAIDs. Chest radiographs may be helpful for patients with suspected pulmonary edema, ARDS, or aspiration pneumonitis or pneumonia. Ultrasound of the kidneys or liver may be helpful in assessing renal or hepatic failure, respectively, but are not uniformly required.

Treatment of Acute Overdose

Treatments for salicylate and acetaminophen toxicity are not included in this chapter; the treatment of these toxicities differs significantly from what is described below, please refer to these chapters, specifically, if a patient suffers from salicylate or acetaminophen poisoning.

General: Treatment is primarily supportive and expectative. Watch for respiratory compromise. Patients with significant NSAID ingestions may show evidence of GIBs due to the risk of GI irritation, ulceration, and bleeding which may be attenuated by employing an H₂-receptor antagonists [1, 34] (Grade I recommendation). Hypotension generally responds to intravenous fluids, but occasionally vasopressors are employed [56, 57]. Wood et al. report a case of vasopressor-resistant hypotension, eventually resulting in cardiac arrest and death, after massive ibuprofen overdosage [47]. Since functional adrenal insufficiency has been reported in a patient with massive NSAID overdose, hypotension with a concomitant low cortisol level could be treated with systemic steroids [57]. Extracorporeal membrane oxygenation has been utilized for cardiovascular support in the treatment of massive ibuprofen overdose with cardiac failure [56]. Severe metabolic acidosis can be treated with fluid resuscitation and bicarbonate; occasionally, renal replacement therapy is necessary (see below) [47, 57]. Liver transplantation has been utilized to treat fulminant hepatic failure from NSAIDs [46, 66].

Elimination: Oral administration of activated charcoal, without gastric emptying, may reduce NSAID absorption if patients present within 1 h of ingestion and if the airway is protected (e.g., patient is alert or endotracheally intubated for depressed mental status). However, it is unknown if charcoal administration alters the outcome in these patients. Because most NSAIDs are highly protein bound and extensively metabolized, forced diuresis, urinary alkalization, and hemodialysis are generally not indicated to enhance drug

elimination. When studied, these methods do not appear to alter clearance significantly [31, 32, 55]. However, patients with severe acid/base abnormalities, severe electrolyte abnormalities, or acute renal failure may benefit from renal replacement therapy (e.g., high-flux hemodialysis, sustained low efficiency dialysis, continuous hemofiltration, etc.) [30–32, 35, 47, 55]. When renal failure occurs, hemodialysis may be required for weeks to months, but it is generally reversible [52]. Virji, et al. report on a case of severe phenylbutazone poisoning treated with plasmapheresis, but this is not generally performed [61].

Intravenous lipid emulsion therapy (LET) has been used to treat naproxen and ibuprofen toxicity in dogs (case report and series in veterinary literature) [67, 68]. Since most cases of human overdose are not life-threatening, LET is generally unnecessary; however, LET could be tried if cardiac arrest resulted from an overdosage of a lipophilic NSAID, such as ibuprofen or naproxen. Its benefit, if any, following NSAID overdose is strictly theoretical. There are no data indicating that it is beneficial or improves outcome in these patients.

Indications for ICU Admission After NSAID Overdose (Patients May Be Transferred Out of the ICU, Once These Resolve)

Seizures
 Encephalopathy (agitation, psychosis, coma)
 Angioedema with impending airway compromise
 Respiratory failure
 Pulmonary edema or ARDS
 Hemodynamic instability (hypotension, shock, dysrhythmias)
 Gastrointestinal hemorrhage
 Fulminant hepatic failure
 Renal failure with clinical compromise
 Significant electrolyte or acid/base disturbances (e.g., severe metabolic acidosis)
 Multiple organ failure

Special Populations

Geriatric: Elderly patients are known to be more susceptible to the adverse effects of NSAIDs, such as renal toxicity and central nervous system effects. Rarely, NSAIDs produce confusion, hallucinations, and psychoses [69].

Pediatric: Although the rate of life-threatening and fatal events from overdosage of ibuprofen (1.6%) is much less than that of acetaminophen (5.6%) and aspirin (5.9%) in adults; these rates are similar and much lower (approximately 0.4% of reported overdoses for each agent are life-threatening) in children [16]. This is likely due to the higher frequency of unintentional overdoses in children compared with adults. Adolescents may be more susceptible to seizures after mefenamic acid overdose, compared to adults [45]. Randomized controlled trials show an increased risk of renal failure in children taking ibuprofen for fever [16].

Neonatal: There are several reports of iatrogenic overdosage of indomethacin in premature infants, due to the use of indomethacin to treat patent ductus arteriosus (PDA) and to prevent intracranial hemorrhage (ICH). There is concern about indomethacin decreasing mesenteric, cerebral, and renal blood flow; altering platelet and renal function; and disrupting gastric mucosal integrity. In fact, there have been anecdotal reports of necrotizing enterocolitis (NEC) and intestinal perforations with suspected causal contribution from indomethacin. Following planned treatment with indomethacin, patients may experience transient renal impairment, with decreased diuresis, edema, hyponatremia, and hyperkalemia. Narayanan et al. performed a retrospective review of iatrogenic tenfold overdoses of intravenous indomethacin to 4 premature infants (secondary to dosing error) and compared the cases to a large population of premature infants who received appropriate intravenous indomethacin dosing [70]. All 4 patients received only one dose of a tenfold dosing error, with 3 patients experiencing transient drops in urine output and 2 experiencing

transient increased BUN or creatinine; however, none experienced NEC, ICH, or chronic lung disease [70]. Due to the low number of patients (4 patients, with one dosing error each), this data is similar to a case series of 4, and it is difficult to be completely reassured by this data due to the rarity of NEC. Schuster et al. report on a preterm infant who received a single 100-fold overdose of indomethacin for the treatment of PDA. The infant experienced transient renal failure with oliguria and mild hyponatremia and hyperkalemia, with full resolution by 4 days [71].

Obstetric: A large epidemiological study found that nonselective and selective NSAIDs may lead to abortion in the first trimester, with an odds ratio of 2.4 (95% confidence interval 2.1–2.8), compared with pregnant women not taking NSAIDs. Misoprostol, which is sometimes given with NSAIDs for GI protection, should not be administered to pregnant patients due to the risk of miscarriage [15].

Nonsteroidal anti-inflammatory drugs may delay labor, may prematurely close the ductus arteriosus, and may increase blood loss at delivery. Pregnant patients are at increased risk of fetal ductus arteriosus closure as the pregnancy progresses. Indomethacin, diclofenac, and naproxen are known to produce premature closure of the ductus arteriosus. With closure, fetal ultrasound may reveal dilation of the right ventricle, absence of flow in the pulmonary trunk, tricuspid regurgitation, pulmonary insufficiency, or oligohydramnios. The fetus may develop pulmonary hypertension [72–74]. When severe, fetal hydrops and death ensue [72]. Therefore, NSAIDs generally should not be administered during the last trimester [15, 16]. Intrauterine fetal exposure to NSAIDs may also produce hyponatremia and hyperbilirubinemia, recognized at delivery [72, 75].

Lactating mothers may take nonselective and selective NSAIDs, as levels of celecoxib and ibuprofen have been shown to be very low in breast milk [15].

Key Points in Overdosage

Most NSAID overdoses do not produce life-threatening toxicity.

Phenylbutazone and oxyphenbutazone are more toxic than other NSAIDs.

Mefenamic acid overdoses are commonly associated with seizures (much more so than other NSAIDs).

When massive NSAID overdosage occurs, it may be life-threatening.

Critical care is required when the NSAID overdose results in: encephalopathy, status epilepticus, respiratory failure, hypotension, dysrhythmias, cardiac failure, GI bleeding, GI perforation, hepatic failure, renal failure, significant metabolic acidosis or electrolyte abnormalities, cytopenias, and ischemia.

Severely poisoned patients may acutely have fixed, pin-point pupils yet proceed to a full neurological recovery.

NSAID overdosage may produce psychosis, especially in the elderly.

Some NSAIDs may falsely elevate the serum bilirubin concentrations (assay dependent).

Remember to assess for concomitant salicylate and acetaminophen toxicity, as the treatment for these poisonings differs from the treatment of NSAID poisoning.

Renal replacement therapy can be commenced for severe metabolic acidosis but is unlikely to facilitate significant removal of NSAIDs.

generally be taken, although the first dose should be taken under medical supervision.

- *Pregnancy*: Avoid NSAIDs. When NSAID use is essential, limit the dose during early pregnancy because of the risk of miscarriage and in late pregnancy because of the risk of increased blood loss and closure of the ductus arteriosus.

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Key Prescribing Points Box [15]

- *High risk for adverse GI effects*: age >65 years; previous ulcer, gastrointestinal bleeding, or perforation; other drugs known to increase gastrointestinal adverse events (anticoagulants, aspirin, serotonin reuptake inhibitors, corticosteroids); and serious comorbidities (hepatic, renal, or cardiac impairment; excessive alcohol intake; heavy smoking).
- *Aspirin sensitive asthma*: Avoid nonselective NSAIDs, due to cross-reactivity. Selective COX-2 inhibitors can

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Indications for ICU Admission in Opioid**Poisoning**

Requirement for mechanical ventilation
Symptomatic poisoning with methadone, buprenorphine, or other extended-release or long-acting opioid
Requirement for naloxone infusion
Acute lung injury or other hypoxic insult
Cardiovascular manifestations of hypotension, bradycardia, QRS prolongation, or QT lengthening requiring treatment
Seizures, life-threatening symptoms attributed to serotonin toxicity
Neonatal withdrawal
Symptomatic body packers
Potential complications of prolonged coma, brain injury, compartment syndrome, and severe rhabdomyolysis with risk or evidence of renal failure

Criteria for ICU Discharge in Opioid Poisoning

Resolution of ventilatory depression with adequate respirations
Resolution of acute lung injury or other hypoxic insult
Cessation of a naloxone infusion
Resolution of hypotension or bradycardia
Resolution of neonatal withdrawal

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Key Points in Opioid Poisoning

1. Miosis is *not* present in all opioid users and cannot be used diagnostically.
2. Naloxone should be administered in small amounts (starting with 0.04–0.05 mg if opioid dependent) to avoid withdrawal. If opioid withdrawal results, do not attempt to reverse the withdrawal symptoms with another opioid. Allow naloxone's effect to wane spontaneously (typically 20–60 min).
3. Methadone and other semisynthetic or synthetic opioids do not cross-react with the standard urine opioid drug assay.

Opium production dates back to the fourth century BC, and the first written documentation of its use dates to the writings of Theophrastus in the third century BC [1, 2]. Opium, which is the crude extract of the opium poppy plant, *Papaver somniferum*, was used for medicinal, recreational, and religious purposes. Morphine was isolated from opium in 1806 and was named after Morpheus, the Greek god of dreams. Diacetylmorphine, also called *heroin*, ironically was synthesized in the search for a safer, less addictive opioid. The endogenous opioid peptides, enkephalin, β -endorphin, and dynorphin, were isolated sequentially starting in 1975 [3].

Although the medicinal benefits of opioids are undeniable, opioid use is fraught with tribulations for the patient and for society. Poisoning is now the leading cause of injury death in the USA, with 41% (16,917 deaths) of poisoning deaths in 2011 involving opioid analgesics [4, 5]. Recent data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System revealed significant increases in opioid prescriptions and diversion and abuse of prescription opioids between 2002 and 2010 [6]. There has been a slight reduction from 2011 to 2013, suggesting potential benefit to local, regional, state, and federal interventions that have been implemented to address the growing problem. In addition, the rates of opioid-related deaths increased from 2002 to 2006, plateaued from 2006 to 2008, then slightly decreased from

2009 to 2013. Despite these improvements in prescription opioid-related deaths, the rates of heroin-related deaths (from the National Poison Data System) steadily increased from 2010 to 2013. This most likely occurred due to the reduced availability of prescription opioids, leading to the use of this cheaper and more available substitute [6]. This chapter focuses on the clinical issues concerning the acute and chronic adverse effects of opioid use.

The term *opioid* refers to an agent that is capable of specific binding to an opioid receptor. This term is inclusive and alludes to all such agents, whether they are endogenous peptides, plant or animal-derived, or synthetic, and does not specify whether the agent is an agonist or an antagonist at the receptor. *Opiates* are the subclass of drugs derived from the opium poppy plant. More than 20 naturally occurring opiates can be extracted from this plant, including morphine, codeine, and thebaine. Semisynthetic opioids, such as heroin, oxycodone, and hydromorphone, are derived from structural alteration of morphine's base structure with functional groups (Fig. 1). For example, heroin has acetyl functional groups added at both positions 3 and 6 to make diacetylmorphine.

Endogenous opioid peptides include three individual classes of peptides – enkephalins, dynorphins, and endorphins – that serve as innate agonists of the various human opioid receptors. The term *narcotic*, derived from the Greek word meaning “stupor” or “numbness,” is used to refer to any drug that induces sleep, although it can also refer to other illegal drugs of abuse including cocaine. Although this use of the term encompasses one of the primary clinical roles of the opioid agonists, the term often is used to designate an illicit substance.

Pharmacology

Opioids interact with opioid receptors (Table 1) to modulate their various clinical effects. Opioid receptors may be categorized based either on location within the body or on the binding affinities for various endogenous or exogenous opioid agents.

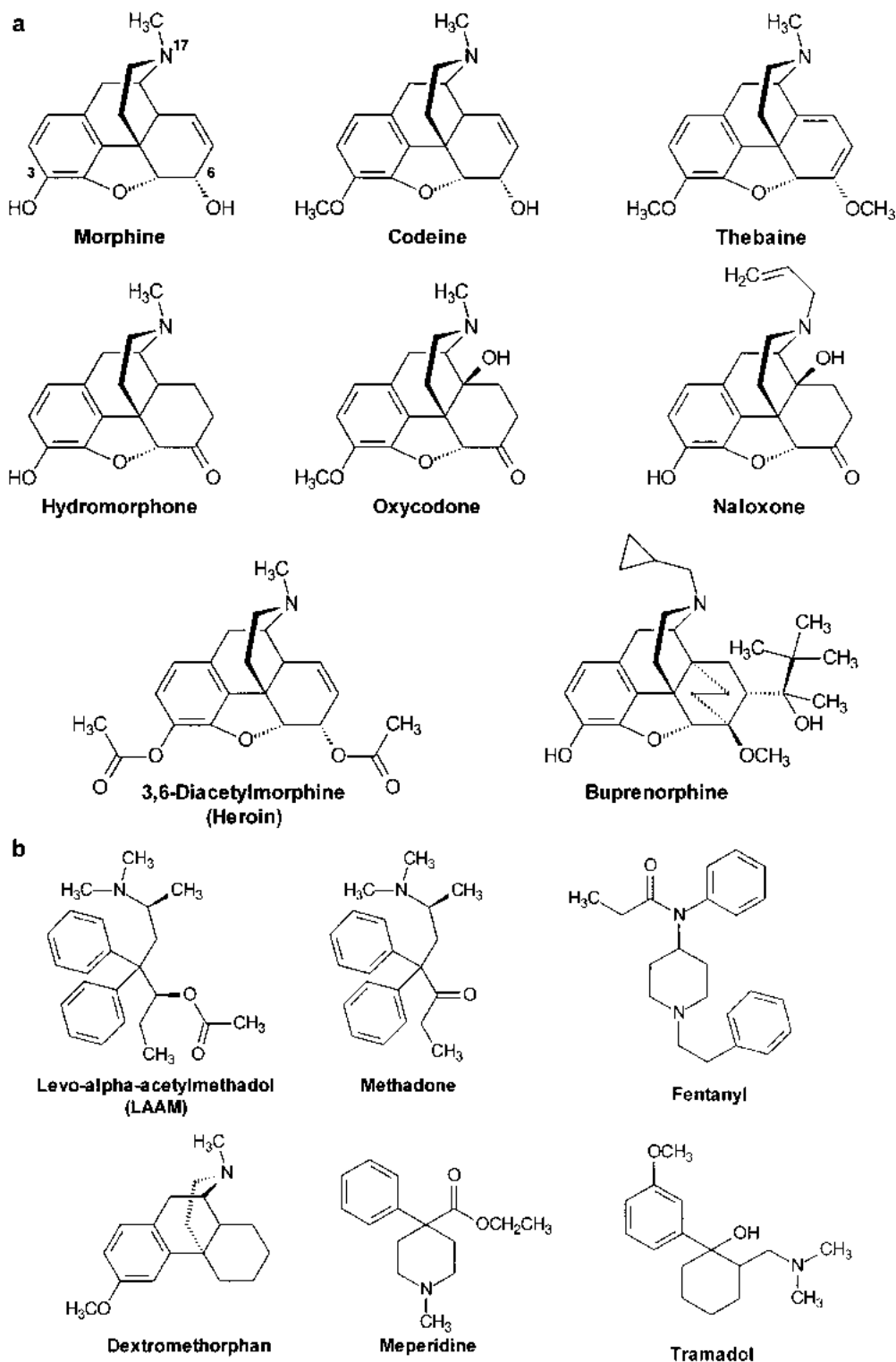


Fig. 1 (continued)

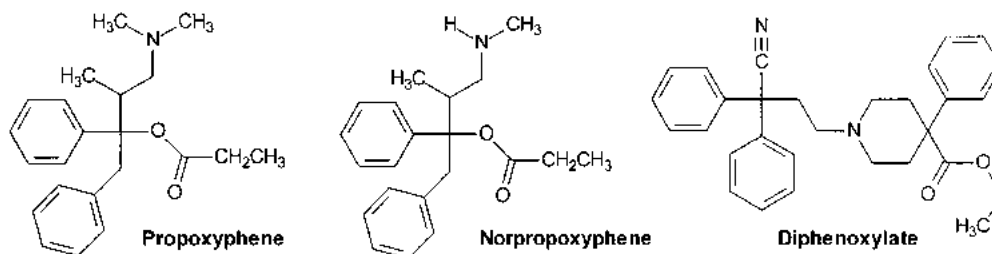


Fig. 1 Chemical structures of opioids discussed in the text

Table 1 Interaction of opioids and their receptors in modulating various clinical effects

Opioid receptors	Agonists	Clinical effects	Location
μ_1, μ_2	Morphine	μ_1 – supraspinal analgesia, peripheral analgesia, euphoria, sedation, prolactin release	Periaqueductal gray matter, nucleus raphe magnus, medial thalamus, limbic system, medulla
		μ_2 – spinal analgesia, respiratory depression, physical dependence, gastrointestinal dysmotility, miosis, pruritus, bradycardia	
$\kappa_1, \kappa_2, \kappa_3$	Ketocyclazocine – κ_1	κ_1 – spinal analgesia, miosis, diuresis	Spinal cord, antinociceptive regions of brain as listed above, substantia nigra
	Pentazocine, salvinorin A – κ_2	κ_2 – psychotomimesis, dysphoria	
	Nalorphine – κ_3	κ_3 – supraspinal analgesia	
δ	Enkephalins – δ_1, δ_2	Spinal and supraspinal analgesia, cough suppression, modulate motor activity	Nigrostriatal pathway
σ (no longer considered opioid receptor)	Dextromethorphan, pentazocine, ibogaine	Spinal analgesia, psychotomimesis, movement disorders	Hypothalamus, limbic forebrain, midbrain, cerebellum, brainstem, hippocampus

Similarly, opioids may be classified by their receptor preference or by pharmacologic characteristics. Because of this multiplicity of receptor and drug characteristics, most opioids produce a wide array of clinical effects. Opioid receptor families are identified in the central nervous system and are differentiated by anatomic location and function. The opioid receptor is stereospecific, and only the levorotatory (–) opioid isomers elicit clinical effects. The μ receptor, which exists in two subtypes, μ_1 and μ_2 , is the binding site for the endogenous ligand β -endorphin [7]. When stimulated, the μ_1 receptor subtype produces supraspinal (e.g., brain) analgesia, euphoria, and peripheral anti-inflammatory effects. Stimulation of the μ_2 receptor subtype mediates spinal-level

analgesia and is the cause of most of the negative effects of opioid use, such as respiratory depression, miosis, constipation, pruritus, bradycardia, and physical dependence. These receptor subtypes are localized to the areas of the brain responsible for analgesia (periaqueductal gray matter, nucleus raphe magnus, medial thalamus), euphoria (limbic system), and respiratory depression and cough (medulla) [8, 9]. In the periphery, the μ_2 receptor is found in the gastrointestinal tract and peripheral terminals of nerve fibers in human synovia and immune cells, such as lymphocytes, macrophages, and mast cells [10].

Although the κ receptors are named for their ability to bind ketocyclazocine, their endogenous ligand is dynorphin A [11]. κ receptors are found

Table 2 Opioids available for clinical use^a

AGENT	CLASS	COMMENTS
Agonists		
Codeine	Natural	Often combined with acetaminophen; used as antitussive
Dextromethorphan (Robitussin [®] DM)	Semisynthetic	Antitussive; abused for psychoactive effects
Fentanyl (Sublimaze [®])	Synthetic	Very short acting
Heroin	Semisynthetic	Diacetylmorphine, more euphoric than morphine
Hydrocodone (Vicodin [®] , Zohydro [®] ER)	Semisynthetic	Potent opioid for chronic pain therapy
Hydromorphone (Dilaudid [®])	Semisynthetic	Potent opioid for chronic pain therapy
Methadone (Dolophine [®])	Synthetic	Very long acting (approximately 24 h), QT interval prolongation
Morphine	Natural	Gold standard opioid
Oxycodone (Percocet [®])	Semisynthetic	Sustained-release preparation (OxyContin [®])
Tramadol (Ultram [®])	Synthetic	Seizures may occur
Antagonists		
Naloxone (Narcan [®])	Semisynthetic	Short acting (0.5 h)
Naltrexone (Trexan [®])	Semisynthetic	Very long acting (24 h)
Mixed Agonists-Antagonists		
Butorphanol (Stadol [®])	Semisynthetic	Not widely used class
Nalbuphine (Nubain [®])	Semisynthetic	
Partial Agonist		
Buprenorphine (Buprenex [®] , Suboxone [®])	Semisynthetic	Gaining wide acceptance in opioid substitution therapy

^aExamples of US trade names are given in parentheses. These vary from country to country

primarily in the spinal cord but also are found supraspinally in the antinociceptive regions of the brain, substantia nigra, cortex, and cerebellum. The functional opioid receptors in the cerebellum may be involved not only in motor control and pain but also in motivational aspects of behavior and cognitive functions [12–14]. The κ_1 receptor subtypes produce primarily spinal analgesia, miosis, and diuresis (via inhibition of antidiuretic hormone release). Agonism at the κ_2 receptor subtype is associated with dysphoria and psychotomimesis. The κ_3 receptor subtype, in contrast to the κ_1 receptor, provides supraspinal analgesia [15]. κ receptor-mediated analgesia occurs independent of μ receptor activity, as evidenced by the inability of μ -selective antagonists to reverse κ effects [16]. Dysfunction of the κ opioid receptor system may underlie some of the neurochemical mechanisms of drug abuse. Chronic administration of drugs with positive reinforcing properties, such as morphine, amphetamine, and cocaine, increases brain dynorphin

levels, which suggests that dynorphin may be part of homeostatic mechanisms to oppose the mood-enhancing and reinforcing effects of these drugs of abuse [17, 18].

The δ receptor affects spinal and supraspinal analgesia. δ_1 and δ_2 receptor subtypes are established, and the enkephalins are their endogenous ligands [19]. Other δ receptor effects include alteration of nigrostriatal dopamine release, which modulates motor activity [20], and inhibition of the cough reflex [21].

A variety of opioid agonists are available for clinical use (Tables 2 and 3). Although useful for classification, whether the drug is natural, synthetic, or semisynthetic has little relevance to the clinical effects or pharmacology of the individual opioid agonists. Their predominant roles are in the management of acute and chronic pain syndromes or substitution therapy for illicit opioid use (e.g., methadone, buprenorphine). Their primary differences relate to their duration of effect, although most of the agents used for acute pain

Table 3 Comparison of opioid analgesics with respect to dosage and duration of action [2, 22, 23]

Drug	Equianalgesic doses		Plasma half-Life (HR)	Duration of effect (HR)
	(mg)			
	PO	Parenteral		
Codeine	200	100–130	2–4	3–5
Fentanyl (Sublimaze®)	Variable ^a	0.1	3–4	<1
Heroin (diacetylmorphine)	60	5	0.5	2–3
Hydromorphone (Dilaudid®)	7.5	1.5	2–3	3–5
Methadone (Dolophine®)	Variable ^b	Variable ^b	15–40	12–24
Morphine	30	10	2	2–3
Oxycodone	20–30	N/A	2	3–5

PO, oral; Parenteral, includes subcutaneous, intramuscular, and intravenous

Opioid equianalgesic dosing in this table are approximate and should be used only as a guideline. They are based on single-dose studies in opioid-naïve patients with acute pain. Incomplete cross-tolerance exists among different drugs. When changing drugs, it is often recommended to start with a 50% lower dose than the equianalgesic dose and then individually titrate to clinical response

^aNoninjectable fentanyl products are for opioid tolerant patients only. Conversion between different noninjectable fentanyl products (e.g., transmucosal, buccal, nasal spray, sublingual, transdermal) should not be done

^bMethadone conversion is highly variable and depends on factors such as patient tolerance and length of dosing (acute vs. chronic dosing)

management are short acting, with duration of approximately 3–5 h after a single dose [2]. Agents used for other indications typically are longer acting and the ability to predict the duration of effect after chronic use is limited [2].

Buprenorphine is a partial agonist with complex pharmacology predominated by partial agonism at the μ opioid receptor; its effects are also mediated through antagonism at κ or δ opioid receptors and interaction with opioid receptor-like receptors [24]. Partial agonists can be effective opioid analgesics in opioid-naïve patients. In opioid-dependent patients, buprenorphine competes with the existing opioid for the μ receptor and, due to higher binding affinity of buprenorphine for the μ receptor, can produce the opioid withdrawal syndrome [25].

Diphenoxylate is a congener of meperidine that is used as an agent to reduce gastrointestinal motility. Because of its insolubility, diphenoxylate acts locally within the gastrointestinal tract. Typically, diphenoxylate is combined with atropine (Lomotil) for the treatment of diarrhea. Opioid and anticholinergic effects may occur in overdose.

Delayed and recurrent presentation may be noted secondarily to the delay in gastric emptying by both agents. Naloxone is effective in reversing recurrent central nervous system and respiratory depression. One patient was noted to present 18 h after ingestion with marked signs of atropinism, whereas other patients presented with delayed respiratory depression [26]. Because of the possibility of delayed and severe effects, all patients with potentially large ingestions of diphenoxylate-atropine should be admitted for monitored observation (Level III).

Certain agents with opioid activity also have additional pharmacologic effects mediated by nonopioid mechanisms. Dextromethorphan, an abused, nonanalgesic, opioid antitussive agent [27, 28], at high doses produces sedation and a dissociative state similar to that produced by phencyclidine [29, 30]. This effect is due to noncompetitive antagonism at *N*-methyl-D-aspartate (NMDA) receptors by an active metabolite dextrorphan, which binds to the phencyclidine site on the NMDA receptor. This produces concentration-dependent inhibition of calcium influx through this receptor-linked ion channel,

causing psychotomimesis [31]. The results of an in vitro study suggested that dextromethorphan may exert anticonvulsant and neuroprotective effects by reducing Ca^{2+} influx through voltage-activated Ca^{2+} channels [32]. Dextromethorphan also blocks presynaptic serotonin reuptake and may lead to serotonin toxicity, specifically in patients taking selective serotonin reuptake inhibitors or monoamine oxidase inhibitors [33, 34]. Tramadol overdose may produce mild serotonergic effects [35, 36], and a retrospective, observational case series suggests that lethal serotonin toxicity is unlikely [37].

Other Opioids

Several opioids, including pentazocine, propoxyphene, and meperidine, have previously been used extensively; however, they are now used extremely rarely or have been discontinued altogether in the USA.

Pentazocine is a mixed opioid agonist–antagonist (κ agonist, μ antagonist) that may produce pain relief in an opioid-naïve person but produce a withdrawal phenomenon in a patient dependent on a μ opioid agonist [2]. Propoxyphene is an opioid agonist that may act as a proconvulsant and an arrhythmogen [38]. The parent drug and its metabolite norpropoxyphene possess myocardial sodium channel-blocking effects analogous to those of class I antidysrhythmics. Tramadol may also cause sodium and potassium channel blockade leading to QRS and QTc prolongation, respectively [39]. Meperidine is an opioid agonist that causes substantial euphoria and therefore carries a significant addictive potential; as such, it has been removed from the formulary at many health care institutions [40]. Normeperidine, the renally eliminated metabolite of meperidine, is a proconvulsant. Patients who use high doses of meperidine, especially patients who have renal insufficiency, are at risk for developing normeperidine toxicity [41]. In addition, meperidine inhibits reuptake of serotonin and, especially in combination with other serotonin agonists, may lead to serotonin toxicity [40, 42]. Intravenous meperidine has

been reported to cause QTc prolongation and ventricular dysrhythmia [43, 44].

Pathophysiology and Clinical Presentation

At sufficient doses, all opioid agonists produce the opioid toxidrome, a constellation of signs consisting of depression of mental status, ventilatory rate, and tidal volume; miosis; and reduced bowel motility. Many of these effects are due to the μ receptor-mediated reduction in sympathetic autonomic tone. Patients exposed to opioids, whether therapeutically or otherwise, typically present with bradycardia or hypotension, generally to a degree that is appropriate for their level of consciousness. Profound hemodynamic disturbances are unlikely to be the direct effect of an opioid agonist but represent an epiphenomenon secondary to hypoxia.

Most opioid-induced mortality relates directly to hypoxia, and patients rarely suffer significant discomfort from the other acute effects of opioids (e.g., gastrointestinal hypomotility, miosis). The opioid-induced reduction in ventilation occurs secondary to a reduced sensitivity of the medullary chemoreceptors to hypercapnia and hypoxia [45]. This effect is dose related, and in sufficient dose agents with full agonist effect may produce apnea. Opioid agonist–antagonists and partial agonists have ceilings on their ventilatory depressant effects [46]. After overdose with these agents, life-threatening hypoventilation is rare, although it may still occur in select patients, particularly children [47]. The ventilatory effects may manifest as a decreased respiratory rate, decreased tidal volume, or both. The initial ventilatory effects of the opioids commonly include a reduction in tidal volume, which is difficult to assess and often overlooked [48]. Because all currently available μ_1 agonists also exert effects at the μ_2 receptor, all opioids should be expected to produce respiratory depression.

Miosis is a relatively consistent finding among patients exposed to opioid agonists and likely results from a complex excitatory action on parasympathetic nerves [49]. Alternatively, patients

using opioids may occasionally present with mydriasis, so this finding cannot be relied on diagnostically. For example, patients using heroin in combination with cocaine, called a *speedball*, may present with dilated pupils depending on the relative balance of the two agents. Patients who have asphyxia or hypoxic encephalopathy also may have mydriasis.

Nausea and vomiting result from stimulation of dopamine-2 receptors at the chemoreceptor trigger zone. This effect has not been proved to be alleviated by low-dose naloxone [50]. Opioid agonists reduce gastrointestinal motility, producing constipation and bloating. These effects occur through increasing myenteric smooth muscle tone mediated through μ opioid receptors and can be reversed by low-dose oral naloxone, which is poorly bioavailable and rarely induces any opioid withdrawal symptoms [51]. Other agents that could be used to reverse constipation include methylnaltrexone, alvimopan, and naloxegol, opioid receptor antagonists that do not cross the blood-brain barrier in humans (Level I) [52]. These agents reverse the unwanted peripheral opioid effects, including constipation, without reversing the desired central effects, such as analgesia [53]. Little gastrointestinal tolerance develops, and patients who chronically take opioids generally remain constipated [54].

Although the cardiovascular effects of opioids are mediated primarily by regulation of the autonomic nervous system, certain opioids, such as propoxyphene, may be directly cardiotoxic following overdose. Historically, quinine-adulterated heroin was associated with cardiac dysrhythmias and death [55, 56].

Acute respiratory distress syndrome, formerly called acute lung injury or *noncardiogenic pulmonary edema*, is associated commonly with opioid overdose. Its cause is likely multifactorial, and its association with naloxone administration, although likely valid, is probably overestimated. Pulmonary edema is unmistakably described in autopsy series in the 1880s, long before the introduction of naloxone. The association more probably relates to the improved auscultative ability of the examining physician after reinstitution of spontaneous ventilation with naloxone. Still,

precipitation of a fulminant opioid withdrawal syndrome after naloxone may produce a catecholamine surge sufficient to impair myocardial relaxation and produce transitory congestive heart failure [57]. Canine models suggest that an elevated PCO_2 at the time of opioid-antagonist reversal of opioid-induced respiratory depression is associated with a more dramatic increase in mean arterial blood pressure and heart rate, suggesting a role for assuring adequate ventilation prior to naloxone administration (Level II-3) [58].

Another mechanism implicated in opioid-associated acute respiratory distress syndrome involves inspiration against a closed airway glottis, the so-called Müller maneuver. Such a respiratory effort, occurring when the larynx is occluded due to pharyngeal laxity, creates negative intrathoracic pressure and may result in fluid being drawn into alveoli through hydrostatic forces [59]. Alternatively, hypoxic damage producing an alveolar capillary leak syndrome may result in pulmonary edema.

Rapid administration or high doses of fentanyl can produce life-threatening chest wall rigidity. This effect occurs most commonly during anesthesia but also occurs in intravenous drug users who unknowingly inject fentanyl-adulterated heroin. Although incompletely characterized, it seems that the locus coeruleus and the caeruleospinal noradrenergic pathways in the spinal cord are responsible [60]. Naloxone produces a variable, but generally beneficial, response [2].

Although not part of the opioid toxidrome, seizures are another rare manifestation of therapeutic opioid use. After opioid overdose, patients may seize as a result of hypoxia or as a direct result of a drug or its metabolite. Accumulation of proconvulsant metabolites of certain opioids, such as tramadol and meperidine, cause seizures. Morphine injected into various regions of the brain of experimental animals causes epileptic activity not inhibited by naloxone [61]. In humans, only neonates have morphine-induced seizures, presumably due to the immaturity of the blood-brain barrier [62].

Though not direct effects of opioids themselves, many subacute complications commonly occur following significant opioid exposures

related both to prolonged immobility and to CNS and respiratory depression. Prolonged immobility may lead to rhabdomyolysis, characterized by skeletal muscle injury with release of intracellular contents such as myoglobin, creatine kinase, lactate dehydrogenase, aminotransferases, and potassium [63]. In addition to skeletal muscle injury, cardiac rhabdomyolysis may occur in rare instances, and, coupled with metabolic disturbances, may lead to cardiac dysrhythmias [64]. Acute rhabdomyolysis may be complicated by compartment syndrome, peripheral neuropathy, acute kidney injury, and disseminated intravascular coagulopathy [63, 65]. Prolonged respiratory depression following opioid overdose may produce acute cerebral hypoxic-ischemic injury [66] and rarely, delayed posthypoxic leukoencephalopathy [67]. Aspiration pneumonia is another common complication.

Diagnosis

Opioid poisoning is a clinical diagnosis, linking data from the patient's medical and presenting history, physical examination, and, perhaps, response to naloxone therapy. Laboratory data (blood and urine testing) are not necessary for the management of patients with opioid poisoning, other than to assess for concurrent medical conditions or to evaluate complications. In general, urine screens for recreational drugs are of little direct clinical value in the acute setting and they often do not return in a timely fashion. Analytically, they are subject to cross-reactivity with other compounds and may not detect synthetic or semisynthetic compounds. However, drug screens may be helpful for monitoring patients in addiction therapy or on therapy for chronic pain and may be used to establish a dual-diagnosis psychiatric disorder. Coingestants, such as ethanol and acetaminophen or aspirin, also must be considered, and laboratory testing ordered as indicated. The differential diagnosis of opioid poisoning includes other causes of depressed mental status, such as intracranial hemorrhage; postictal state; sepsis; postanoxic encephalopathy; hypoglycemia; hypothermia; and poisoning by various agents, including carbon monoxide, clonidine,

and other imidazolines, phenothiazines, atypical antipsychotics, and sedative-hypnotics (benzodiazepines and ethanol). Of note, some severely hypotensive patients presumed to be septic turn out to be late presenting opioid intoxicated patients.

Treatment

Proper airway management is crucial to managing opioid-poisoned patients. Patients experiencing ventilatory depression or hypoxia require either mechanical respiratory support or antidote administration. Use of nasopharyngeal or oral airway support can be considered in obtunded patients with non-life-threatening ventilatory depression and the absence of a gag reflex. Because both of these maneuvers can result in emesis, however, which can be life-threatening in a patient without an appropriate protective reflex, they should be used only with extreme caution. More appropriately, patients who are hypoventilating or hypoxic should be ventilated initially using a bag-valve-mask device with 100% oxygen supplementation. The decision to place an endotracheal tube or laryngeal mask airway depends on the patient's clinical condition, his or her response to less aggressive means of ventilation, response to naloxone, and the environment in which care is delivered.

Patients experiencing inadequate ventilation, as defined by an inadequate respiratory rate or tidal volume, may benefit from the administration of an opioid antagonist, such as naloxone. In adult patients who are unconscious for undefined reasons, a respiratory rate of less than 12 breaths/min is most predictive of response to naloxone [68]. Although this finding is neither highly sensitive nor specific, opioid poisoning rarely is diagnosed in patients with respiratory rates at or above normal. Because unneeded treatment with naloxone, regardless of the dose delivered, is rarely detrimental in patients who are not opioid dependent, a therapeutic trial in such patients with depressed respiration or mental status generally is warranted (Level II-3). Alternatively, in opioid-dependent patients, emesis due to precipitated opioid withdrawal in the setting of a

non-naloxone-responsive etiology for mental status depression (e.g., ethanol intoxication) risks pulmonary aspiration. Regardless, if chronic opioid use cannot be determined, judicious administration of small doses of naloxone, with titration upward to effect, should allow the therapeutic trial to be aborted if signs of withdrawal develop (Level III). In the USA, depending on the population served and region (e.g., availability of methadone maintenance therapy), the prevalence of opioid dependence varies widely, so the empirical use of naloxone must be tailored to the clinical setting. Naloxone is not only beneficial in treating tramadol-induced respiratory depression and somnolence [69, 70] but also preventing tramadol-induced seizures in both animal models [71] and humans [72]. Certain opioids, primarily buprenorphine, will respond to naloxone less predictably and in a nonlinear fashion compared to other opioid receptor agonists. Standard naloxone dosing will often not result in clinical improvement in patients with buprenorphine toxicity [73], as reversal tends to occur along a bell-shaped dose–response curve, with doses of 2–4 mg intravenous naloxone being effective and larger doses exacerbating the respiratory depression. The clinical pharmacology of naloxone and other opioid antagonists is discussed in detail in ► Chap. 157, “Opioid Receptor Antagonists.”

Dosing of Naloxone

Opioid dependence unlikely: 0.4 mg IV, escalating to 10 mg

Opioid dependence possible: 0.04–0.05 mg IV, additional doses every 1–2 min until response or signs of withdrawal

Positive response, short-acting opioid suspected: observe for resedation for 6 h

Positive response, with resedation: redose as needed or continuous infusion starting at two-thirds of the initial reversal dose hourly, titrated to effect IV, intravenously

The need for gastrointestinal decontamination is case specific and controversial (Level II-3). If given within the first hour postingestion it may decrease the absorption of ingested opioids.

However, it is unknown if it alters the clinical course or outcome in such situations. The administration of oral activated charcoal to nonintubated patients should be done cautiously because mental status depression increases the risk of pulmonary aspiration. The only opioid-exposed patients likely to benefit from more aggressive gastrointestinal decontamination are those who are attempting to conceal large amounts of drug in their gastrointestinal tract (e.g., *body packers*) to avoid detection by law enforcement. For details of the management of non-ICU-related aspects of opioid poisoning the reader is directed to a comprehensive general clinical toxicology text [74].

Special Populations

Children

Neonatal opioid withdrawal syndrome occurs in newborns of opioid-using mothers. Although it is similar to the adult opioid withdrawal syndrome in many respects, fever, myoclonic jerks, and life-threatening seizures are unique to the neonatal syndrome. The withdrawal syndrome typically presents within minutes to 2 weeks after birth. The half-life of the particular opioid used by the mother directly correlates with the time at which opioid withdrawal symptoms manifest in the neonate [75]. Treatment of neonatal opioid withdrawal includes various regimens, such as paregoric, phenobarbital, diazepam, diluted opium tincture, and methadone. Further discussion of this withdrawal syndrome can be found in ► Chap. 27, “Withdrawal Syndromes.”

Pregnant Patients

Reversal with naloxone of a pregnant opioid-tolerant patient who is acutely opioid intoxicated may precipitate uterine contractions and possible induction of labor [76]. Slow titration of naloxone will minimize this effect. Pregnant women who are opioid dependent are generally maintained on methadone or buprenorphine until after delivery.

Elderly Patients

Because of altered liver or kidney function in elderly patients, the pharmacokinetics of certain opioid agents may be unpredictable, and toxic effects may develop. Morphine is metabolized by the liver; any patients with cirrhosis or on medications that can interfere with liver function may be at risk for increased toxicity. In particular, elderly patients in the intensive care unit receiving ranitidine and morphine may have enhanced effects leading to confusion and hallucinations [77, 78]. In one study in humans, ranitidine was found to inhibit morphine glucuronidation, decreasing the morphine-3-glucuronide (M3G)-to-morphine-6-glucuronide (M6G) ratio and increasing the presence of morphine [79]. The active morphine metabolites, M3G and M6G, are renally excreted. M3G and M6G need to be considered when administering morphine as both metabolites can cause significant toxicity in elderly patients and patients with renal failure [80]. M6G has potent opioid agonist effects and is considered 4–20-fold more potent than morphine. M3G has no antinociceptive properties yet has neuroexcitatory effects (allodynia, myoclonus, seizures) [81].

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Salicylate intoxication carries significant morbidity and mortality that are compounded when the seriousness of the situation is not recognized by the treating physician [1]. Progressive central nervous system (CNS) depression demands several immediate, aggressive actions, not just endotracheal intubation and ventilation. A small decrease in arterial pH to 7.3 may be of little consequence to most patients in a critical care unit, but in patients with salicylate intoxication, this decrease may result in rapid shifts of salicylate into the brain and heart, causing surprisingly swift deterioration and death. A decrease in serum drug concentrations is accompanied by clinical improvement in most other drug intoxications, but this frequently is not the case with serious salicylate poisoning. Patients may deteriorate and die as serum salicylate levels decrease.

A successful outcome for a patient with salicylate poisoning frequently requires prolonged physician time at the bedside with rapid responses to frequently changing laboratory and clinical parameters. The intensivist must become familiar with the pathophysiology, pharmacokinetics, potential pitfalls, and treatment options for salicylate intoxication in order to be successful in preventing death.

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Sources of Salicylate

Numerous forms of salicylate are available in over-the-counter and prescription preparations (Table 1). Regardless of the product, all of these formulations are converted to salicylate during or shortly after absorption.

Many keratolytic agents contain salicylic acid, and toxicity and death have followed dermal application [2, 3]. Various liniments and some flavoring agents contain methyl salicylate (oil of wintergreen). Death has resulted from the ingestion of these liniments or from exposure to pure methyl salicylate [4]. Although salicylate is poorly absorbed after single ingestions of bismuth subsalicylate, the repeated use of large quantities of bismuth subsalicylate, such as those used in the treatment of diarrhea associated with acquired immunodeficiency syndrome, can result in serum salicylate concentrations in the toxic range.

Pathophysiology

General and Metabolic Effects

Salicylate toxicity produces numerous metabolic derangements (Table 2), including respiratory alkalosis, metabolic acidosis, ketosis, hypokalemia, hypoglycemia, and hyperglycemia. Salicylate stimulates the respiratory center in the brainstem to produce tachypnea, hyperpnea, and respiratory alkalosis [5]. Most adults who present early with acute salicylate toxicity display alkalemia. As toxicity progresses, the onset of metabolic acidosis (described later) first normalizes pH and then produces acidemia as respiratory alkalosis is overwhelmed by acidosis or as respiratory depression ensues from worsening toxicity (e.g., coma, apnea). The coingestion or iatrogenic administration of CNS depressants (e.g., benzodiazepines, opiates) or neuromuscular blockade with controlled mechanical ventilation may blunt hyperventilation and respiratory alkalosis, allowing for clinical expression of only metabolic acidosis [6].

Salicylate impairs adenosine triphosphate (ATP) synthesis through various mechanisms,

Table 1 Salicylate-containing products available as over-the-counter or prescription medications^a

Aspirin (acetylsalicylic acid)
Bismuth subsalicylate
Choline salicylate
Magnesium salicylate
Methyl salicylate (oil of wintergreen)
Salicylic acid
Salsalate (salicylsalicylic acid)
Sodium salicylate
Sodium thiosalicylate
Triethanolamine salicylate

^aAll of these agents undergo conversion to salicylate during or shortly after absorption

Table 2 Toxic actions of salicylate^a

Causes corrosive injury to the gastrointestinal tract
Stimulates respiratory center in the brainstem
Uncouples oxidative phosphorylation
Inhibits tricarboxylic acid cycle
Enhances glycogenolysis
Increases glucose consumption
Inhibits gluconeogenesis
Enhances lipolysis
Prevents activation of vitamin K-dependent coagulation factors
Inhibits platelet aggregation (significant only with aspirin)

^aThese actions are thought to account for most of the clinical syndromes seen with salicylate poisoning. In vitro, additional and often contradictory effects can be seen

and impaired ATP production from mitochondrial toxicity is the common denominator for much of salicylate’s toxicity. A mitochondrion is surrounded by an external and an inner membrane. As electrons travel down the electron transport chain on the inner mitochondrial membrane (cristae), the released energy is used to pump H⁺ ions out of the matrix into the mitochondrial intermembrane space, producing an electrical and pH gradient across the inner mitochondrial membrane. The electrons moving down the transport chain within the mitochondrion eventually combine with oxygen, the terminal electron acceptor, to form water. Meanwhile, hydrogen

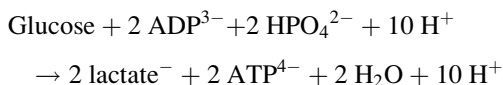
ions that have been concentrated within the intermembrane space reenter the mitochondrion through a pore in ATP synthase, a protein spanning the inner membrane, providing the energy needed to generate ATP from adenosine diphosphate (ADP) and phosphate inside the organelle. In mitochondria, ATP production via oxidative phosphorylation normally is “coupled” to oxygen consumption.

Salicylate uncouples oxidative phosphorylation through at least two mechanisms. First, similar to many weak organic acids, un-ionized salicylate crosses the inner mitochondrial membrane to release an H^+ into the matrix, where the pH is higher [7]. The remaining salicylate anion or other anions or both are transported out of the mitochondria. Second, salicylate may cause formation of pores in the inner mitochondrial membrane that are permeable to numerous substances, including H^+ [8]. The end result of these two processes is a decrease in the H^+ gradient across the inner mitochondrial membrane, allowing H^+ ions to reenter the mitochondrial matrix without traveling through ATP synthase, decreasing ATP formation [8]. Electron transport and oxygen consumption continue and even accelerate in an effort to generate ATP in the face of uncoupled oxidative phosphorylation. When uncoupling is severe, hyperthermia may develop as a consequence of heat production rather than ATP generation.

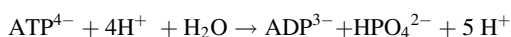
Impairment of ATP production also occurs within the mitochondrial matrix, where salicylate inhibits α -ketoglutarate dehydrogenase and succinic acid dehydrogenase of the tricarboxylic acid (Krebs) cycle [9, 10]. This activity decreases the formation of reduced nicotinic adenine dinucleotide and reduced flavin adenine dinucleotide, the main electron donors for the respiratory chain.

The metabolic acidosis accompanying serious salicylate poisoning is incompletely understood. Glycolysis (anaerobic conversion of glucose to lactate) is accelerated in salicylate poisoning in an attempt to meet ATP requirements in the presence of impaired oxidative phosphorylation. As emphasized by others [11–13], however, the conversion of glucose to lactate does not result in the

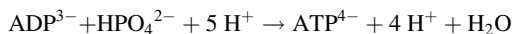
production of hydrogen ions, as illustrated in a balanced equation of glycolysis:



Cellular pH and concentrations of substrates influence the amounts of ATP and H^+ produced during glycolysis, but glycolytic production of lactate and ATP is not acidifying, regardless of pH [12, 13]. A large portion of the acidosis of salicylate poisoning most likely results from hydrolysis of ATP:



Just as the hydrolysis of ATP always results in a net production of a H^+ , the synthesis of ATP via oxidative phosphorylation in the inner mitochondrial membrane results in H^+ consumption by the reverse reaction:



During normal metabolism, H^+ consumption via oxidative phosphorylation balances H^+ production from hydrolysis of ATP. Impaired oxidative phosphorylation (from uncoupling and inhibition of the tricarboxylic acid cycle) provides a state in which the hydrolysis of ATP produced in glycolysis generates H^+ faster than they can be buffered, excreted, or, most importantly, consumed via oxidative phosphorylation.

Circulating lactate concentrations are usually within the normal range or are slightly elevated in most patients with salicylate toxicity [14]. Occasionally lactate concentrations can be notably elevated.

The metabolic acidosis of salicylate toxicity is also in part a ketoacidosis [5, 14]. Salicylate stimulates lipolysis and ketone formation. Most patients with salicylate toxicity excrete increased urine ketones that are detected easily by laboratory studies.

Elevated circulating cytokine concentrations have been described in patients with salicylate toxicity [15]. Their role in contributing to disease

is undefined, however, because various cytokines are elevated in the blood of patients who are critically ill from many different causes.

Serum glucose concentrations vary during salicylate intoxication. During serious salicylate intoxication, glucose consumption is increased as glycolytic generation of ATP increases to compensate for impaired oxidative phosphorylation. Increased epinephrine and glucagon secretion results in mobilization of glycogen stores, commonly producing hyperglycemia early in the intoxication. Serum glucose concentrations commonly reach 200–300 mg/dL (11–17 mmol/L). As salicylate toxicity continues, glycogen stores become depleted, and increased glucose demands can be met only by a marked increase in gluconeogenesis. Salicylate is an inhibitor of alanine aminotransferase, preventing the conversion of alanine to pyruvate to fuel gluconeogenesis [16]. Serum glucose concentrations normalize and can reach the hypoglycemic range, especially in children [17, 18] but also in adults [19].

Hypoglycorrhachia and neuroglycopenia are noted in animal models of salicylate toxicity [20], even without hypoglycemia. It has been suggested that some CNS toxicity from salicylate may reflect low CNS glucose concentrations and that this might occur without hypoglycemia.

Most patients with moderate-to-severe salicylate toxicity have hypokalemia, unless severe dehydration, impaired renal function, or rhabdomyolysis has resulted in hyperkalemia. Hypokalemia probably reflects gastrointestinal losses (vomiting) and obligate urinary excretion of potassium, with the salicylate anion or other organic acids or both resulting from toxicity.

A symptomatic adult patient with moderate-to-severe salicylate toxicity typically has a fluid deficit of at least 4–6 L on presentation. Water losses from hyperventilation, diaphoresis, third spacing of fluids in the muscle from rhabdomyolysis, and vomiting are easily underestimated. Failing to rehydrate the patient adequately and maintain adequate intravascular volume is a common error made by treating physicians.

Gastrointestinal Tract and Liver Effects

Aspirin produces corrosive injury to the gastrointestinal tract. Patients with acute intoxications frequently have abdominal pain, vomiting, and hematemesis. Rare reports of gastric perforation after acute aspirin overdose appear in the literature [21, 22]. Gastrointestinal toxicity contributes to dehydration and electrolyte losses, and occasionally anemia is severe enough to require transfusion. Salsalate produces less gastrointestinal injury than aspirin. Methyl salicylate can be very irritating, and salicylic acid keratolytic agents may produce oropharyngeal burns and more severe distal corrosive injury [23].

Asymptomatic elevation in serum transaminases may be noted in patients with chronic ingestion of salicylates, most commonly in patients with connective tissue diseases [24]. A few of these patients have abdominal pain, nausea, and jaundice. Although clinical evidence of meaningful hepatotoxicity is not typical of acute salicylate toxicity, investigators have reported a high prevalence of hepatic microvesicular steatosis in children who died as a result of salicylate poisoning [25]. Microvesicular steatosis, as a reflection of impaired fatty acid oxidation, can be secondary to mitochondrial dysfunction from numerous causes. In the outer mitochondrial membrane, however, salicylate also sequesters extramitochondrial coenzyme A, preventing the activation of fatty acids and fatty acid β oxidation.

Pulmonary Effects

Adult respiratory distress syndrome occasionally complicates acute salicylate toxicity but is more common in chronic salicylate toxicity [26, 27].

Cardiovascular Effects

Impaired myocardial ATP production and, to a lesser extent, acid–base disorders produce sinus tachycardia, despite correction of hypovolemia.

Heart failure and hypotension occur in seriously ill patients [28] but usually are not a problem until patients are near death. Ventricular arrhythmias, including sudden, unexpected ventricular fibrillation, and conduction disturbance including heart block are possible [29].

Effects on Coagulation and Platelets

Of all salicylate products, only aspirin significantly impairs platelet function. Salicylate (resulting from the ingestion of any product) inhibits the formation of vitamin K-dependent coagulation factors in a manner similar to that of warfarin (Coumadin), mainly by preventing the reduction of vitamin K quinone to the active hydroquinone [30]. Elevated prothrombin times usually occur 8–24 h after acute overdose and respond promptly to the administration of vitamin K₁. Despite coagulopathies and potential platelet dysfunction, hemorrhage remains a rare cause of serious morbidity or mortality in patients with salicylate toxicity, with the exception of occasional gastrointestinal bleeding.

Central Nervous System Effects

Given the large energy requirements of the brain, it is not surprising that neurotoxicity from impaired ATP formation may accompany salicylate toxicity. Agitation, combativeness, disorientation, confusion, and hallucinations characterize severe toxicity. Even more severe cases progress (sometimes rapidly) to convulsions, coma, respiratory depression, cerebral edema, and brain death [1, 28, 30–32].

Hill [33] showed in rats that elevated CNS salicylate concentration, leading to coma and seizures, was the most critical determinant of death, and this is consistent with clinical experience. Serious neurotoxicity, especially CNS depression or convulsions, carries a high mortality and commonly portends death in the next few minutes to hours. Even patients exhibiting shock and

hypotension almost always develop CNS dysfunction before life-threatening cardiovascular toxicity. CNS depression, disorientation, agitation, or convulsions always should be interpreted as an ominous sign when due to salicylate toxicity [28, 32–34].

Miscellaneous Effects

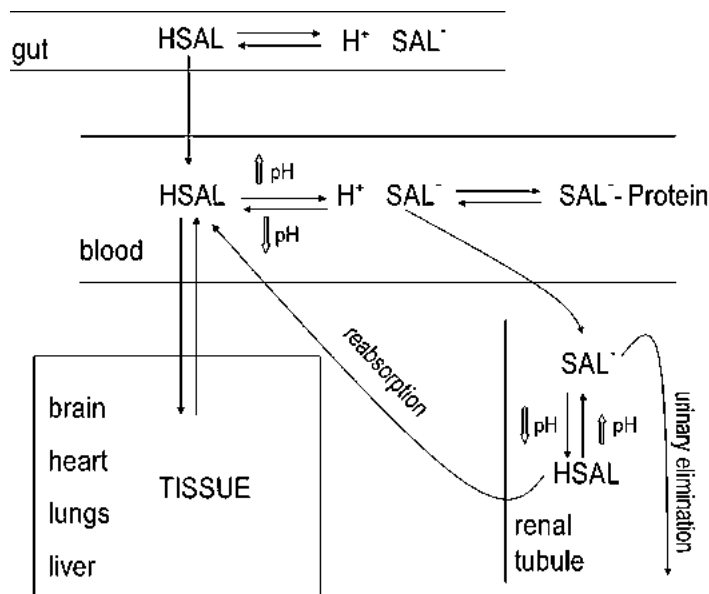
Hypocalcemia and hypercalcemia have been described as a component of serious salicylate toxicity [35, 36]. Rhabdomyolysis [37], commonly seen in any metabolic poisoning, may produce the typical complications, including disseminated intravascular coagulation, compartment syndromes, renal failure, hyperkalemia, and hypocalcemia. Acute tubular necrosis has been reported in the absence of rhabdomyolysis [38].

Tinnitus generally occurs when serum salicylate levels are greater than 20 mg/dL (>1.46 mmol/L). The patient may not complain of tinnitus, but instead simply may complain of difficulty in hearing. Auditory musical hallucinations also have been reported [39].

Significant hyperthermia is seen in only a few cases and is seen more commonly in patients who die, reflecting more severe toxicity [28]. Even comatose patients may have a normal temperature.

Finally, we have encountered two cases of severe poisoning (leading to coma) in which the administration of succinylcholine was followed immediately by diffuse rigidity and hyperthermia resistant to neuromuscular blockade. That both patients could have had familial malignant hyperthermia seems extremely unlikely. Rather, because ATP also is required for muscle relaxation, presumably low muscle ATP levels prevented relaxation after initial depolarization by succinylcholine. As in any poisoning characterized by low ATP levels (e.g., nitrophenol, fluoroacetate), rigor mortis may develop within a few minutes after death. We have noticed similar rigidity as a near-terminal finding on one occasion in which no succinylcholine was given.

Fig. 1 Salicylate exists in blood in an equilibrium between the ionized and un-ionized forms. HSAL, un-ionized salicylate; SAL^- , ionized salicylate



Pharmacokinetics

Pharmacokinetics of Salicylates

Volume of distribution: 0.15–0.35 L/kg or greater

Protein binding: 40–80%

Elimination: (1) mainly hepatic at low salicylate concentrations; (2) mainly renal at upper therapeutic and toxic serum salicylate concentrations

Active metabolites: none

Methods to enhance clearance: hemodialysis, alkaline diuresis

Absorption

During and after ingestion, all salicylate products are converted rapidly to salicylate. Salicylate impairs gastric emptying, and gastric bezoars have formed in patients with chronic ingestion of enteric-coated aspirin tablets [40]. We have seen salicylate concentrations increase for more than 24 h after large acute ingestions, although toxic levels commonly occur within 6 h. Enteric-coated and extended-release aspirin tablets may undergo delayed absorption, with nontoxic levels seen at

6 h despite serious ingestions [41, 42]. Liquid salicylate preparations (e.g., methyl salicylate, salicylic acid, pediatric aspirin products) undergo more rapid absorption than solid products. Toxic and fatal amounts of salicylate can be absorbed across the skin after the use of salicylic acid-containing keratolytic agents [2, 3, 43]. Of topical salicylate, 60% is absorbed across the psoriatic skin when covered with an occlusive dressing [43].

Distribution

About 40–80% of salicylate is bound to serum proteins, mainly albumin. As binding sites become saturated at high serum salicylate concentrations, the free, unbound fraction increases. Hypoalbuminemia, azotemia, and elevated serum salicylate levels all result in increased unbound serum salicylate concentrations [44–46]. The wide range of reported protein-bound fractions represents, to a large extent, variations in serum drug levels and albumin concentrations.

Salicylate exists in blood in an equilibrium between the ionized and un-ionized forms (Fig. 1). At physiologic pH, most salicylate resides in the ionized form. Only unbound, un-ionized salicylate readily crosses cell

membranes. Any condition that increases the unbound fraction (e.g., high serum salicylate concentrations, hypoalbuminemia) or increases the un-ionized fraction of salicylate (e.g., decrease in pH) increases salicylate's apparent volume of distribution. A decrease in pH can result in a movement of salicylate from the blood into the tissue, raising the tissue levels of salicylate and worsening systemic toxicity, while serum salicylate concentrations decline. A drop in pH of only 0.25 (e.g., 7.45–7.2) almost doubles the amount of un-ionized drug capable of diffusing into the tissue. In a healthy patient with low serum salicylate concentrations, the typical volume of distribution is about 0.16 L/kg. Salicylate's volume of distribution in the same patient with an elevated serum salicylate concentration and acidemia may reach 0.34 L/kg or greater [47].

The changing volume of distribution of salicylate makes interpretation of serum salicylate concentrations potentially misleading. Two patients with identical serum salicylate concentrations may differ markedly in the degree of toxicity because their tissue burden of salicylate may vary tremendously, depending on plasma albumin concentration, pH, and other factors that influence the volume of distribution for salicylate. Similarly, serum salicylate concentrations decline not only because of renal and hepatic elimination but also because a rise in the volume of distribution causes salicylate to leave the blood and enter the tissue, producing more severe toxicity. Patients may deteriorate and die as serum salicylate concentrations decrease [28, 31]. Similarly, it is important to treat the patient and not simply the serum salicylate concentration. This point is especially important in patients with chronic salicylate toxicity, who characteristically have a large volume of distribution and more severe toxicity for a given serum salicylate concentration.

Elimination

Salicylate undergoes hepatic metabolism, mainly by glucuronidation and by conjugation with glycine to form salicyluric acid (see Fig. 1) [48]. Both of these pathways become saturated within the range of therapeutic serum salicylate concentrations, leading to zero-order elimination kinetics

and an increasing role for renal elimination. During zero-order elimination kinetics, a set amount of drug is eliminated per unit time (not a set fraction of drug, as in first-order elimination), regardless of how much serum salicylate concentrations increase. The elimination “half-life” (a term that should not be used in zero-order kinetics) is changing constantly and increases as the serum salicylate concentration increases.

An increased fraction of unbound salicylate at high plasma concentrations also enhances renal clearance, making the kidneys the major route of elimination during salicylate toxicity [49]. Un-ionized salicylate undergoes reabsorption by renal tubules, prolonging elimination. Alkaline urine favors the formation of ionized salicylate, preventing reabsorption and enhancing secretion of un-ionized salicylate down its concentration gradient, both of which increase urinary elimination. The urinary clearance of salicylate can increase more than 500% by raising urine pH from 7.0 to 8.0 [50].

Saturable hepatic elimination kinetics, an increasing volume of distribution, dehydration, and aciduria act to prolong markedly the elimination of salicylate. In untreated or dehydrated patients with aciduria who have moderate-to-severe salicylate toxicity, more than 1–2 days may be required for serum salicylate concentrations to decrease by half, and prolonged absorption further attenuates the decline in serum salicylate levels.

A shift to zero-order elimination also allows serum salicylate concentrations to increase out of proportion to the daily dose. Doubling a daily aspirin intake may result in a threefold or fourfold increase in serum salicylate concentrations; this explains why chronic salicylate toxicity is produced with relatively small increases in salicylate doses.

Toxic Doses

The acute ingestion of 150 mg/kg of aspirin or an equivalent amount of another salicylate-containing product mainly produces gastrointestinal irritation and vomiting. Ingestion of

150–300 mg/kg of aspirin results in mild-to-moderate toxicity with abdominal pain, vomiting, dehydration, hyperpnea, tinnitus, and acid–base disturbances. Ingestion of more than 300 mg/kg of aspirin produces moderate-to-severe toxicity and death. Patients with medical conditions that predispose them to a large volume of distribution (e.g., renal failure, hypoalbuminemia, acidemia) and patients who have ingested salicylate previously within the last 12–24 h become more toxic for a given amount ingested.

Attempts to develop a nomogram of salicylate concentration against time have been unsuccessful in accurately predicting toxicity. Historically, the Done nomogram [51] was suggested to assist in determining the degree of toxicity after salicylate ingestion in children. A serum salicylate level drawn 6 h or more after ingestion could be plotted on the nomogram, and the patient could be placed at various degrees of toxicity. The Done nomogram can be misleading, however. The nomogram can overestimate and, most importantly, greatly underestimate the degree of toxicity. A person with a level in the “mild” range may still become severely ill hours later if acidemia or dehydration is not corrected or if salicylate levels continue to increase. The use of the Done nomogram is not recommended [52]. All symptomatic patients should be treated regardless of where their serum salicylate levels fall on a nomogram.

Clinical Presentation

Acute Salicylate Toxicity

Presenting complaints and findings after acute ingestion of a salicylate product include vomiting (sometimes with hematemesis), abdominal pain, tinnitus, tachypnea, hyperpnea, diaphoresis, tachycardia, dehydration, leukocytosis, and ketonuria (Table 3). If rhabdomyolysis is not present or severe and if dehydration has not limited potassium excretion, laboratory analysis in most patients reveals hypokalemia. Adults usually present with respiratory alkalosis with or without a mild metabolic acidosis and with alkalemia. Young children commonly present with acidemia.

Table 3 Clinical findings of salicylate toxicity

Gastrointestinal
Nausea, vomiting, abdominal pain
Gastrointestinal bleeding
Gastric perforation (rare)
Metabolic
Respiratory alkalosis
Metabolic acidosis
Ketosis
Hypokalemia
Hyperglycemia, normoglycemia, or hypoglycemia
Ketosis
Central nervous system
Confusion, agitation, combativeness, hallucinations
Seizures, coma, cerebral death
Cerebral edema
Low cerebrospinal fluid glucose (in animals)
Cardiovascular
Sinus tachycardia
Hypotension, ventricular arrhythmias
Shock, asystole
Pulmonary
Acute respiratory distress syndrome
Hematologic
Leukocytosis
Prolongation of prothrombin time
Miscellaneous
Diaphoresis
Hyperthermia
Rhabdomyolysis
Renal failure
Tinnitus, auditory hallucinations (e.g., musical)

Serum glucose concentrations usually are normal or elevated early in acute poisoning.

As the severity of poisoning progresses, worsening acidosis, worsening tachycardia, and diaphoresis appear, with progressive CNS dysfunction characterized by agitation, lethargy, confusion, combativeness, seizures, or coma. Metabolic acidosis is typically accompanied by an elevated anion gap. In many cases, however, laboratory interference causes salicylate to be misread as chloride, leading to a falsely low or negative anion gap [53, 54]. The absence of an elevated anion gap in a patient with clinical symptoms of salicylate toxicity should not deter pursuit of the diagnosis. Although young children are

more likely to develop hypoglycemia as glycogen stores are depleted, adults can develop hypoglycemia as well. Acute respiratory distress syndrome is more common in chronic salicylate poisoning but can occur in severe, acute poisonings. Elevated prothrombin times do not occur until hours after ingestion.

Patients who will die from acute salicylate poisoning usually exhibit CNS dysfunction and then die from refractory shock with terminal ventricular arrhythmias or asystole. Acidemia usually is present by this time, and the combination of tachycardia, diaphoresis, and CNS dysfunction, especially in the presence of acidemia, is an ominous indication of severe toxicity and great risk of deterioration and death if aggressive action is not taken immediately [28, 32–34]. Clinical deterioration can be rapid; patients who are awake and alert may die within 6 h [1]. Because of the increasing volume of distribution with higher salicylate concentrations and acidemia, patients may die, while serum salicylate concentrations are declining.

Chronic Salicylate Toxicity

Chronic salicylate toxicity is described best as a syndrome rather than as a specific dose over a particular time. A dehydrated and azotemic patient may develop chronic toxicity while taking doses that would not affect an otherwise healthy person.

Most patients with chronic salicylate toxicity are brought in by family members because of altered mental status characterized by lethargy, irritability, confusion, hallucinations (including auditory), seizures, or coma. Although dehydration is common, vomiting and abdominal pain usually are not major complaints. Tinnitus is common, and an elevated prothrombin time frequently is noted. Many patients are acidemic. Elevated hepatic transaminases are seen commonly in many patients using salicylate products regularly and are not specific for this syndrome. Tachypnea is common.

Leatherman and Schmitz [15] described invasive hemodynamic measurements in five selected hypotensive patients with chronic salicylate toxicity who exhibited low systemic vascular

resistance and cardiac outputs ranging from 5.1 to 8.5 L/min. How representative these hemodynamic findings are of all patients with salicylate toxicity, including patients without hypotension, is unknown.

Because of a large volume of distribution, patients with chronic salicylate toxicity appear sicker than acutely toxic patients with the same serum salicylate level. Patients taking carbonic anhydrase inhibitors and salicylate may develop serious salicylate toxicity [55, 56] at therapeutic or minimally elevated serum salicylate concentrations because carbonic anhydrase inhibitors alkalize cerebrospinal fluid while lowering blood pH [57, 58], both of which processes concentrate and trap salicylate within the CNS. Salicylate increases the unbound and active fraction of acetazolamide in blood [56], enhancing acetazolamide's effect on salicylate distribution.

Differences between acute and chronic salicylate toxicity are not always clear, but rather represent a progression of signs and symptoms. The longer a patient presents after an acute ingestion, the more he or she behaves like a patient presenting with chronic toxicity. Altered CNS function, elevated prothrombin times, and acidemia that characterize chronic salicylate toxicity also are typical of an acute overdose patient hours after ingestion.

Differential Diagnosis

The differential diagnosis for salicylate toxicity is large and includes many disorders that produce metabolic acidosis (with an increased anion gap in more ill patients), respiratory alkalosis, gastroenteritis, and CNS dysfunction. Examples include sepsis, Reye's syndrome, diabetic ketoacidosis, hepatic failure, and alcoholic ketoacidosis. Poisonings by theophylline, caffeine, ethylene glycol, methanol, iron, ethylene glycol ethers, and heavy metals may produce acidemia, gastrointestinal symptoms, coma, and convulsions. A generalized seizure from any cause (e.g., isoniazid, cocaine, meningitis) usually produces transient metabolic acidosis that resolves over 20–60 min after the seizure is terminated. Direct or indirect

β -adrenoceptor stimulation (e.g., bronchodilators, theophylline, sympathomimetics) produces tachycardia, metabolic acidosis, respiratory alkalosis, hypokalemia, hyperglycemia, leukocytosis, ketosis, and, depending on the agent (e.g., amphetamines, theophylline), convulsions. Diflunisal, a nonsteroidal antiinflammatory drug, does not produce salicylate toxicity but causes falsely elevated serum salicylate concentrations by some colorimetric laboratory methods [59].

Evaluation and Treatment

Special Airway and Ventilatory Considerations

Special considerations must be addressed when instituting sedation or mechanical ventilation. The administration of a sedative or narcotic to a patient poisoned with salicylate may decrease respirations, lessen respiratory alkalosis, and result in a prompt decrease in arterial pH from an unopposed metabolic acidosis. This situation may produce a prompt movement of salicylate into the brain with resultant clinical deterioration. A similar scenario occurs when a physician sedates or relaxes the patient for endotracheal intubation and then provides normal minute ventilation volumes with mechanical ventilation. Because of adverse hemodynamic effects and risks for barotrauma, aggressive mechanical hyperventilation should not be used to maintain pH in these settings, but rather the physician should recognize the probable consequences of sedation or controlled mechanical ventilation and should administer additional intravenous sodium bicarbonate to prevent dangerous decreases in arterial pH.

Decontamination and Initial Evaluation

Oral activated charcoal alone has been reported to be superior to induction of vomiting with ipecac syrup [60, 61]. Activated charcoal (e.g., 100 g) adsorbs salicylates and should be given to patients who have ingested potentially toxic doses of salicylate products, although no controlled trials in

poisoned patients have evaluated outcomes (level III evidence). Although repeated-dose oral activated charcoal has been claimed to be effective in shortening elimination half-life in a retrospective study [62], a prospective randomized study in human volunteers who ingested nontoxic doses of salicylate suggested that the routine use of repeated-dose charcoal might be without benefit [63]. If serum salicylate concentrations continue to increase after administration of activated charcoal, most toxicologists administer additional oral charcoal. Severe nausea and vomiting in an acutely poisoned patient may limit charcoal dosing.

In symptomatic patients, laboratory studies should include analysis of serum or plasma for electrolytes, blood urea nitrogen, glucose, creatine kinase, creatinine, prothrombin time, and salicylate concentration. Because of the ready availability of acetaminophen and frequency of acetaminophen overdose and because acetaminophen-containing products may have brand names that are similar to the names of products containing aspirin, serum acetaminophen concentration should be measured whenever salicylate toxicity is being considered. Urinalysis and complete blood count also should be obtained. Arterial blood gases should be measured to determine the type and degree of acid–base imbalance. A chest radiograph should be obtained on all moderately to severely ill patients or any patient with respiratory distress or hypoxemia.

A patient who appears ill from salicylate toxicity should be treated regardless of serum salicylate concentration. Most symptomatic patients have serum salicylate concentrations greater than 20 mg/dL (>1.46 mmol/L). Severe toxicity commonly accompanies serum salicylate concentrations greater than 70 mg/dL (>5.1 mmol/L). Severe toxicity and death can be seen at lower levels, however. Because of the variability in volume of distribution, serum salicylate concentrations in patients who die are, on average, similar to concentrations in patients who live. Chapman and Proudfoot [64] reported plasma salicylate concentrations ranging from 55 to 120 mg/dL (4.01–8.76 mmol/L) in fatal cases and ranging from 18 to 135 mg/dL (1.31–9.85 mmol/L) in survivors.

The acute ingestion of enteric-coated and extended-release salicylate may result in nontoxic serum salicylate concentrations for the first few hours after ingestion but high serum salicylate concentrations and severe toxicity later [41, 42]. Because of inaccurate histories provided from overdose victims or relatives and the delayed and prolonged absorption of enteric-coated products, anyone who may have ingested more than 150 mg/kg of enteric-coated aspirin should be admitted for observation and measurement of serial serum salicylate concentrations for 18–24 h.

Moderately to severely ill patients belong in the intensive care unit. The purpose of admitting relatively asymptomatic patients or patients with only mild symptoms is usually concern for possible clinical deterioration that can be rapid. Patients who are awake and alert can die within 6 h. This fact, along with the need for frequent vital signs and laboratory studies, means that almost all patients requiring admission for salicylate toxicity should be placed in an intensive care unit setting.

Supportive Treatment

All patients with an abnormal mental status or seizures should be presumed hypoglycemic and should receive appropriate doses of intravenous glucose, especially if bedside determinations of serum glucose levels are not immediately available. As with all drug-induced and toxin-induced seizures, benzodiazepines and barbiturates are the anticonvulsants of choice (level III evidence).

The average adult patient who presents several hours after an acute ingestion of salicylate with vomiting, perhaps tinnitus, and hyperventilation typically is dehydrated by 4–6 L or more. The insensible fluid losses from diaphoresis, hyperventilation, and third spacing into muscles undergoing rhabdomyolysis are frequently underestimated and limit initial attempts at rehydration and prevention of further negative fluid balances, which impairs salicylate elimination. Aggressive initial rehydration should be monitored carefully, and the treating intensivist must recognize that despite continuous intravenous

infusions of 500–600 mL/h, many patients continue to experience negative fluid balances with rising hematocrits and serum sodium concentrations that must be met with additional fluid boluses and increases in continuous infusion rates. These actions can be undertaken only with frequent bedside assessments and frequent laboratory studies. Frequent blood and urine collections are facilitated by indwelling arterial and urinary catheters.

After initial hydration, primary efforts should be directed at keeping arterial pH greater than 7.4 in symptomatic patients. A reasonable goal is an arterial pH of 7.5 to limit increases in volume of distribution and tissue (e.g., CNS) salicylate concentrations. A secondary goal of therapy is to alkalinize urine to enhance urinary salicylate excretion. The more alkaline the urine (up to a pH of approximately 8.0), the greater the excretion of salicylate. Intensivists must recognize that the main reason for alkalization is to elevate blood pH. Alkaluria, although desirable, is of secondary concern. Alkaluria seems to be more important than diuresis with regard to enhancing salicylate excretion [65].

Two important methods for sodium reabsorption in the renal distal and collecting tubules are tubular secretion of potassium ions and tubular secretion of hydrogen ions. Even during alkalemia and normokalemia, aciduria persists, impairing salicylate elimination, if the kidney is preferentially reabsorbing sodium by excreting hydrogen ions rather than potassium ions into the tubular lumen. Therefore, both bicarbonate and potassium supplementation are usually required to ensure alkaluria.

There are no randomized trials examining outcomes in patients treated with different infusion solutions. Based on experience, we initially rehydrate patients aggressively with either 0.9% sodium chloride or Ringer's lactate (if hyperkalemia is not present). In moderately to severely ill patients, we begin a continuous infusion of 1000 mL of 5% dextrose in water, to which is added 150 mEq of sodium bicarbonate and at least 50 mEq of potassium as potassium chloride at 250–300 mL/h, assuming the adequate urine output and the absence of hyperkalemia.

Additional simultaneous infusions of crystalloid (e.g., 5% dextrose in 45% sodium chloride) usually are required to maintain adequate hydration, and total infusion rates greater than 500 mL/h may be required in moderately to severely ill patients. A urinary output of 2–3 mL/kg/h is desirable. Hemoglobin concentrations and hematocrits are followed to detect occult gastrointestinal bleeding. Arterial blood gases, serum electrolytes, serum salicylate concentrations, and urine pH are measured every 2–4 h in moderately ill patients and at least every 1–2 h in severely ill patients to ensure the absence of acidemia and to detect disorders in serum potassium concentrations that may require adjustment in the electrolyte composition of the infusion solution. This monitoring also detects hyponatremia and hemoconcentration, which suggest insensible losses requiring further replacement. Serial (e.g., daily) serum creatine kinase activity is monitored to detect rhabdomyolysis.

Decreases in arterial pH from metabolic acidosis are treated with repeated intravenous boluses of 1–2 mEq/kg of sodium bicarbonate as needed. A decrease in urine pH less than 7.5–8 despite normokalemia is treated with additional potassium (intravenous or oral) as long as hyperkalemia is not present. After ensuring adequate hydration and urine flow, the potassium requirements in some patients with moderate-to-severe salicylate toxicity exceed 25 mEq/h to ensure alkaluria. We administer 10–15 mg of vitamin K₁ intravenously to all patients with moderate-to-severe toxicity because prothrombin times usually are elevated within several hours without such therapy, although there are no trials demonstrating a change in outcome (level III evidence).

If objective evidence of hypervolemia develops and there is no appropriate increase in urine flow, intravenous furosemide can be given. However, the most common cause of oliguria is hypovolemia. Pulmonary edema usually represents adult respiratory distress syndrome, not fluid overload.

In patients with renal failure and oliguria who require less than 200 mL/h to maintain good hydration, we commonly infuse crystalloid

solutions containing 10% dextrose to prevent neuroglycopenia, which in animals may occur despite normoglycemia. Carbonic anhydrase inhibitors, such as acetazolamide, are best not given to alkalinize urine because they also alkalinize cerebrospinal fluid [57, 58], trapping salicylate in the CNS – opposing the aforementioned goals of therapy.

Severe neurotoxicity, characterized by lethargy, agitation, confusion, seizures, coma, or continued deterioration in level of consciousness despite supportive care, is an ominous sign and an indication for immediate hemodialysis, even if serum salicylate concentrations have been declining yet remain greater than 20–40 mg/dL (>1.46–2.91 mmol/L). Some toxicologists also administer intravenous mannitol (0.25–0.5 g/kg) in an effort to reduce or prevent further worsening of cerebral edema in these patients (level III evidence).

Serum salicylate levels that have declined may rise again in a delayed manner from continued absorption after discontinuation of an alkaline diuresis [66]. Thus, serum salicylate levels should be rechecked in patients who have been significantly ill after bicarbonate infusions are halted to be sure drug concentrations are remaining low.

Hemodialysis

Salicylate's high water solubility, relatively low protein binding, small volume of distribution, and low molecular weight allow for effective removal by hemodialysis [67]. Hemodialysis is indicated for patients with one or more of the following: significant neurotoxicity (e.g., lethargy, agitation, coma, convulsions), renal failure, cardiovascular instability, and extremely elevated serum salicylate concentrations that are increasing despite hydration and attempts at alkaline diuresis. Others have recommended hemodialysis for pulmonary edema as well. On the one hand, previous recommendations that all patients with serum salicylate concentrations greater than 80–100 mg/dL (>5.84–7.3 mmol/L) must undergo hemodialysis immediately were too extreme because awake and alert patients with good blood pressure and urine

output who have a serum salicylate concentration of 105 mg/dL (7.66 mmol/L) that is known to be falling can do well with intensive medical therapy. On the other hand, successful treatment of these patients requires a great deal of physician time, frequent bedside evaluations, frequent laboratory studies, and often 2–3 days in the intensive care unit. Most patients with serum salicylate concentrations greater than 100 mg/dL (>7.3 mmol/L) eventually meet the criteria for hemodialysis (e.g., CNS dysfunction), even while serum salicylate concentrations decrease. Failure to institute hemodialysis promptly in deteriorating patients leads to unnecessary deaths [1, 64]. Mildly to moderately encephalopathic patients with chronic salicylate toxicity, in whom absorption has peaked, can do well with intensive medical therapy alone.

At our center, extraction ratios across the dialysis cartridge commonly range from 35% to 70% using double-lumen dialysis catheters and high-flux membranes with blood flow rates of 400 mL/min. In general, hemodialysis is performed until serum salicylate concentrations have decreased to less than 20 mg/dL (<1.46 mmol/L). Most patients with salicylate toxicity require 4–6 h of hemodialysis to achieve this goal. Because of prolonged absorption, some patients require more than 6 h of hemodialysis or require a repeat session of hemodialysis if salicylate levels increase again to produce serious toxicity.

Occult or minor gastrointestinal bleeding from the corrosive action of salicylate can become more severe and apparent when the patient is heparinized for hemodialysis, but this is uncommon. We routinely type and screen the patient for transfusion, however, when arranging for hemodialysis and monitor hemoglobin concentrations and hematocrit values more closely during and shortly after dialysis. Because clinically significant gastrointestinal bleeding during hemodialysis is uncommon, concern for gastrointestinal bleeding from salicylate rarely should be considered a contraindication for heparinization and hemodialysis for life-threatening salicylate toxicity. Blood volume can be supported with transfusions, if needed, whereas death from salicylate is possible and often probable without hemodialysis.

Charcoal hemoperfusion also removes salicylate well; however, hemodialysis has the valuable added advantage of immediately correcting electrolyte and acid–base balance without the potential adverse effects associated with hemoperfusion (e.g., thrombocytopenia, hypocalcemia) [64, 67]. Peritoneal dialysis is relatively ineffective at removing salicylate compared with hemodialysis and should be used only when hemodialysis is not an option.

Intensive Care Unit Discharge

Criteria for ICU Discharge in Salicylate Poisoning

Awake, alert, and no clinical evidence of toxicity

Serum salicylate concentrations <20 mg/dL (1.46 mmol/L) and known to be declining

Patients can be discharged from the intensive care unit when they are awake and alert and metabolically stable and when serum salicylate concentrations are less than 20 mg/dL (<1.46 mmol/L) and known to be decreasing.

Common Errors in the Management of Salicylate Poisoning

Underestimating the seriousness of salicylate toxicity

Failing to consider the diagnosis of chronic salicylate toxicity in elderly patients with altered mental status

Failing to recognize potential for delayed and continued absorption of salicylate for >24 h after overdose

Forgetting that coingestion of central nervous system depressants masks hyperventilation and respiratory alkalosis

Believing that most patients with salicylate poisoning are hyperthermic

(continued)

Confusing units of measurement for serum salicylate concentrations, which vary among laboratories (10 mg/dL = 100 mg/L)

Using the Done nomogram

Failing to recognize potential for clinical deterioration and death despite decreasing salicylate serum concentrations

Underestimating insensible fluid losses and allowing patients to become hypovolemic despite what may seem like liberal fluid administration

Failing to recognize that salicylate toxicity is commonly accompanied by falsely elevated serum chloride concentrations and resultant falsely low anion gaps

Focusing on alkalizing urine rather than alkalizing blood

Not giving required potassium supplementation to alkalize urine successfully

Failing to obtain and review laboratory studies frequently

Failing to institute hemodialysis at the onset of neurotoxicity

Allowing arterial pH to decrease with the use of sedatives or the institution of endotracheal intubation and mechanical ventilation

Giving furosemide to hypovolemic patients with pulmonary edema from adult respiratory distress syndrome

Failing to consider or monitor for hypoglycemia and rhabdomyolysis

3. Direct main efforts at correcting and maintaining euvoemia and keeping blood pH alkaline. Urinary alkalization usually requires sodium bicarbonate *and* potassium supplementation.

4. Bedside evaluations and laboratory studies (electrolytes, blood gases, salicylate concentrations, urine pH) every 1–2 h are required for patients with serious salicylate toxicity.

5. Decreases in pH and elevated serum salicylate levels result in an increase in volume of distribution, with a movement of salicylate from the blood into the brain and other tissues. Patients can deteriorate and die while serum salicylate concentrations are decreasing. Awake and alert patients can die within 6 h.

6. Monitor for and prevent decreases in arterial pH when giving sedatives/relaxants or controlling ventilation.

7. Hemodialysis should be instituted at the onset of neurotoxicity.

8. Pulmonary edema usually reflects adult respiratory distress syndrome.

9. Do not confuse units of measurement for serum salicylate concentrations, which vary among laboratories (10 mg/dL = 100 mg/L).

Key Points in the Management of Salicylate Poisoning

1. Salicylate absorption may continue for >24 h, and onset of absorption may be delayed with enteric-coated aspirin.
2. Patients with moderate-to-severe salicylate toxicity typically are 4–6 L dehydrated and may exhibit large maintenance fluid requirements because of insensible losses from hyperventilation, sweating, and vomiting.

Special Populations

Pregnant Patients

Salicylate crosses the placenta and concentrates in the fetus at higher serum levels than in the mother [68, 69]. The relative acidemia of the fetus also contributes to higher fetal *tissue* salicylate levels for already elevated fetal *serum* salicylate concentrations (large fetal volume of distribution). The fetus possesses less capacity to buffer acidemic stress imposed by salicylate and, compared with the mother, a reduced capacity to excrete the toxin. This situation collectively places the fetus at greater risk of death for a

given maternal serum salicylate concentration than the mother.

Because the fetus has greater toxicity than the mother, it seems wise to institute hemodialysis for lesser degrees of maternal toxicity than those in nonpregnant patients. Maternal hemodialysis can decrease placental blood flow. There are no studies to guide clinicians in deciding what maternal serum salicylate concentration crosses the threshold for hemodialysis. In a woman with a premature fetus, we institute hemodialysis for signs of fetal distress in the presence of maternal chronic salicylate toxicity or whenever maternal salicylate concentrations are greater than 40 mg/dL (>2.92 mmol/L) [70]. In a woman with a mature fetus, immediate delivery might allow more intensive care for the infant [71]. Alternatively, maternal hemodialysis might remove salicylate more safely and effectively from the fetus (through redistribution) than fetal therapies after delivery. In general, we lean toward hemodialysis in the latter situation because it is much easier to perform hemodialysis on the mother than on a newborn.

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Part X

Medications: Antimicrobial

Alison L. Jones

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Chloroquine

Chloroquine is used to prevent and treat malaria in limited geographical areas (e.g., Central America and the Far East) and to manage immunological disorders such as systemic lupus erythematosus and rheumatoid arthritis. It represents the most severe and frequent cause of poisoning by any antimalarial drug. Chloroquine is a frequent method of suicide in Africa [1], France [2, 3], Asia, and the Pacific [3, 4]. In Zimbabwe, a marked association with pregnancy was reported as a result of the mistaken belief that it is an abortifacient [1]. The development of the Internet over the last 20 years or so has led to increased information about drugs and their toxic effects and has dramatically increased the availability of drugs illicitly. Evidence also demonstrates that suicidal people search the Internet to choose their drug(s) for suicide [5].

Among 167 chloroquine poisoning cases admitted to a toxicology critical care unit, the mortality was less than 10%; these are the best survival figures quoted in the literature to date [2]. The average fatal dose is 8 g, with the lowest reported fatal dose being 5 g [5]. An ingested dose of chloroquine of >5 g is a good predictor of fatality, with a specificity of 0.98 [3]. Messant et al. [6] describe survival in a patient ingesting 10 g. In some reported cases across the literature, death could have been avoided by appropriate medical care. Other readily available indices such as systolic blood pressure less than or equal

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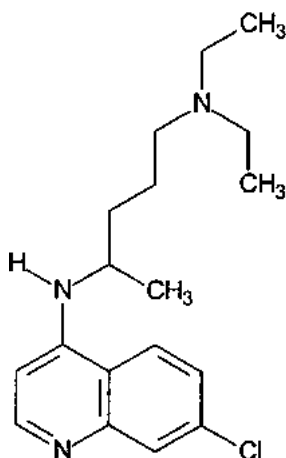


Fig. 1 Chemical structure of chloroquine

to 80 mmHg and QRS duration greater or equal to 120 msec on EKG are also used to indicate the need for ventilation, epinephrine, and diazepam clinically [7, 8]. Children ingestions of greater than 10 mg/Kg of chloroquine demand observation and monitoring for 4–6 h [9].

Chemistry and Pharmacology

The chemical name of chloroquine is 7-chloro-4-(4'-diethyl-amino-1'-methylbutylamino)-quinoline ($C_{18}H_{26}ClN_3$) (Fig. 1). Its molecular weight is 319.9, and it has pK_a values of 8.4 and 10.8. It is insoluble in water.

Chloroquine is absorbed readily from the gastrointestinal tract; the bioavailability is 78% for solution and 89% for tablets [10]. It accumulates in high concentrations in tissues such as the kidneys, liver, lungs, and spleen [10]. Chloroquine is bound strongly in melanin-containing cells, such as those in the eyes and retina. It has a low toxic/therapeutic margin, and care must be taken in prescription to prevent unintentional intoxication.

Pharmacokinetics of Chloroquine* [10]

Apparent volume of distribution: 116–285 L/kg

Protein binding: 50–65% in plasma

Mechanism of clearance: 61% urinary excretion

Active metabolite: desethylchloroquine

Terminal half-life:[†] 60 days

Methods to enhance clearance: none effective other than activated charcoal

*The half-life correlates well with peak plasma concentration; toxicokinetics is dose-dependent.

[†]Terminal half-life of desethylchloroquine is longer than the parent drug.

Pathophysiology of Toxic Effects

Cardiovascular toxicity of chloroquine is due to its quinidine-like (class Ia) actions. It inhibits spontaneous depolarization, slows conduction, lengthens the refractory period, and raises the electrical depolarization threshold. These actions cause depressed contractility, impaired conductivity, and decreased excitability but heighten the possibility of reentrant arrhythmias [11]. The pathophysiology of the effects of these sodium channel blocking agents is described in ► Chaps. 21, “Cardiac Conduction and Rate Disturbances,” and ► 39, “Sodium Channel-Blocking Antidysrhythmics.” Hypotension and shock are due to negative inotropic activity rather than peripheral vasodilation [12]. Neurologic symptoms of chloroquine are due to either direct central nervous system toxicity, which lowers the threshold for convulsions, or cerebral ischemia secondary to cardiovascular disturbances.

The mechanisms of hypokalemia have not been established, but its close temporal relationship with chloroquine toxicity suggests a potassium transport disturbance that favors transport of potassium into the cells and blockade of cardiac potassium channel human ether-a-go-go-related gene (HERG) [13, 14]. The data collected in the study by Clemessy and colleagues [14] do not support hypokalemia as a result of potassium depletion. Hypokalemia cannot be attributable to gastrointestinal losses because diarrhea is not common, and vomiting occurs in only about 30% of cases and is not prolonged. Urinary potassium wasting is not responsible because potassium losses in urine are low. Alkalosis is not the cause because most patients are acidotic [14].

Clinical Presentation and Life-Threatening Complications

Chloroquine overdoses usually have several characteristics in common. The interval between ingestion and onset of symptoms is short, and death, when it occurs, is often within 12 h. However, the risk of delayed death may persist up to 48 h, following the ingestion of high doses. At autopsy, common findings include cerebral and pulmonary edema. Tissue concentrations in a fatal overdose are shown in Table 1 [15]. The therapeutic plasma concentration is 1 mg/L (3.1 $\mu\text{mol/L}$) [16]. Plasma values reflect only a small proportion of total body chloroquine load because its apparent volume of distribution is high 10. The mortality rate in published studies is 12–35% and is among the highest in clinical toxicology [17]. Symptoms of chloroquine overdose usually start within 1–3 h of ingestion and include nausea, vomiting, agitation, drowsiness, hypokalemia, headaches, and visual disturbances [18]. After large ingestions, rigidity, coma, convulsions, hypotension, and arrhythmias occur.

Cardiovascular

In severe poisoning, cardiovascular signs promptly follow the appearance of the initial symptoms [17]. Cardiac arrest can be the first sign of overdose, however [12]. Systemic hypotension is one of the most frequent signs of chloroquine poisoning and without appropriate therapy may progress rapidly to cardiogenic shock with increased central venous pressure.

EKG abnormalities include modifications of repolarization with prolonged QT_c or QRS interval, increased U waves, and depression of the ST-T segment and flattened or inverted T waves. Intraventricular conduction delay and QRS widening are common. Atrioventricular block is less common. Ventricular tachycardia or fibrillation is observed early in chloroquine poisoning, and cardiac arrests tend to occur during the first hours. Ventricular extrasystoles and torsades de pointes may occur after 8 h. Delayed cardiac arrest (after 8 h) has been reported secondary to ventricular arrhythmias. A case of inverted Takotsubo cardiomyopathy (diagnosed by echocardiography) has

Table 1 Chloroquine concentrations in a fatal case

Specimen	Concentration
Blood	33 mg/L (103 $\mu\text{mol/L}$)
Kidney	110 mg/kg (344 $\mu\text{mol/kg}$)
Liver	169 mg/kg (528 $\mu\text{mol/kg}$)
Lung	73 mg/kg (228 $\mu\text{mol/kg}$)
Urine (antemortem)	367 mg/L (1147 $\mu\text{mol/kg}$)

From Ref. [15]

been reported in a 35-year-old female following ingestion of 7 g chloroquine – the pathophysiology of this remains uncertain [19].

Respiratory

Tachypnea is common in chloroquine poisoning. Apnea may occur suddenly, especially when convulsions start [20].

Central Nervous System

Neurologic effects appear rapidly after ingestion and include central nervous system depression and visual disturbances, such as blurred vision, diplopia, photophobia, and sometimes blindness. Blindness in acute chloroquine poisoning is transient and resolves without sequelae, in contrast to acute quinine poisoning or long-term chloroquine-induced retinopathy. Coma is less common and tends to be associated with circulatory failure, although cases with cerebral edema have been described [20]. Central nervous system excitation with agitation and seizures usually precedes cardiac arrest.

Myopathy and Neuropathy

Chloroquine overdose can cause a painless proximal myopathy with normal or slight elevation of creatine kinase in plasma. It can also be associated with a peripheral neuropathy [21].

Hypokalemia

Hypokalemia in chloroquine poisoning has been recognized since the 1980s. It is almost always present in severe chloroquine intoxication [20] and tends to appear within 3 h of ingestion. In one series stratified by severity, mild, moderate, and severe intoxications were associated with mean serum potassium concentrations of 3.5, 3.26, and 3 mmol/L, respectively [18]. Potassium

administration may lead to sudden hyperkalemia as chloroquine is eliminated, and rapid rigorous correction of early hypokalemia is not recommended [14].

Diagnosis

In the first 12 h after overdose, serum chloroquine concentrations correlate well with severity of intoxication, with severe effects being seen when serum concentrations are greater than 5 mg/L (15.5 μ mol/L) [18]. Mild intoxication without clinical symptoms is associated with serum concentrations less than 2.5 mg/L (7.8 μ mol/L). High serum chloroquine concentrations have been reported for 8–10 days, however, whereas clinical symptoms have resolved after 2 days [20]. Recent data demonstrates that blood concentrations are a better predictor of poisoning severity than plasma concentrations [8]. No patient with a blood chloroquine concentration of less than or equal to 6.7 mg/L (16 μ mol/L) had significant cardiovascular events. None with peak blood concentration of less than 10.5 mg/L (25 μ mol/L) had cardiac arrest or died [8]. The lowest reported blood concentration associated with a fatal outcome due to discontinuation of the epinephrine infusion was 6.5 mg/L, but up to 53 mg/L in blood and 7.0 mg/L in plasma survival is possible with meticulous supportive care [8]. However, blood or serum chloroquine concentrations are not routinely available in the majority of hospitals. In general, serum chloroquine concentrations are not needed to make the diagnosis or guide therapy.

Treatment

General Considerations

Although a human volunteer study has indicated that activated charcoal given within 1 h of ingestion decreases chloroquine absorption [22], it is unknown if such therapy alters the outcome of seriously poisoned patients. There is concern about patients developing seizures or altered mental status while taking activated charcoal, which

may lead to aspiration. Intubated patients who ingested more than 15 mg/kg of chloroquine and who present within the first hour can safely be given activated charcoal.

The use of antiarrhythmic agents should be avoided if possible because this may precipitate further arrhythmias by additional negative inotropic or chronotropic activity. Overdrive pacing is the treatment of choice (level IV evidence – clinical experience) for ventricular tachycardia or torsades de pointes [20]. Positive inotropic support, e.g., with epinephrine (adrenaline), may be required [20]. Plasma potassium must be monitored. Hypokalemia may have a protective effect and should not be corrected aggressively in the early stages of poisoning (level III evidence) [14]. If hypokalemia persists longer than 8 h, potassium should be replaced but cautiously, because rebound hyperkalemia often occurs during the recovery phase [14]. High-dose diazepam (2 mg/kg intravenously over 30 min followed by 2 mg/kg/day) may have a protective effect in chloroquine poisoning (level IV evidence), but respiratory support should obviously be present before it is given [20]. Early and continuous cardiorespiratory and neurologic support of these patients is crucial to their survival. The role of therapeutic hypothermia postarrest in chloroquine poisoning remains to be evaluated.

Indications for ICU Admission in Chloroquine Poisoning

ICU admission is dictated by clinical need and country- and hospital-specific policy. In some countries with greater availability of HDU/ICU facilities, any patient with >2 g chloroquine is admitted for meticulous observation and monitoring. In many countries, the following severe complications are indicators for ICU admission.

Cerebral edema
Pulmonary edema
Coma
Persistent seizures
Ventricular arrhythmias
Hypotension (systolic <80 mmHg)
QRS > or equal to 120 msec on EKG

Special Airway and Ventilatory Considerations

It is essential to intubate and ventilate patients early in chloroquine poisoning if arrhythmias, QRS prolongation, or hypotension is present. Based on Riou's study [24], endotracheal intubation and diazepam and epinephrine infusion are recommended for patients presenting with one or more of the following signs:

- Presumed ingested dose >4 g
- Systolic blood pressure >100 mmHg
- QRS length >100 msec

In the absence of any of those signs, cardiovascular monitoring (in the ICU during about 24 h) is sufficient.

Similarly, early intubation is advised if central nervous system features, such as recurrent seizures or coma, occur, especially if the use of high-dose diazepam is contemplated.

Role of Diazepam in Chloroquine Poisoning

Diazepam (0.1–0.3 mg/kg) given by slow intravenous injection, repeated as necessary, is effective at controlling convulsions [20]. In addition, diazepam at approximately 10 times higher doses has been reported to have a specific cardioprotective action in severe chloroquine poisoning [20]. Crouzette and coworkers [23] subsequently reported that diazepam reduces mortality in rats acutely poisoned with chloroquine, whereas Riou and colleagues [24] showed cardioprotection and increased urinary chloroquine excretion in chloroquine-poisoned pigs after treatment with diazepam.

Diazepam (2 mg/kg intravenously over 30 min) together with early mechanical ventilation and intravenous epinephrine (0.25 µg/kg/min and increased until systolic blood pressure was >100 mmHg) for 4 days was used to treat 11 patients with severe chloroquine poisoning. All of these patients would have been expected to die on the basis of historical control data. Ten of these 11 patients survived. Mechanical ventilation was instituted in part because of the respiratory depressant effect of high-dose diazepam.

The mechanism of the cardioprotective effect of diazepam in acute chloroquine poisoning is unknown. Croes and coworkers [25] reported a patient with severe chloroquine poisoning who also had ingested clorazepate (initial whole-blood chloroquine and plasma nordiazepam [a clorazepate metabolite] concentrations 7.9 mg/L [24.7 µmol/L] and 2.3 mg/L [8.4 µmol/L], respectively) and in whom mechanical ventilation was instituted. The patient was treated successfully with diazepam (2 mg/kg over 30 min, followed by 1–2 mg/kg over 24 h) and norepinephrine (0.25 µg/kg/min for 18 h). Despite plasma diazepam and nordiazepam concentrations of equal to or greater than 3 mg/L (10 µmol/L) (therapeutic level is 2 mg/L), however, the patient required additional sedation with piritramide to facilitate mechanical ventilation [25]. Although it is possible that chloroquine antagonized the sedative effects of diazepam, the patient may have acquired tolerance to these effects because of prior use of clorazepate. A study in animals suggested that barbiturate anesthesia and isoprenaline (isoproterenol) infusion may be a more effective combination than diazepam and epinephrine in treating severe chloroquine poisoning [26].

Cardiotoxicity

Studies in animals and humans suggested that early aggressive management of severe chloroquine intoxication has a cardioprotective effect and reduces the fatality rate [2, 24]. Hypotension should be managed initially with intravenous fluids. Epinephrine (1–5 µg/kg/min) may be necessary for hypotension that is nonresponsive to an intravenous fluid bolus. The epinephrine infusion rate is a good guide to poisoning severity for chloroquine, with the proviso that the ingested dose can be reliably obtained [7]. A threshold value of >3 mg/h (%) was the indicator for extreme poisoning severity [7].

Sodium bicarbonate intravenously is considered the treatment of choice for arrhythmias and should be used in patients with widened QRS and QT_c intervals (1–2 mL/kg of 8.4% sodium bicarbonate repeated if necessary, aiming for a pH of

7.45–7.5). There are no randomized controlled trials of efficacy of sodium bicarbonate in chloroquine poisoning, but its use now is recommended widely (level III and level IV evidences, respectively) [2, 27]. Its use has rationale, given the quinidine-like action of the drug and the efficacy of sodium bicarbonate in reversing similarly induced cardiovascular effects in poisoning by tricyclic antidepressants [1, 27, 28]. It also may reverse the cardiotoxic effects of hyperkalemia [29]. The treatment of choice for ventricular tachycardia and torsades de pointes is overdrive pacing [20]. All antiarrhythmic drugs are potentially arrhythmogenic and should be avoided. Class I agents in particular are contraindicated, and lidocaine should not be used because it may precipitate convulsions [2, 27].

The role of intravenous lipid emulsion (ILE) in chloroquine poisoning is controversial but theoretically beneficial given the lipophilic nature of chloroquine (lipid aqueous partition coefficient log P4.3). No benefit was found in one chloroquine case, when ILE was given 11 h post-ingestion [30]. A subsequent case was reported of a 24-year-old who was estimated to have ingested 14.5 g of chloroquine, together with 150 mg midazolam, 50 mg domperidon, and 40 mg ondansetron at an unknown time prior to admission. He initially developed a junctional rhythm with a blood pressure of 70/40 mmHg and then ventricular fibrillation and subsequent pulseless electrical activity (PEA) [31]. A bolus of 20% intralipid was given to the patient (1.5 ml/Kg followed by a continuous infusion of 0.25 ml/kg/min) and the PEA converted to a shockable rhythm, and a DC shock of 200 J was administered with transient reversion to sinus rhythm with a blood pressure of 120/90 mmHg [31]. This patient did not survive probably due to prolonged resuscitation, but the case raises the intriguing possibility of a role for ILE rescue therapy in life-threatening ventricular arrhythmias due to chloroquine. A discussion of the clinical pharmacology of ILE can be found in ► Chap. 3, “Therapeutic Approach to the Critically Poisoned Patient.”

Hypokalemia

Exogenously administered potassium has an effect on the heart similar to quinidine-like drugs in that it depresses excitability, slows the rate of depolarization, and decreases conduction [29]. The slowed depolarization and increased refractory period favor reentrant tachycardia. It is therefore recommended to avoid potassium replacement in the early hours of chloroquine intoxication, especially when cardiovascular effects are present [20]. In the second phase of poisoning, when ventricular extrasystoles and torsades de pointes are present, administration of potassium may be helpful, but it must be given cautiously to avoid sudden hyperkalemia. The best recommendation to date is to give patients with hypokalemia of less than 2 mmol/L no more than the equivalent of 160 mmol of K^+ per 24 h for an adult (level IV evidence) [14]. Lesser degrees of hypokalemia may be treated with 80 mmol of K^+ per 24 h for an adult (level IV evidence) [14]. The rationale for this relatively conservative therapy is that there is no total body deficit of potassium, and because the hypokalemia is due to a transport problem, it is difficult to correct. Although there is a correlation between the degree of hypokalemia and death, in most cases hypokalemia is not the direct cause of death [14]. As the intoxication resolves, there is serious documented risk of hyperkalemia [14].

Extracorporeal Removal Techniques

Hemofiltration, hemodialysis, and hemoperfusion have no role in the management of chloroquine poisoning because of the large volume of distribution and relatively high protein binding (see Table 1) [10].

Extracorporeal Membrane Oxygenation Treatment (ECMO)

The therapeutic intent of ECMO is to provide a “bridge to recovery” [32]. There are no randomized controlled trials of ECMO in poisoned patients with shock or ARDS [32]. Most case reports or series suffer from publication bias, i.e., more likely to be reported/published if outcome is successful. Vanzetto and colleagues [33] and Riou et al. (1988) [3] report successful outcome of VA-ECMO in patients with (hydroxy)/chloroquine overdose.

Relative contraindications to ECMO include advanced age, severe irreversible brain injury, untreatable metastatic cancer, severe organ dysfunction (e.g., Sequential Organ Failure Assessment score >15), and high-pressure positive ventilation for more than 7 days [32]. There is one absolute contraindication to ECMO: uncontrolled coagulopathy [32]. Patients require anticoagulation to avoid clots in the ECMO circuit. Complications include bleeding at the cannulation site (VV-ECMO) or surgical entry site (VA-ECMO), and the daily estimated blood transfusion requirement is approx 275 ml/day [32], and in contrast (where anticoagulation is not sufficient) embolic phenomena occur. Use of ECMO in experienced centers is associated with better clinical outcomes [34–36]. A detailed discussion of the use of ECMO can be found in ► Chap. 4, “Extracorporeal Membrane Oxygenation and Cardiopulmonary Bypass in the Poisoned Patient.”

Criteria for ICU Discharge in Chloroquine Poisoning

Resolution of cerebral edema
Resolution of pulmonary edema
Resolution of coma
Resolution of persistent seizures
Resolution of ventricular arrhythmias
Resolution of QRS prolongation

Special Populations

Elderly patients and patients with preexisting cardiovascular disease are likely to be more susceptible to the cardiotoxicity of chloroquine.

Key Points in the Management of Chloroquine Poisoning

1. The interval between ingestion and clinical signs is usually short (1–3 h).
2. The main risks are cardiovascular and central nervous system effects.
3. Early aggressive therapy is needed. The dose of epinephrine required to support the patient indicates the severity of poisoning.

4. Use diazepam combined with a positive inotrope such as epinephrine for severe chloroquine poisoning.
5. Chloroquine level in blood is not necessary for management – clinical features are more important.
6. Correcting hypokalemia early worsens cardiovascular toxicity.
7. Treating arrhythmias with antiarrhythmic drugs may result in negative inotropic and chronotropic effects, and cardiovascular status worsens.
8. Treating with high-dose diazepam without recognizing the need for ventilation may result in pulmonary aspiration.

Quinine

Quinine is an alkaloid extracted from the bark of various species of cinchona tree (*Rubiaceae*). It first was employed as an antipyretic, albeit not a very effective one, by the Portuguese in the first half of the seventeenth century.

Quinine salts are used in the treatment of chloroquine-resistant malaria. It also commonly is employed for the treatment of nocturnal cramps, for which it has limited efficacy [37]. Quinine has been used as an illegal abortifacient [38]. Quinine also has been used “to cut” street heroin [39]. It is used widely in tonic water for its bitter taste, and there are several case reports of allergic reactions when it has been consumed this way [40]. Detailed review of overdoses in Scotland showed that 64% of overdoses occurred with prescriptions for other family members, and in only 36% of cases had patients taken their own quinine [41].

Chemistry and Pharmacology

The chemical name of quinine is 6-methoxy- α -(5-vinyl-2-quinudindinyl)-4-quinoline-methanol ($C_{20}H_{24}N_2O_2 \cdot 3H_2O$) (Fig. 2). It is the *d*-isomer of quinidine. Its molecular weight is 378.5, pK_a values are 4.1 and 8.5, and it has low solubility in water. Quinine is absorbed rapidly

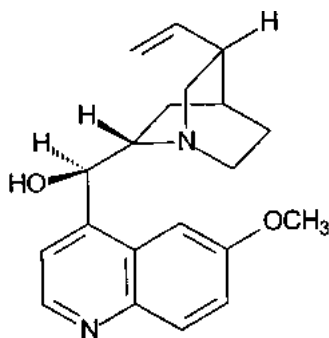


Fig. 2 Chemical structure of quinine

and almost completely from the gastrointestinal tract when given orally, with peak plasma concentrations occurring 1–3 h after ingestion [20].

Pharmacokinetics of Quinine [42]

Apparent volume of distribution: 2.1–3.1 L/kg.

Protein binding: 70–89%.

Clearance rate: 0.22–0.29 mL/min/kg*.

Elimination half-life: 26.5 ± 5.8 h at toxic levels.

Active metabolites: the liver, kidneys, and muscles metabolize 80% of ingested dose[†].

Methods to enhance clearance: multiple-dose activated charcoal is effective.

*20% is excreted unchanged in urine.

[†]Quinine is metabolized by P-450 CYP3A4; there is interindividual variance in expression of this coenzyme.

Pathophysiology

Toxicity of quinine can be divided into effects that are immunologically induced, such as purpura and skin rashes, and effects that are direct toxic actions, such as cardiotoxicity and ocular toxicity. Quinine has sodium channel blocking or local anesthetic actions but also is an irritant. The latter effects may be responsible for nausea in clinical use. The actions on cardiac muscle are class IA antiarrhythmic. It produces sodium channel blockade with moderate phase 0 depression, resulting in slowed conduction and repolarization.

The effects on cardiac muscle include an increased threshold in atrial, ventricular, and Purkinje fibers. As a result, the rate of Purkinje cell firing is decreased, and conduction velocity is decreased in ventricular muscle. The refractory period of cardiac muscle is increased. In the pacemaker cells of the sinoatrial node, spontaneous depolarization is inhibited, and this phenomenon extends particularly to the site of ectopic pacemaker activity. In larger doses, quinine causes atrioventricular beat generation (i.e., R-on-T phenomenon) because of its effects on ventricular refractory periods. When higher doses are used, ventricular fibrillation may supervene. The pathophysiology of sodium channel blockade effects on the myocardium is described in detail in ► Chaps. 21, “Cardiac Conduction and Rate Disturbances,” and ► 39, “Sodium Channel-Blocking Antidysrhythmics.” There is a direct myocardial depressant effect of quinine on cardiac muscle in addition to the sodium channel blockade. Quinine is a vasodilator, probably owing to its α -blocking activity [43].

Quinine has an oxytocic action on the uterus, which becomes more pronounced as pregnancy progresses. The exact mechanisms for this action are poorly understood. In skeletal muscle, quinine has a curare-like effect, reducing end motor plate excitability. Its use is known to cause deterioration in patients with myasthenia gravis [43]. Quinine probably does not have an effect on gastric smooth muscle. The emetic effect is likely due to a central action on the chemoreceptor trigger zone [43].

Quinine has been reported to stimulate insulin release in patients receiving treatment for falciparum malaria and causes hypoglycemia [44]. The mechanism of quinine-induced insulin release is a sulfonylurea-like suppression of potassium efflux, leading to β cell membrane depolarization and release of insulin and proinsulin from secretory granules in response to calcium influx via voltage-gated calcium channels.

Quinine has toxic effects that can result in blindness [45, 46]. This effect was postulated to be due to retinal arteriole vasoconstriction, but quinine has a direct toxic effect on retinal photoreceptor cells [45, 47]. There are no reports of retinal vascular changes being observed before

the onset of severe peripheral field constriction or blindness [48]. Normal arteriolar caliber has been observed with fluorescein angiography in a blind patient, and electroretinographic and electrooculographic studies performed soon after patients became blind all showed that the primary disturbance was in retinal function rather than impaired blood flow [46, 48]. Photoreceptor cells are affected first, followed by the ganglion layer and possibly the pigment epithelium [46, 48]. Visual evoked responses show abnormal waveform and prolonged latency from 3 days after poisoning to several months later, implying some damage to the nerve fiber, the retina, or both [49, 50].

Quinine has direct toxicity on the auditory nerve. Audiometry reveals bilateral nerve deafness due to inhibition of the transducing outer hair cells of the organ of Corti [51]. The decreased acuity is not usually clinically apparent, although the patient recognizes tinnitus [51]. Auditory toxicity is reversible.

Clinical Presentation and Life-Threatening Complications

Many clinical effects are common to an acute single overdose in self-poisoning and accumulation of quinine during therapy for malaria. These effects are known as *cinchonism* and include auditory symptoms, gastrointestinal disturbances, vasodilation, sweating, and headache [43]. As concentrations become greater, visual disturbance (plasma concentration >10 mg/L [31 $\mu\text{mol/L}$]) followed by cardiac and neurologic features (plasma concentration >15 mg/L [46 $\mu\text{mol/L}$]) occurs [52]. Similar levels in individuals who are ill with malaria do not result in toxicity owing to reduced free quinine present as a consequence of increased binding to α_1 acid glycoprotein. No clear fatal concentrations of quinine have been identified however, and the patient with the highest plasma concentration of quinine at presentation in one series (20.4 mg/L [63 $\mu\text{mol/L}$]) survived with retinal damage. The usual approximate fatal dose of quinine in an adult is approximately 8 g [53], but the smallest reported fatal dose in an adult was 1.5 g

[54–56]. AAPCC TESS reported no fatal quinine exposures in children under 6 years from 1983 to 2002 [56].

Cardiovascular

Vasodilation [53] and sweating are common. Mild systemic hypotension can occur in the absence of disturbance of cardiac rhythm due to dose-related depression of myocardial contractility. Cardiotoxicity of quinine is the predominant cause of death in overdose patients and the ultimate predictor of outcome. These features usually occur within 8 h of ingestion, although one case report claimed that torsades de pointes occurred 25 h after ingestion [57]. Electrocardiographic changes include prolonged PR, QRS, and QT_c intervals; ST segment changes and T wave changes; and the appearance of U waves [49]. EKG changes are common in overdose of >5 g in adults [55]. A large overdose often sees progressive PR and QRS interval widening, bundle branch block, and then sinus and atrioventricular blocks accompanied by bradycardia, followed by ventricular escape rhythms that may then yield asystole [56]. After large overdoses, broad-complex tachycardias, such as torsades de pointes, ventricular tachycardia, and ventricular fibrillation, may be seen [20].

Pulmonary

A 17-year-old man took 5 g of quinine bisulfate and presented 3.5 h later with deafness. He collapsed shortly after with broad-complex tachycardia. He had pulmonary edema and infection with *Pseudomonas* and *Staphylococcus*. His highest blood level of quinine was 17.8 mg/L (55 $\mu\text{mol/L}$). Autopsy revealed adult respiratory distress syndrome, but whether it was due to direct toxicity of quinine or due to severity of illness in the patient is unknown. Adult respiratory distress syndrome is not widely reported in patients seriously poisoned with quinine [58].

Gastrointestinal Tract

Mild nausea may be the only symptom in therapeutic doses. Profuse vomiting, epigastric pain, and diarrhea characterize large overdoses, however [43]. These symptoms are due to direct

irritant action on the gastrointestinal tract and central effects on the chemoreceptor trigger zone [43].

Hematologic

Quinine is a well-recognized cause of drug-induced thrombocytopenia and purpura [59]. The amounts needed are small, and these complications have been documented even after consumption of soft drinks containing quinine [43]. Agranulocytosis also has been reported [60]. In patients with malaria due to *Plasmodium falciparum*, anemia and intravascular hemolysis with renal failure are recognized complications. Attacks are reported to follow irregular quinine use.

Renal

Intravascular hemolysis can precipitate oliguria and acute renal failure. Notelovitz [61] reported a case of a 21-year-old woman who ingested 90 g of quinine during her 8th week of pregnancy. The patient subsequently became drowsy with dark red urine, which was positive for blood and protein. The patient became oliguric, and urea levels increased to 2080 g/L. The patient was treated with blood transfusion and hemodialysis and was discharged within 72 h.

Auditory

Tinnitus is common, and with large overdoses, the patient may be deaf [43]. Vertigo also can occur [43]. The auditory symptoms nearly always resolve within a few days of the overdose. There have been no cases reported of permanent deafness as a result of quinine overdosage.

Ocular

In quinine overdose, ocular toxicity depends on plasma concentration and often develops 6–15 h after the overdose but may be delayed for 1 or more days [49, 52]. The first symptoms are blurring of vision and disturbance of color perception; this can occur during quinine accumulation in antimalarial therapy. After acute overdose, however, more severe disturbances may occur with progressive constriction of the visual fields, reduced central acuity, and finally complete blindness. Many years after quinine-induced

blindness, retinal pigment degeneration still may be apparent, giving the appearance of retinitis pigmentosa.

The fundus appears normal when visual symptoms begin. The pupils may be fixed and dilated some time before light perception is lost, particularly if the patient has marked tunnel vision. Thereafter, there may be progressive constriction of retinal arterioles, a cherry-red macular spot, and macular edema; several days or weeks after the overdose, optic atrophy appears [62]. There are, however, reports of entirely normal fundoscopic appearances after the onset of blindness and of normal retinal artery appearances after blindness has developed [50, 63]. Many patients recover completely, although a significant number are rendered permanently blind. In general, the quicker the onset of recovery, the lower the degree of permanent impairment [49]. Of 30 overdose patients in a Scottish study, 8 had documented evidence of visual impairment, of whom 6 had visual problems at 32 months [41]. Fixed dilated pupils strongly suggest blindness due to quinine. Disk pallor does not indicate that permanent blindness will result [63–65].

Central Nervous System

Headache, confusion, and vertigo can occur [20]. Ataxia can occur after moderate overdose [20, 64]. After massive overdoses, convulsions, coma, and respiratory depression occur and have high associated cardiovascular mortality [20]. A case of “myeloopticoneuropathy” after quinine poisoning has been reported, but this case most likely represents vitamin B₁₂ deficiency and alcoholic neuropathy [65].

Hypoglycemia

Hypoglycemia is thought to be due to quinine-stimulated insulin release and can be a severe problem [66].

Diagnosis

All patients should have a 12-lead electrocardiogram, and plasma should be assayed for urea and electrolytes and glucose because quinine can cause

hypokalemia and hypoglycemia. Quinine can be assayed in plasma by immunoassay, and there is a correlation between plasma concentration and clinical features. Usually levels less than 10 mg/L (31 $\mu\text{mol/L}$) within 10 h of ingestion are not associated with clinically significant poisoning [56, 67]. Quinine concentrations are not performed routinely in the management of quinine-poisoned patients because knowledge of concentrations does not alter the patient's management.

Along with methanol, quinine should be considered in the differential diagnosis of patients presenting with acute bilateral blindness. The two can be differentiated easily because patients with methanol toxicity have a high anion gap acidosis and a positive methanol assay. Ergot derivatives, lead, and mercuric chloride are less common causes of blindness secondary to poisoning.

Treatment

General Considerations

Maintenance of the airway, breathing, and ventilation is crucial. If respiratory failure with or without pulmonary edema occurs, positive-pressure ventilation may be required. Intensive supportive therapy should be the mainstay of treatment, with meticulous correction of electrolyte abnormalities and any hypoxia. As with chloroquine, it is theoretically likely that mild hypokalemia protects the myocardium from the effects of quinine, so zealous overcorrection of hypokalemia is not advised. The guidelines provided earlier for chloroquine reasonably may be applied to the management of hypokalemia in quinine poisoning as well. Blood glucose concentrations should be monitored.

Multiple-dose activated charcoal (see ► Chap. 3, "Therapeutic Approach to the Critically Poisoned Patient") should be given to all patients who may have ingested greater than 15 mg/kg of quinine. The justification for this approach comes from the study of Prescott and colleagues [67], which showed that after treatment with repeated oral charcoal, plasma quinine concentrations decreased rapidly with a mean half-life of 8.1 ± 1.1 h compared with more than 24 h in a report of similarly poisoned patients. The visual impairment, which was expected in a

patient with cardiotoxicity and a plasma quinine concentration of 12.6 mg/L (39 $\mu\text{mol/L}$), did not occur. Repeated doses of oral charcoal have been shown to increase the rate of elimination of a therapeutic dose of quinine in healthy volunteers [68]. In another study [49], the rate of spontaneous quinine elimination was much slower, pointing to a dose-dependent metabolism of quinine [67]. Activated charcoal remains the only practical means of enhancing removal of this drug after overdose. The effect is not due so much to interference with absorption as it is to concentration-dependent diffusion of drug from the circulation to the gastrointestinal lumen, where it is bound irreversibly by charcoal [69]. Activated charcoal usually is given in repeated doses until the patient improves clinically (i.e., cardiotoxicity has settled, ocular toxicity is improving). Caution must be exercised, however, if the patient is not intubated and has an alteration in mental status. Such patients are at risk of aspiration, and thus activated charcoal should not be administered under those circumstances. It is not possible to show from the literature to date that treatment with charcoal enhanced the outcome of these patients [67].

Indications for ICU Admission in Quinine Poisoning

Admission to the ICU is common worldwide, given the risks of cardiovascular complications, and in most countries occurs on the basis of a high ingested dose, even if asymptomatic. The following severe complications are key indicators for ICU admission.

Persistent systemic hypotension
QRS elongation >120 msec or ventricular arrhythmias
Significant intravascular hemolysis
Convulsions
Coma
Persistent hypoglycemia

All patients with quinine overdoses should be placed on a cardiac monitor. Antiemetics may be given if vomiting is prolonged and severe, but

theoretically agents with cardiotoxic or neurotoxic actions should be avoided (e.g., antihistamines). Intravenous fluids and electrolyte replacement are necessary in cases with profuse vomiting or diarrhea.

Cardiotoxicity

Systemic hypotension should be treated initially with intravenous fluids. If fluids do not correct the hypotension, inotropic agents may be necessary. Intravenous sodium bicarbonate is recommended (level IV evidence) to treat quinine-induced sodium channel blockade (e.g., QRS prolongation). The recommended initial dosing is 1–2 mL/kg of 8.4% sodium bicarbonate repeated if necessary, aiming at obtaining a QRS width <100 msec and keeping the arterial pH < 7.55 if possible. Intravenous sodium bicarbonate is considered the treatment of choice for arrhythmias and should be used in patients with widened QRS and QT_c intervals (1–2 mL/kg of 8.4% sodium bicarbonate repeated if necessary, aiming at obtaining QRS width <100 msec, trying to keep the arterial pH < 7.55 if possible). There are no randomized controlled trials of efficacy of sodium bicarbonate in quinine poisoning, but its use is widely recommended (level IV evidence) [27]. Its use has rationale, given the class Ia action of the drug and the efficacy of sodium bicarbonate in reversing similarly induced cardiovascular effects in poisoning by tricyclic antidepressants [28]. The treatment of choice for ventricular tachycardia and torsades de pointes is overdrive pacing [57]. The threshold for pacing may have to be increased to above 1 V because the quinine-poisoned heart is relatively insensitive to pacing stimuli [20].

All antiarrhythmic drugs are potentially arrhythmogenic and should be avoided. Class I agents specifically are contraindicated, and theoretically lidocaine in particular should not be used because it may precipitate convulsions and it potentiates the action of quinine on the heart [27]. Similarly, class III drugs (e.g., sotalol, bretylium) are unsuitable because they may result in further QT prolongation and torsades de

pointes. Transvenous pacing may be indicated for complete heart block.

If an inotropic agent is required, epinephrine, norepinephrine, or both are recommended. Epinephrine is the drug of first choice, unless vasodilation predominates, when a mixture of epinephrine and norepinephrine (vasoconstrictor action) is preferred.

Ocular

Visual effects of quinine are largely untreatable because the mechanism of toxicity still is poorly understood. In the past, many measures were advocated, such as bilateral stellate ganglion block [62], retrobulbar injections [60, 70], and vasodilators, including nitrates and nimodipine [71, 72]. As with all rare conditions with some spontaneous recovery, it has been difficult to evaluate the outcome of these procedures. In my experience, however, these procedures make no difference to outcome, and therefore I would not advocate their routine use. A report suggested efficacy for hyperbaric oxygen, but the same caveats of spontaneous recovery apply [73]. The role of multifocal electroretinography and optical coherence tomography in assessing retinal damage due to quinine remains to be fully evaluated.

Central Nervous System

Quinine-induced convulsions are often short-lived, but if they persist, they should be treated with diazepam (0.1–0.3 mg/kg) or a similar benzodiazepine [20]. Phenobarbital can be used for seizures refractory to benzodiazepines [56]. Coma should be managed conventionally.

Extracorporeal Removal Techniques

Visual recovery has been taken by some workers to indicate the benefit of treatment. This improvement frequently is spontaneous and rapid. The actual amount of quinine cleared is limited, however, and cannot account for improvement.

Hemodialysis and hemoperfusion are ineffective in quinine poisoning because there is rapid

tissue distribution, a relatively large volume of distribution, and extensive protein binding. Studies of the efficacy of hemodialysis showed that in 6 h, only 25–30 mg (77–93 μmol) of quinine were removed [74]. In other patients, only a few hundred milligrams of quinine were removed by hemoperfusion [52, 75]. In one patient, charcoal hemoperfusion was complicated in one reported case by repeated clotting of the charcoal cartridge despite heparinization, thrombocytopenia, and hypoprothrombinemia. The patient died [53]. Resin hemoperfusion is equally ineffective because it removes toxicologically insignificant amounts [76].

In one report, peritoneal dialysis was claimed to remove 640 mg (1970 μmol), but no analysis of plasma quinine concentrations was done to validate these findings [77]. Other authors recorded less than 60 mg (184 μmol) removed in 24 h [78]. In another case report, plasmapheresis was similarly ineffective, removing only 8.5 mg (26 μmol) of quinine [74]. There currently is no evidence that any of the previously advocated extracorporeal elimination techniques for quinine are effective in practice.

Urinary acidification or forced diuresis is not advised. Although it may increase renal quinine excretion slightly, it would be expected to worsen cardiotoxicity. Quinine has two pK_a values (8.0 and 4.11), causing confusion in analysis of urine pH manipulation data.

Role of Octreotide

The hyperinsulinemia and resultant hypoglycemia, which complicate quinine treatment of falciparum malaria, respond to octreotide. In Thai volunteers, octreotide (100 μg intramuscularly) suppressed quinine-induced hyperinsulinemia within 15 min [79]. The effect lasted for 6 h. Octreotide (50 μg intravenously over 15 min followed by 50 $\mu\text{g}/\text{h}$ by intravenous infusion, increasing to 200 $\mu\text{g}/\text{h}$ or decreasing to 10 $\mu\text{g}/\text{h}$ as appropriate) together with intravenous glucagon or *D*-glucose or both were effective in treating hyperinsulinemia and hypoglycemia in

five patients with falciparum malaria who were treated with quinine [79]. The clinical pharmacology of octreotide is described in detail in ► Chap. 70, “Antidiabetic Agents.”

Criteria for ICU Discharge in Quinine Poisoning

Resolution of systemic hypotension

Resolution of ventricular arrhythmias and electrocardiographic abnormalities

Resolution of significant intravascular hemolysis

Resolution of convulsions

Resolution of coma

Special Populations

In children, quinine's volume of distribution is less, and its elimination half-life is shorter than in adults, and it is significantly less protein bound in children under 2 years of age [20, 56]. The free (unbound) quinine is responsible for the toxicity, and an immature blood–brain barrier and cardiovascular system may make children under 2 years especially sensitive to quinine [56]. Most cases of quinine toxicity in toddlers occur after ingestion of more than two tablets, but a report of severe toxicity has occurred after exactly 2 tablets [56]. Hence, admission for observation is recommended for a toddler ingesting more than one tablet.

In patients with malaria, there is increased protein binding, an increased elimination half-life, and a decreased volume of distribution [20]. The pharmacokinetics of therapeutic doses is altered in patients with chronic liver disease; the time to maximum plasma concentrations was prolonged, and the terminal elimination half-life was prolonged to 23.4 h versus 9.7 h in healthy controls. No change in quinine clearance was seen, however [80]. The volume of distribution of quinine is decreased in the third trimester of pregnancy, but the clearance of therapeutic concentrations is similar, and toxicokinetics is not expected to be different from the nonpregnant state [81].

Key Points in Quinine Poisoning

1. Toxicity can occur quickly (within 1–3 h).
2. Cardiovascular toxicity is a poor prognostic sign.
3. No specific therapy works in ocular toxicity.
4. Extracorporeal elimination methods are of no value.
5. Multiple-dose activated charcoal is a well-supported treatment modality.
6. Correcting hypokalemia early worsens cardiovascular toxicity.
7. Antiarrhythmic drugs may worsen cardiovascular toxicity and should be avoided.

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Isoniazid (isonicotinic acid hydrazide [INH]) was first released in 1952 as a drug to treat tuberculosis. Although tuberculosis was already on the decline in the United States and much of the Western world at the time INH was released, there has since been resurgence since the 1980s largely as a consequence of human immunodeficiency virus. According to the US Centers for Disease Control and Prevention (CDC), there were 9,582 new cases of tuberculosis in the US in 2013, disproportionately affecting racial/ethnic minorities; compared to non-Hispanic whites, the TB rate was approximately six times higher in Asians and double in both non-Hispanic blacks and Hispanics [1]. Other social and medical ills, such as homelessness, overcrowding, alcoholism, and intravenous drug use, have contributed to the rise of tuberculosis infection. The CDC estimates that approximately one-third of the population has been infected by this disease, which caused 1.5 million deaths in 2013 [2].

The World Health Organization also stated that directly observed administration of antituberculin drugs in the developing world would help curb the spread. Without further public health measures such as these, it estimated that a 41% increase in new cases would be seen from 1998 to 2020, representing a change from 7.4 to 10.6 million cases [3]. The need for efficacious and cost-effective treatment has been answered largely by INH, which is useful both in combination therapy for acute TB as well as for prophylactic treatment in individuals with positive exposure testing [4]. However, with

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increased use of INH came, predictably, a notably increased number of acute toxicity cases from overdose [5].

Isoniazid comes in pill, elixir, or a parenteral form. The commonly used adult dose is 5 mg/kg (maximum of 300 mg daily); the recommended pediatric dose is 10–15 mg/kg daily (also with a maximum of 300 mg). Various combination products are available, such as a capsule containing 150 mg of INH with 300 mg of rifampin (Rifamate (U.S. trade names are given as examples. Trade names may be different in other countries.)) and a tablet preparation of 50 mg of INH, 300 mg of pyrazinamide, and 120 mg of rifampin (Rifater) [6]. According to the American Association of Poison Control Centers, in 2013, there were 149 reported exposures to INH, with 55 (37%) of them being unintentional. Although 68 (46%) of these required hospital care, only 15 (10%) had major effects, and fortunately there were no deaths [7]. These data depend on voluntary reporting of exposures, however, and they undoubtedly underestimate the true incidence of INH poisonings.

Biochemistry of Isoniazid and Hydrazines

INH is also referred to as *isonicotinylhydrazide*. As its name implies, it belongs to a family of related chemicals called *hydrazines* (Fig. 1), all of which exert similar effects in acute poisoning. Hydrazine itself has many nonmedical uses. Highly combustible, it is notably used as a jet fuel; furthermore, its powerful reducing properties give it many roles in industry, where it is used in the manufacture of anticorrosive materials, dyes, textiles treatments, and various agricultural chemicals and pharmaceuticals such as pesticides.

Another notorious member of the hydrazine group is gyromitrin (*N*-methyl-*N*-formyl hydrazone) (see Fig. 1), a toxin found in *Gyromitra* mushrooms that is ultimately hydrolyzed to monomethylhydrazine in vivo. Species of this mushroom group include *G. esculenta*, *G. californica*, *G. brunnea*, and *G. infula*, and

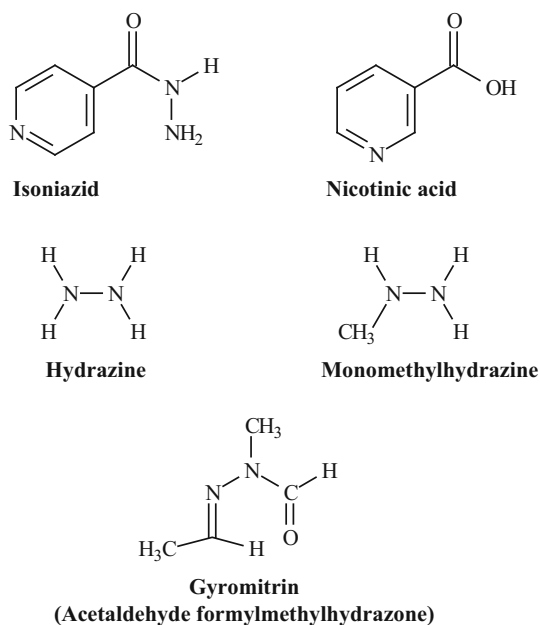


Fig. 1 Chemical structures of isoniazid and related hydrazines

their toxicity is discussed in detail in ► [Chap. 109, “*Gyromitra* Mushrooms.”](#)

Isoniazid is produced initially as a white crystal; its injectable form is a clear to slightly greenish-yellow liquid with a pH of 6–7 and a pK_a of 1.9 [7, 8].

Pharmacokinetics of Isoniazid and Related Hydrazines

Volume of distribution: 0.6–0.75 L/kg

Cerebrospinal fluid concentrations: 90–100% of plasma 3–4 h after standard oral dose

Protein binding: 4–30%

Oral bioavailability: 90%

Metabolites: acetylisoniazid, isonicotinic acid, monoacetylhydrazine, diacetylhydrazine, isonicotinyl glycine, isonicotinyl hydrazones, methylisoniazid

Elimination: inactivated by liver acetylation* and dehydrazination, P-450 system hydrolysis, methylation; 75–96% of standard

(continued)

dose excreted in urine within 24 h as parent drug or metabolites (assuming normal renal function)

Methods to enhance elimination: hemodialysis or peritoneal dialysis in specific populations

*Acetylation rate is genetically influenced; see text.

Pathophysiology of Therapeutic and Toxic Effects

In mycobacteria, INH undergoes a series of enzymatic reactions that has the net result of inhibition of mycolic acid synthesis during cell division, producing breaks in the mycobacterial cell wall. This is its main therapeutic action as an antituberculosis drug; however, in humans, its toxicity centers upon two main effects: (1) its interference with pyridoxine (vitamin B₆) metabolism, and (2) its conversion into hydrazine metabolites.

Pyridoxine is an essential cofactor in the production of γ -aminobutyric acid (GABA), the main inhibitory central nervous system neurotransmitter. Normally, pyridoxine is converted to pyridoxine 5' phosphate (P5P) by pyridoxine kinase. P5P is a necessary coenzyme for glutamic acid decarboxylase (GAD), which is responsible for the conversion of glutamic acid to GABA (Fig. 2), the body's main inhibitory neurotransmitter. Isoniazid, however, inhibits pyridoxine kinase, resulting in a deficiency of P5P. The end result is a deficiency of GABA relative to excitatory glutamate, and a resultant excitatory state with the potential for seizures.

Secondly, INH is metabolized into hydrazine, which also binds pyridoxine, further contributing to the same excitatory state through the same mechanism described above. The acute deficiency of pyridoxal phosphate is also believed to inhibit catecholamine synthesis, contributing to cardiovascular instability and coma [9]. Furthermore, these hydrazine metabolites play a central role in INH's well-known hepatotoxicity in chronic therapeutic use [10].

Acute ingestions of 1,500 mg or less of INH can cause minor toxicity in adults and major toxicity in children. Ingestion of 6–10 g in an adult can produce severe metabolic acidosis, seizures, cardiovascular collapse, and death [11].

Clinical Presentation in Acute Toxicity

The effects of INH in acute overdose predominantly involve the central nervous system (CNS), and in milder overdoses may include psychosis, ataxia, memory impairment, nystagmus, hyperreflexia, areflexia, light-headedness, and cerebellar syndrome [12–16]. In severe acute INH poisoning, however, the classic triad consists of refractory seizures, coma, and metabolic acidosis [9, 17, 18]. The metabolic acidosis caused by INH is thought to be secondary to lactate production from seizure activity [19] and is typically associated with a high anion gap. Respiratory depression in the setting of intractable seizures, as well as reduced metabolic clearance of lactate, may also contribute. Typically, however, lactic acidemia from seizures will clear quickly once the convulsions are controlled [20].

Secondary mechanisms for the degree of acidosis have been proposed. Being structurally similar to nicotinic acid (vitamin B₃) (see Fig. 1), INH is believed to block nicotinamide-adenine dinucleotide activity, which is important for the conversion of lactate to pyruvate; however, studies did not successfully prove that this is a significant contributor to the acidosis. Ketonemia with ketonuria, as an alternate explanation for the acidosis, has been found in some cases [21]. Hyperglycemia and glycosuria have also been reported [15, 17] but is not common and overall seems to be an incidental finding. Finally, it is important to note that the intravenous (IV) preparation of pyridoxine has a pH < 3; in a RCT of 5 patients, a significant but transient elevation in the base deficit was observed [22]. Regardless of the mechanism of acidosis, it can be of impressive magnitude: in one report, a 14-year-old had a serum pH of 6.69; [23] in another, an adult patient had a pH of 6.49 [9]. Both of these patients recovered without sequelae.

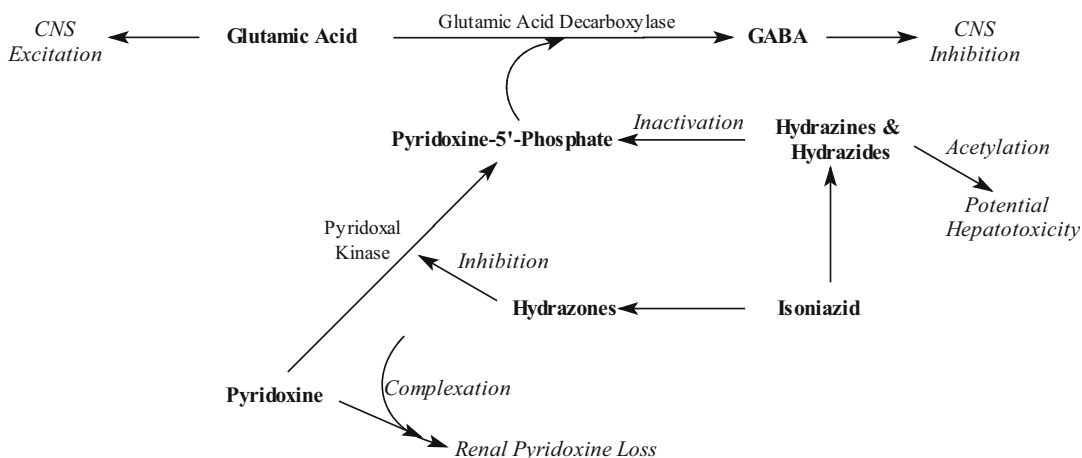


Fig. 2 Inhibitory effect of isoniazid on pyridoxine-related metabolic processes. *CNS* central nervous system, *GABA* γ -aminobutyric acid

Although INH's hepatotoxic effect is of far greater consequence during chronic therapy, as detailed below, it should be noted that in one series of eight acute overdoses, six had aspartate aminotransferase levels ranging from 40 to 1,581 U/L [15]. This suggests acute hepatotoxicity as a potential complication, although fulminant hepatic failure in this setting would not be expected.

Chronic Toxicity

Peripheral neuropathy is a side effect of long-term INH therapy that is believed to result from pyridoxine deficiency. In a 1954 case report, therapy with pyridoxine relieved the peripheral neuropathy of a patient taking INH. The neuropathy recurred after pyridoxine therapy was discontinued [24]. On a microscopic level, evaluation of patients with INH-associated peripheral neuropathy has shown wallerian degeneration [25]. Risk factors for INH-induced peripheral neuropathy include malnutrition, pregnancy, diabetes, alcoholism, and slow acetylator status. Because pyridoxal phosphate is removed by hemodialysis, patients receiving HD chronically are theoretically at risk for neurotoxicity [26]. In a study of 38 children receiving INH, 13% were found to be pyridoxine deficient, although none had definitive symptoms of the deficiency

[27]. Doses of INH greater than 6 mg/kg/day also are considered to place the patient at risk for peripheral neuropathy. Pellagra also may result from deficiency of pyridoxal phosphate. Optic neuritis is another recognized adverse effect of INH therapy [28, 29] and may be exacerbated by concomitant use of ethambutol, another antituberculous drug with established optic toxicity.

Although rhabdomyolysis has been reported in patients taking INH intermittently, it is primarily a consequence of seizure activity [30]. Other, less commonly reported adverse effects of INH include isolated fevers, rash, worsening of asthma symptoms, pancreatitis, red blood cell aplasia, and a lupus-like syndrome [31–39].

Hepatotoxicity in Chronic Use

One of the interesting properties of all hydrazines is the ability to cause hepatotoxicity, although attempts to quantify this burden are hampered by the small number of studies, varying definitions of hepatotoxicity, heterogeneous patient populations, and confounding causes of liver injury, such as concomitant hepatotoxic medications. Elevations of liver function tests are typically transient and normalize despite continued therapy with the drug, a phenomenon known as “adaptation”

[40]. Nonetheless, it is estimated that 20% of patients receiving INH develop an elevation in liver function tests [41, 42]. In contrast, other studies found incidences ranging from 0.15% to 0.6%, with a trend toward higher rates of hepatotoxicity in women [43–45]. In many of these studies, serial serum transaminases were not performed, and toxicity was defined on the basis of clinical findings only.

Elevations in liver transaminases can appear within the first 2 weeks of therapy to 6 months after initiation with most cases developing within the first 3 months of therapy. Some authors have recommended discontinuing the use of INH when transaminases exceed three times the normal values. Clinically, a patient with INH hepatotoxicity may voice vague digestive complaints (55%) or viral-like complaints (35%), according to one review comprising 114 patients [46]. A 1972 report described 2,321 patients who required INH prophylaxis, 19 of whom (mean age 49.4 years) developed clinical symptoms of hepatic injury, occurring within the first 2 months in 9 patients [47]. This attracted the attention of the US Public Health Service, which in 1972 undertook a surveillance study of 13,838 persons taking INH prophylaxis therapy and identified 8 deaths (0.06%). In the 21 cities examined, the rate of hepatotoxicity varied; 92 cases were determined to be probably related to INH, 82 cases were possibly related, and 22 cases had insufficient data [48]. These data also showed the higher incidence of hepatotoxicity in persons older than age 35 years and persons with daily alcohol intake. In 1983, the American Thoracic Society changed its recommendation for INH prophylaxis, recommending chemoprophylaxis for persons at increased risk of developing active tuberculosis and persons younger than 35 years. If patients are at high risk for developing tuberculosis and they are older than 35 years old, periodic liver function tests are recommended [49].

The fatality rate of patients with fulminant hepatitis has been reported to be 5% [48, 50]. There seems to be a higher mortality in women, particularly during pregnancy and in the postpartum period [51, 52]. Risk of hepatotoxicity also seems to increase with age and in patients on

combination therapy with INH and rifampin [45]; however, a hepatitis B carrier state does not seem to confer more risk [53]. Ethanol consumption is considered a significant factor by some authors; however, this is difficult to quantify in retrospective evaluations [48, 54]. Liver transplantation has provided rescue treatment in select cases of fulminant hepatitis [55, 56].

Since hepatotoxicity is thought to be at least in part due to directly toxic effects of acetylhydrazine, one of INH's metabolites, there has been considerable research focused on acetylation status, which is genetically determined and does not change with age. The slow acetylation phenotype is found in 50–60% of American whites and blacks, while the fast acetylator phenotype is found primarily in Japanese and Inuit populations. Slow acetylators exhibit longer elimination half-life and higher plasma concentrations of INH and acetylhydrazine, particularly if they are taking high INH doses (>10 mg/kg/day). Both acetylhydrazine and the nonacetylated metabolite, hydrazine, yield hepatotoxic intermediates [57, 58]. Although a preponderance of the literature has focused on these genetic determinants, more recent research has revealed a possible role for other mechanisms, such as activation of the immune system, disruption of endogenous metabolism, and mitochondrial dysfunction [59].

Food and Drug Interactions

Although reports of food and drug interactions with INH are infrequent, the potential for interactions does exist. INH weakly inhibits the enzyme monoamine oxidase (MAO) and is a congener of isocarboxazid, an early MAO inhibitor used as an antidepressant and antituberculosis agent. The typical drug and dietary precautions given to patients on MAO inhibitors generally are not expanded, however, to include INH. It is likely that because INH is only a weak inhibitor of MAO, patients often appear to tolerate the drug without dietary precautions. As an MAO inhibitor, however, INH decreases the metabolism of tyramine, present in some wines, cheeses, and soy products. Increased sensitivity to dietary

tyramine is associated with long-term INH administration and is manifested by flushing, palpitations, pruritus, headache, nausea, vomiting, and hypertension [60].

Reports of other notable drug interactions with INH have surfaced. A case of meperidine and INH in combination resulting in hypotension has been reported [61]. Caution has been advised when combining INH and tricyclic antidepressants [62, 63]. Aside from the weak MAO inhibition attributed to INH, it inhibits the metabolism of several benzodiazepines, phenytoin, carbamazepine, warfarin, and valproic acid [64, 65]. Rifampin administration may induce the formation of hepatotoxic hydrazine metabolites. Patients who are slow acetylators are considered to be at greater risk for hepatitis when taking both of these drugs [66]. Isoniazid also inhibits the enzyme diamine oxidase, which metabolizes histamine.

Some INH drug interactions are thought to result from INH-induced inhibition of the cytochrome isoenzyme CYP2E1 [67], the same enzyme responsible for metabolism of two of the world's most commonly consumed substances: acetaminophen and ethanol. Acetaminophen clearance has been shown to decrease by 15.2% when INH is given [68]. Paradoxically, INH not only inhibits but also induces CYP2E1. This is the basis of what seems to be an increased risk of hepatotoxicity in patients who take acetaminophen during INH therapy [69, 70].

Industrial Hydrazines

Industrial hydrazines have toxic effects similar to those of INH, including seizures and hepatotoxicity. Additionally, they can produce direct tissue damage. Hydrazines are corrosive to the skin, resulting in manifestations ranging from simple itching to severe burns. Solutions with hydrazine concentrations greater than 25% are likely to produce significant dermal injury. High ambient concentrations can lead to hydrazine vapor exposure with irritation of mucous membranes and eyes. Similarly, concentrated vapor exposure can result in irritation of the respiratory tract,

producing cough, shortness of breath, or pulmonary edema [71]. Combustion of hydrazines liberates nitrogen oxides, which can be toxic to the lung parenchyma. Methemoglobinemia (see ► Chap. 30, “Toxicant-Induced Hematologic Syndromes”) and hemolysis may occur after hydrazine exposures.

Diagnosis of Hydrazine Poisoning

Toxic exposures associated with seizures, metabolic acidosis, or both include cyanide, salicylates, tricyclic antidepressants, theophylline, iron, ibuprofen, cocaine, amphetamines, phencyclidine, ethylene glycol, and methanol. Ethanol/benzodiazepine withdrawal also should be considered in the differential diagnosis. Hyperglycemia and acetonuria should suggest the diagnosis of diabetic ketoacidosis, particularly if the history does not include seizure activity. Isoniazid overdose always should be considered in a patient with new onset of seizures of unknown etiology, particularly if the patient is from a tuberculosis-prone population. Generally the diagnosis is made clinically and based on the history of exposure. Laboratory testing usually cannot verify a diagnosis of INH poisoning within a clinically useful time frame. Serum transaminases at baseline and regular intervals are required to identify INH-induced hepatitis.

Treatment of Isoniazid and Hydrazines Poisoning

Skin and Eye Decontamination of Hydrazine Chemicals

Skin and eye decontamination for industrial hydrazine exposure is crucial because these agents are very corrosive. Skin decontamination focuses on administration of copious amounts of water and prompt removal of contaminated clothing, jewelry, watches, and shoes. If possible, decontamination should occur away from other contacts. The patient may be able to participate in decontamination by self-removal of clothing

and self-washing of the skin. If minimal vapor exposure has occurred in an asymptomatic patient, removal of clothing may be all that is required. If doubt exists about the extent of exposure, water decontamination is advisable. The concentration of the chemical also determines the hazard, but for most hospital and prehospital medical providers, that information may not be immediately available. Because hydrazine and monomethylhydrazine are flammable liquids, decontamination should take place away from any possible sources of ignition, e.g., electrical switches, radios, and other electronics. Eye decontamination consists of irrigation with large amounts of water, which may be facilitated by a Morgan lens after topical anesthesia. Because hydrazines are alkalis, the goal of ocular decontamination is to restore a constant pH of 7.0 to the conjunctival sac.

Medical Management

As with all overdoses, supportive care is crucial in the management of intoxication by INH or other hydrazine compounds, with close attention to vital signs, monitoring for early signs of cardiovascular collapse or airway compromise. Secure intravenous access is of particular importance because seizures may occur suddenly, although they are typically preceded by hyperreflexia or areflexia. Supplemental oxygen, fluid volume support, and maintenance of a patent airway are immediate priorities.

The clinician should consider carefully the risks of the various gastrointestinal decontamination methods versus their limited benefit, and these should not be used in a seizing patient due to the risk of aspiration. Activated charcoal, which has been shown to adsorb INH well, may be considered if appropriate [72]. There are no data, however, indicating that gastrointestinal decontamination alters outcome in these patients. The clinician should consider carefully the risks of GI decontamination methods versus limited data on efficacy. Activated charcoal should not be administered to a patient with seizures due to the risk of aspiration. Gastrointestinal

decontamination is discussed further in ► Chap. 3, “Therapeutic Approach to the Critically Poisoned Patient.”

In patients with profound metabolic acidosis, administration of intravenous sodium bicarbonate may be warranted. Sodium bicarbonate should not be used to correct metabolic acidosis in the absence of aggressive efforts to control seizure activity because most of the acidosis is caused by the neuromuscular hyperactivity that occurs with seizures. Rhabdomyolysis should be assessed by following serum creatine phosphokinase or urine myoglobin. In cases of severe rhabdomyolysis, urine alkalization to pH greater than 6.5 may be beneficial.

Indications for ICU Admission in Isoniazid and Related Hydrazines Poisoning

Prolonged or severe metabolic acidosis

Multiple seizures

Significant rhabdomyolysis

Depressed mental status

Hemodynamic instability

Seizures not easily controlled by pharmacologic interventions

Targeted Treatment

Pyridoxine is the mainstay for treating INH (or other hydrazine)-induced seizures, at a dose to match the estimated amount of INH ingested or to a maximum of 5 g (Grade II-3 evidence) [13, 17, 18, 23]. If the dose ingested is unknown, 5 g should be given. This dose may be repeated if needed [17]. The effects are usually dramatic and of quick onset; in one case series, 5 patients demonstrated cessation of seizures, correction of acidosis, and an improvement in mental status within two hours of receiving pyridoxine. Additionally, pyridoxine's effect appears to not be dependent on the time to onset of seizures or coma; it has been shown to prevent seizures if given before their onset, as well as to quickly reverse an INH-induced coma [18, 73].

The high doses of pyridoxine required for adequate therapy mean, unfortunately, that many

hospitals do not have adequate stores of it; it may have to be procured from other hospitals or pharmacies. In a survey of US hospitals with pediatric emergency medicine fellowships or emergency medicine residencies, immediate availability of the recommended 5-g dose was lacking for half of the institutions, and the dose was not kept in the emergency department in an even greater adult proportion of responding programs [74]. One pediatric case series found that the average delay to its administration was 5.8 h [6]. Areas where tuberculosis is relatively endemic should strongly consider keeping pyridoxine close at hand in the emergency department. Poison centers may also be a reference for obtaining information on antidote stockpiles.

Large doses of pyridoxine are not benign, although the toxic dose is not known [75]. A well-known case has been reported where 52 g of pyridoxine produced no adverse effects [17], which was echoed in a case series where 357 mg/kg produced no adverse effects [76]. Massive amounts of pyridoxine were tolerated well in human pharmacologic studies [77]. Severe peripheral neuropathies, some permanent, have been reported in very high short-term and high long-term pyridoxine dosing (0.5–2 g/day) [78, 79]. The clinical pharmacology of pyridoxine is discussed in ► Chap. 163, “Pyridoxine.”

Due to the INH's effect on GABA, it follows that drugs that increase GABA concentration, such as benzodiazepines and barbiturates, could also be of therapeutic benefit [80]. Although case reports suggest that monotherapy with these agents without pyridoxine can rarely provide full control of INH-induced seizures, they have been demonstrated to have a valuable additive effect when given in conjunction with pyridoxine. They also have the significant advantage of being readily available in most acute care settings.

Benzodiazepines have been well demonstrated to potentiate the effects of pyridoxine for INH-induced seizures; among these, diazepam is the most cited in case reports. Phenobarbital is also a rational choice for adjunctive therapy, although its induction of INH's metabolism into

toxic hydrazines has been cited as a potential disadvantage [81]. Thiopental, a short-acting barbiturate, has been used with success in a severe case of toxicity unresponsive to 40 mg IV diazepam and 1 g IV phenobarbital (Grade III evidence) [82].

Phenytoin, which exerts its anticonvulsant actions through affecting sodium channels rather than GABA receptors, is theoretically and empirically ineffective in the treatment of INH-induced seizures. Furthermore, INH is a potent inhibitor of phenytoin metabolism, hindering phenytoin's elimination. In both theory and practice, this has led to phenytoin toxicity [83], the signs of which (lethargy, nystagmus, and ataxia) would be difficult to perceive in a comatose patient [84].

Other Hydrazines

Reports of severe hydrazine and monomethylhydrazine poisoning in the medical literature are few compared with reports involving INH. However, the use of pyridoxine is recommended on theoretical grounds for seizures and coma in victims of serious industrial exposure to hydrazine or major exposures to gyromitrin-containing mushrooms. Because gram-for-gram dosing of pyridoxine may not be calculable in an occupationally exposed patient, the generally accepted empirical adult dosing for seizure control is 5 g administered intravenously as a bolus.

Hemodialysis

Hemodialysis is theoretically likely to enhance INH clearance based on its low degree of protein binding and relatively small volume of distribution. Hemodialysis is generally unnecessary, however, if aggressive supportive care, pyridoxine, and sodium bicarbonate are provided, especially given INH's short elimination half-life and the typically short duration of severe symptoms after INH overdose. Patients non-responsive to

the above outlined treatment, or without the ability to clear INH and its metabolites because of renal failure, could benefit from peritoneal dialysis or hemodialysis (Grade III evidence) [14, 85].

Criteria for ICU Discharge in Isoniazid and Related Hydrazines Poisoning

Resolution of metabolic acidosis and all seizure activity

Return to baseline mental status

Resolving rhabdomyolysis, if present

Common Errors in Isoniazid and Related Hydrazines Poisoning

Overaggressive pyridoxine therapy for prolonged periods

Failure to recognize coma as a toxic effect of overdose from isoniazid

Failure to recognize potential hazards of industrial hydrazines from a contaminated patient

Forgetting the usefulness of adjunctive benzodiazepine therapy in the treatment of seizures

Key Points in Isoniazid and Related Hydrazines Poisoning

1. Never use ipecac syrup.
2. Seizures are most likely to present within the first 3 h of ingestion.
3. Pyridoxine is the drug of choice for seizures.
4. Benzodiazepines may be useful as adjunctive therapy until sufficient pyridoxine is available.
5. Monitor renal function and hydration status if the patient develops multiple or prolonged seizures.
6. Use sodium bicarbonate therapy for metabolic acidosis that persists despite cessation of seizures.

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Rifampin

Rifampin is a macrocyclic antimicrobial agent synthetically derived from many generations of rifamycin B, a virtually inactive metabolite of *Streptomyces mediterranei*. In 1968, an active product was conceived, rifamycin SV, which showed activity against gram-positive organisms [1]. Rifampin, a hydrazone derivative of 3-formylrifamycin SV, is used today in various settings as a broad-spectrum agent against gram-positive organisms (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Neisseria meningitidis*, *Haemophilus influenzae*) and gram-negative organisms (*Escherichia coli*, *Klebsiella*, *Proteus*, *Pseudomonas*) [2]. More commonly, rifampin is used as a synergistic, bactericidal agent against tuberculous and non-tuberculous mycobacteria.

Clinical Pharmacology

The structure of rifampin is shown in Fig. 1.

Pharmacokinetics of Rifampin

Volume of distribution: 0.97–1.6 L/kg

Protein binding: 75–90 %

Mechanism of clearance:* 7 % renal

Active metabolites: 25-desacetylrifampin, 3-formylrifamycin

Methods to enhance clearance: multiple-dose activated charcoal

*Assumes normal renal function.

Pathophysiology

Rifampin binds to DNA-dependent RNA polymerase in bacteria and prevents initiation of messenger RNA synthesis in nonmammalian cells (Fig. 2) [3]. Rifampin induces CYP3A4, resulting in the increased metabolism of numerous drugs (Table 1). Of particular concern in the critical care setting is the increased metabolism (and decreased action) of anticoagulants and corticosteroids.

Clinical Presentation

Daily use of rifampin has few serious side effects. Red-orange discoloration of body fluids (e.g., urine, tears) is common with both therapeutic and toxic dosing, with increased incidence in a dose-dependent fashion [4]. Mild elevation of hepatic transaminases and cholestatic jaundice occur, especially when rifampin is used in combination with isoniazid, but symptomatic hepatitis or liver failure tends to be limited to elderly or undernourished patients and to patients with chronic liver disease [5, 6]. When rifampin is administered on an intermittent basis (once-weekly or twice-weekly dosing), or reintroduced after prolonged discontinuation, some patients experience a flu-like syndrome, including fever and chills, headache, malaise, and weakness with colitis and eosinophilia [7, 8]. Hemolytic anemia and thrombocytopenia also occur in these circumstances and may be antibody mediated. Acute renal failure has been reported, including rapidly

Fig. 1 Chemical structure of rifampin

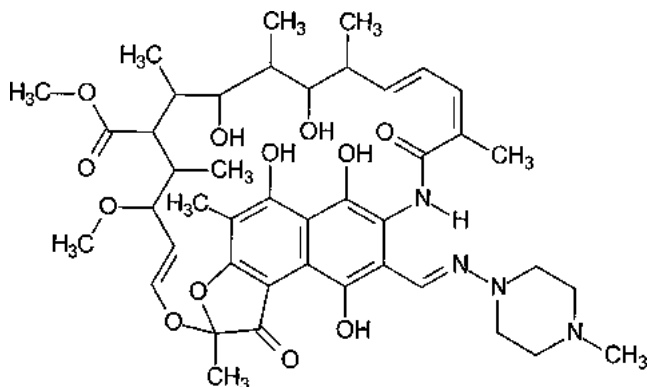


Fig. 2 Mechanism of rifampin action. The drug binds to the β -subunit of DNA-dependent RNA polymerase and inhibits initiation of (but not ongoing) RNA synthesis. (a) Drug is absent. (b) Drug is bound to the polymerase and distorts the conformation of the enzyme so that it cannot initiate a new chain (From Brody H, Larner J, Minneman KP, et al: *Human Pharmacology: Molecular to Clinical*, 3rd ed. St. Louis, Mosby, 1998, p 725, with permission.)

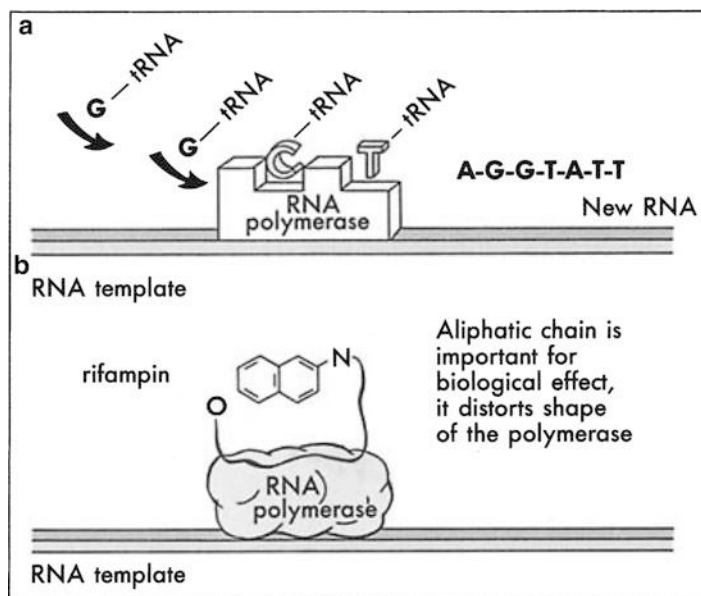


Table 1 Agents with increased metabolism during coadministration of rifampin

Benzodiazepines
β -blockers
Calcium channel blockers
Clofibrate
Corticosteroids
Dapsone
Fungicidal agents
Methadone
Oral contraceptives
Phenobarbital
Quinidine
Sulfonylureas
Theophylline
Warfarin
Lamotrigine
Reverse transcriptase inhibitors
HMG-CoA reductase inhibitors
HMG-CoA 3-hydroxy-3-methylglutaryl-coenzyme A

progressive glomerulonephritis, acute interstitial nephritis, and light-chain proteinuria [9]. The mechanism for renal failure may occur secondary to hemoglobinuria in association with intravascular hemolysis or mediated by rifampin-dependent IgG and IgM antibodies cross-reacting with the I antigen on tubular epithelium [10]. Rifampin-

induced lupus-like syndrome also has been reported when rifampin is used in combination with clarithromycin or ciprofloxacin and may involve autoantibody production [11]. Drowsiness and confusion have been observed in massive overdoses. Anaphylactoid reactions can occur with both therapeutic use and overdosage and may require management in a critical care setting.

Diagnosis

Rifampin serum concentrations are available; correlation with frequency or severity of toxicity is lacking. Determination of hepatic transaminases and fractionated bilirubin may be beneficial, especially when used in combination with isoniazid or other potential hepatotoxins or when used in the elderly. These laboratory parameters should be followed closely in symptomatic patients. There are no commercially available tests for the detection of rifampin-dependent antibodies [12].

Treatment

Discontinuation of rifampin usually is sufficient to correct mild elevations in hepatic transaminases, rifampin-induced renal failure, and

rifampin-induced flu-like syndrome [5, 10]. There are no formally validated or accepted general criteria for discontinuation, however. Red-orange skin discoloration is treated with simple cleansing [4]. In cases of acute liver failure, liver transplantation may be necessary [13, 14]. Supportive care is adequate in most patients with rifampin toxicity. There are no specific antidotes. Several other specific therapeutic interventions are described subsequently.

Indications for ICU Admission in Rifampin**Poisoning**

Severe anaphylactoid reaction

Fulminant hepatic failure

Acute renal failure requiring dialysis

Activated Charcoal

Single-dose activated charcoal may decrease absorption if large amounts of rifampin have been ingested and the charcoal can be administered in the first hour. However, there are no data indicating whether activated charcoal alters the outcome or clinical course after rifampin ingestion. Multiple-dose activated charcoal may increase rifampin clearance; however, improvement in clinical outcome has not been demonstrated and cannot be justified based on the existing data [15].

Extracorporeal Removal

Rifampin's high protein binding and large volume of distribution preclude elimination by extracorporeal removal.

Special Populations**Pediatric Patients**

There are no special considerations regarding rifampin in pediatric patients.

Pregnant Patients

Rifampin has been shown to cause fetal malformations in mice; clinical correlation in humans has not been reported. Rifampin is recommended therapy in pregnant females with active tuberculosis infection.

Elderly Patients

There is an increased incidence of hepatic and renal injury associated with rifampin in elderly patients [6, 9].

Chronic Liver Disease Patients

Patients with chronic liver disease are at increased risk for rifampin-induced hepatic failure [14].

Dapsone

Dapsone is a synthetic sulfone antimicrobial used for the prophylaxis of *Pneumocystis carinii* in immunocompromised patients with documented adverse reactions to trimethoprim-sulfamethoxazole [16]. Sulfones have experimental activity against many mycobacteria, as they are used clinically as a bacteriostatic agent in the treatment of *Mycobacterium leprae*, although drug resistance is increasing [17]. Occasionally, dapsone is used to treat chloroquine-resistant malaria, although resistance to dapsone therapy is increasing as well [18]. Dapsone is capable of suppressing neutrophil migration by blocking integrin-mediated adherence [19]. For this reason, it has been successful in the treatment of dermatologic disorders, such as dermatitis herpetiformis, pemphigus vulgaris, pyoderma gangrenosum, psoriasis, and systemic lupus erythematosus [20]. The often-touted use of dapsone as a treatment for the necrotic lesions caused by the brown recluse spider is poorly supported [21].

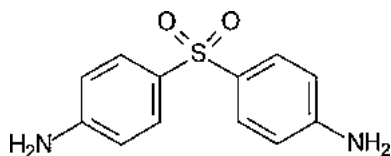


Fig. 3 Chemical structure of dapsone

Clinical Pharmacology

The structure of dapsone is shown in Fig. 3.

Pharmacokinetics

Volume of distribution: 1.0–1.5 L/kg

Protein binding: 70–90 %

Mechanism of clearance:* 15 % renal

Active metabolite: monoacetyldapsone

Methods to enhance clearance: multiple-dose
activated charcoal, charcoal hemoperfusion

*Assumes normal renal function.

Pathophysiology

Dapsone is a bacteriostatic antimicrobial agent that binds to dihydropteroate synthase, which catalyzes the conversion of para-aminobenzoic acid and pteridine into dihydropteroic acid in the first step of folic acid synthesis. Folic acid is essential for the formation of methionine, which is necessary for nucleic acid synthesis. Thus, bacteria that depend on intrinsic folic acid production are adversely affected by dapsone [18].

Dapsone causes oxidant stress to the hematologic system. Hemolysis and methemoglobinemia may occur either separately or together. Dapsone-derived free radicals, formed by the biotransformation of dapsone into free arylamines and hydroxylamines, bind to the red blood cell membrane and to hemoglobin, leading to the formation of precipitated, denatured proteins (Heinz bodies). Heinz bodies attach to red blood cell membranes, inducing affected erythrocytes to be destroyed by

the reticuloendothelial system [22]. Dapsone and other oxidants interact with the iron cation within hemoglobin as electron acceptors, thus oxidizing divalent iron (Fe^{2+}) to trivalent iron (Fe^{3+}) and inducing the formation of methemoglobin, which is unable to transport oxygen. Induction of methemoglobinemia shifts the oxygen-hemoglobin dissociation curve to the left, thus further impairing oxygen delivery to tissues. Although red blood cells carry a natural defense (reduced glutathione) against oxidizing agents, these stores can be depleted rapidly in cases of drug-induced hemolysis or methemoglobinemia, which may occur separately or together [23]. Oxidant stressors on erythrocytes are discussed in greater detail in ► Chap. 30, “Toxicant-Induced Hematologic Syndromes.”

Sulfhemoglobinemia also may be induced by dapsone. Sulfhemoglobin is incapable of carrying oxygen; however, the oxygen-hemoglobin dissociation curve is shifted to the right, which enhances overall oxygen delivery to tissues by remaining oxyhemoglobin [24].

Dapsone-induced maculopathy is presumed to occur secondary to the physical effects of red blood cell fragmentation in the vascular supply to the macular and perimacular regions of the eye, resulting in ischemic necrosis [25]. Dapsone-induced acute renal failure is thought to occur via a similar microvascular compromise [26]. The “sulfone syndrome” (described below) may be induced by antibodies directed toward the free arylamine and hydroxylamine metabolites of dapsone [26].

Clinical Presentation

Hemolysis and methemoglobinemia are the most well-described toxicities of dapsone. Although doses of greater than 200 mg/day are thought to be required to induce hemolysis in adults, the induction of methemoglobinemia seems to be a critical adverse effect of standard therapy. Hemolytic anemia may manifest with tachycardia, pallor, jaundice, hypoxia, acidemia, and shock.

Methemoglobinemia presents with cyanosis after blood methemoglobin concentration exceeds 1.5 g/dL. Excessive hemolysis and/or marked decrease in hemoglobin concentration may cause cyanosis to disappear.

The clinical presentation of dapsone-induced methemoglobinemia may occur immediately after exposure or may be delayed up to 3 days. Clinical effects may be prolonged and recurrent, owing to the drug's delayed peak (up to 20 h in overdose) and long half-life (30 h in therapeutic settings, up to 77 h in overdose) [27, 28]. Children younger than 4 years may express significantly higher methemoglobin concentration secondary to a relative deficiency in reduced nicotinic adenine dinucleotide (NADH)-dependent methemoglobin reductase [29], the enzyme responsible for reducing methemoglobin to hemoglobin.

The clinical presentation of sulfhemoglobinemia is generally similar to, but less severe than, that of methemoglobinemia. Both processes present with a falsely low pulse oximetry readings and normal arterial blood gas PO_2 . Patients with sulfhemoglobinemia rarely present with significant cyanosis, because the amount of sulfhemoglobin generated in most cases is less than 5 % of total hemoglobin [24].

Other nonspecific effects include nausea, vomiting, rashes, and psychosis. Controversial evidence suggests that dapsone may cause axonal degeneration, resulting in peripheral neuropathy [27]. Although dapsone is used as a treatment for leprosy, exacerbation of the condition has also been reported with therapy [17]. Agranulocytosis is a rare effect of dapsone therapy [30]. Also reported is the "sulfone (hypersensitivity) syndrome," which may develop approximately 2 months after starting long-term treatment with dapsone; methemoglobin and hemolytic anemia occur, accompanied by fever, exfoliative dermatitis, and fulminant hepatic necrosis with jaundice [31].

Diagnosis

Dapsone poisoning should be considered in any immunocompromised patient presenting with cyanosis or signs of hemodynamic instability.

Serum concentrations of dapsone are available but do not correlate with signs of toxicity [23]. Long half-life of dapsone and the gradual cumulative process of injury to red blood cells may delay signs of toxicity; patients may be asymptomatic for several hours before developing methemoglobinemia or hemolysis in overdose. In dapsone-induced hemolysis, hemoglobin concentrations may be low or normal, but the appearance of Heinz bodies on the peripheral blood smear may be an early indication of hemolysis. Reticulocyte count also may be elevated, but is typically delayed for several days [22]. During hemolysis, testing for glucose-6-phosphate dehydrogenase (G6PD) activity may not be clinically useful, because these patients have a predominance of young peripheral red blood cells with possibly normal G6PD activity [23]. In dapsone-induced methemoglobinemia, cooximetry can be used to measure methemoglobin concentrations but may read sulfhemoglobin falsely as methemoglobin. Most cooximeters are not designed to distinguish between methemoglobin and sulfhemoglobin [24]. Pulse oximetry is potentially misleading and should not be used alone as a diagnostic tool to assess the degree of tissue hypoxia; however, a low pulse oximetry reading that does not change with oxygen therapy should raise the suspicion of methemoglobinemia [32].

Treatment

Discontinuation of dapsone with subsequent observation usually is sufficient for most cases of mild dapsone-induced hemolytic anemia and methemoglobinemia. Normal bone marrow production typically compensates for mild red blood cell loss. Exchange or conventional (packed red blood cell) transfusion may be required in severe cases. Reduction of methemoglobin in red blood cells normally occurs predominantly via the action of NADH cytochrome- b_5 reductase. This mechanism decreases methemoglobin content by approximately 15 % per hour [33]. Slower endogenous detoxification rates may reflect intrinsic defects in cytochrome- b_5 reductase activity or ongoing production of

methemoglobinemia. Pulse oximetry typically shows falsely low measurements in the settings of sulfhemoglobinemia and methemoglobinemia [27]. Management of oxidant-induced hemolysis and methemoglobinemia is discussed in detail in ► Chap. 100, “Irritant and Toxic Pulmonary Injuries.”

Gastrointestinal Decontamination

Single-dose activated charcoal may decrease dapsone absorption if given within an hour of ingestion. However, there are no data indicating whether activated charcoal administration alters the outcome or clinical course after dapsone overdose.

Indications for ICU Admission in Dapsone Poisoning

Severe hemolysis or methemoglobinemia with secondary hypoxia, cardiovascular impairment, or shock
Renal failure requiring dialysis
Hepatic failure and/or presence of severe cutaneous involvement in the “sulfone syndrome”

Extracorporeal Removal

Hemodialysis is not likely to be of benefit because of dapsone’s high protein binding and large volume of distribution (see Table 1). Charcoal hemoperfusion may decrease the long half-life of dapsone in severe cases that do not respond to conventional treatment [34] (Grade III recommendation). There are no studies documenting improvement, however, in clinical outcome or hospital course with hemoperfusion.

Methylene Blue

Methylene blue’s antidotal action reflects its role as a cofactor for reduced nicotinic adenine dinucleotide phosphate (NADPH) methemoglobin

reductase. This enzyme, normally a minor contributor to methemoglobin reduction, uses products from the hexose monophosphate shunt as a source of electrons for the reduction of methemoglobin. The conversion of glucose-6-phosphate to phosphogluconate by G6PD in the first step of the pentose monophosphate shunt provides electrons for the conversion of NADP to NADPH. Methylene blue first is reduced to leukomethylene blue by electron donation from cellular NADPH stores. Leukomethylene blue, through the actions of NADPH methemoglobin reductase, donates these electrons to methemoglobin, reducing the Fe^{3+} in the heme group to the Fe^{2+} state and consequently reverting back to methylene blue (see ► Chap. 30, “Toxicant-Induced Hematologic Syndromes”). The typical dose of methylene blue is 1–2 mg/kg intravenously over 5–10 min [35]. This can be repeated, if necessary, although the author recommends waiting approximately 1 h unless the patient is unstable (Grade III recommendation). If cyanosis persists, one must consider ongoing methemoglobin production, G6PD deficiency, or sulfhemoglobinemia. There is no antidote for sulfhemoglobinemia.

Other Treatments

Multiple-dose activated charcoal may increase dapsone clearance, but improvement in clinical outcome has not been shown, and the data does not support its routine use. However, there is a role for multidose activated charcoal in patients with protected airways and who ingested a life-threatening amount of dapsone [15] (Grade III recommendation). Details on the administration of multidose activated charcoal are given in ► Chap. 3, “Therapeutic Approach to the Critically Poisoned Patient.” Severe methemoglobinemia and sulfhemoglobinemia unresponsive to conventional therapy may be treated with exchange transfusion [32] (Grade III recommendation). Sulfone syndrome responds to the cessation of dapsone use. The administration of systemic corticosteroids is advocated in case studies, although controlled trials documenting efficacy are lacking [27, 31].

Special Populations

Pediatric Patients

Dapsone doses of 100 mg (one tablet) in a child have been reported to cause hemolysis and methemoglobinemia [32].

Pregnant Patients

Studies documenting teratogenicity in humans are lacking. Dapsone is a possible cause of neural tube defects via impairment of the folate synthesis pathway. The author recommends that nursing mothers avoid dapsone due to the potential for hemolysis and methemoglobinemia in the infant.

Elderly Patients

There are no special considerations in elderly patients.

Patients with Glucose-6-Phosphate Dehydrogenase Deficiency

Patients with G6PD deficiency have a decreased red blood cell capacity to produce adequate levels of NADPH. NADPH is required to maintain appropriate stores of reduced glutathione, the red blood cell's primary defense against oxidants. G6PD-deficient patients are more susceptible to developing hemolysis and methemoglobinemia after dapsone administration. There may be an increased risk of hemolysis or methemoglobinemia induced by methylene blue administration because the antidote itself is a mild oxidant that competes for the same NADPH required for maintenance of glutathione stores [36]. If methylene blue is administered to a known or potentially G6PD-deficient patient, they should be monitored closely for hemolysis and worsening of methemoglobinemia. If any of these occur, methylene blue should be discontinued. Patients of African, South Asian, or Middle Eastern descent have a higher prevalence of G6PD deficiency. In a patient in

whom methylene blue is contraindicated on the basis of G6PD deficiency, exchange transfusion may be beneficial [32].

Vancomycin

Vancomycin is a complex glycopeptide antimicrobial agent derived from *Streptomyces orientalis* bacteria found in the soil in the Far East, used primarily as a parenteral agent against gram-positive bacterial infections, particularly resistant strains of *S. epidermidis* and *S. aureus*, and as a synergistic agent with aminoglycosides against resistant *Enterococcus*, viridans streptococci, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* [37]. Vancomycin is used orally in patients with pseudomembranous colitis secondary to *Clostridium difficile* [38] and in bone marrow transplant patients to maintain gastrointestinal sterility during transplantation [39].

Pharmacology and Pharmacokinetics

The structure of vancomycin is shown in Fig. 4.

Pharmacokinetics of Vancomycin

Volume of distribution: 0.11–0.39 L/kg

Protein binding: 30–55 %

Mechanism of clearance:* 79 % renal

Active metabolites: none

Methods to enhance clearance: hemodialysis, hemodiafiltration

*Assumes normal renal function

Pathophysiology of Therapeutic and Toxic Effects

Vancomycin inhibits cell wall synthesis in bacteria by binding to the D-alanyl-D-alanine moiety of cell wall precursors. Transpeptidase is unable to catalyze the linkage of D-alanine to glycine into the peptidoglycan chain, and cell wall synthesis

children, with a first-phase half-life ($t_{1/2\alpha}$) of 0.80 h and a second-phase half-life ($t_{1/2\beta}$) of 5.63 h. Serum vancomycin concentrations measured earlier than 4 h after a dose may not reflect post-distribution peak concentrations. Measured peak serum concentrations of vancomycin in children may not be predictive of toxicity [50, 51].

Treatment

Reducing the infusion rate and dilution prior to intravenous infusion may prevent the occurrence of red man syndrome. Concomitant or prior administration of diphenhydramine also has been effective [52]. Ototoxicity and nephrotoxicity are generally reversible with dose readjustment or discontinuation [53].

Gastrointestinal Decontamination

Vancomycin is poorly absorbed orally, so gastrointestinal decontamination is not necessary.

Indications for ICU Admission in Vancomycin Poisoning
Severe anaphylactoid reaction

Extracorporeal Removal

Hemodialysis can remove vancomycin effectively in patients with impaired renal function [50, 53]. Charcoal hemoperfusion has been implemented, but superiority over hemodialysis is not documented.

Special Populations

Pediatric Patients

Dosing intervals may need to be adjusted in neonates, secondary to relatively decreased clearance of vancomycin by neonatal kidneys. High vancomycin trough levels in neonates may necessitate twice-daily or once-daily dosing [50].

Pregnant Patients

Because vancomycin appears in cord blood, it is presumed to raise the risk of fetal ototoxicity and nephrotoxicity, but clinical correlation has not been documented.

Elderly Patients

Dosing intervals may need to be adjusted for hepatic or renal insufficiency.

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Part XI

Medications: Hematologic

Sean M. Bryant and Jerrold B. Leikin

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Iron poisoning is a well-respected historically significant toxicologic problem. In the pediatric population, iron has been regarded as the most fatal of all toxic exposures [1]. Fortunately because of regulations on packaging in the USA and other countries, serious poisonings have declined [2]. Visible warning labels and dispensing of tablets and capsules in blister packages have limited the dose a child might consume. For example, iron poisoning fatalities in children less than 6 years of age in the USA decreased from 29 in 10 years before the packaging regulation to one death in the 5 years after [3]. Total reported exposures in children younger than 6 years old have declined from 3026 in 1995 to 2139 in 2013 in the USA [4, 5]. The other patient population at risk is suicidal patients, most notably women of childbearing age with access to iron products. In 2013, 28% of iron exposures in the USA occurred in patients who were teenagers or older [5]. Despite the significant toxic potential of iron, death and serious sequelae are uncommon because most exposures are unintentional and involve negligible amounts.

Biochemistry and Pharmacokinetics of Iron

The primary functions of iron include participation in oxygen delivery as a constituent of hemoglobin and myoglobin and production of adenosine triphosphate via oxidative phosphorylation. It is a highly reactive ion and functions in

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many enzymatic biochemical processes. Iron is a transition metal (number 26 on the periodic table) with an atomic weight of 55.8. It is the second most prevalent metal and the fourth most abundant element in the Earth’s crust.

Iron has interesting and unique properties related to its absorption, distribution, and elimination. Intestinal iron absorption is a complex and active process that occurs mostly in the proximal small intestine [6]. Most dietary inorganic iron is in the ferric (Fe³⁺) form. Iron in the gut lumen may form complexes with other constituents, forming insoluble nonbioavailable products. Mucin, at the cell surface of the enterocyte, binds iron, preparing it for integrin-mediated systemic absorption. Mobilferrin binds the iron within the enterocyte cytoplasm. Iron eventually is transferred to paraferitin and ferritin before entering the bloodstream complexed to transferrin. Because the proportion of iron absorbed decreases with increasing dose [7], an overdosed patient absorbs disproportionately less of the dose ingested than the amount absorbed when iron is given therapeutically. In healthy adults, 2–10% of dietary iron eventually is absorbed. A canine model showed that only 14% of a fatal oral dose of ferrous sulfate was absorbed [8]. In contrast, people with iron deficiency may absorb 80–90% of an oral dose [9].

After oral ingestion, iron either remains in the gut mucosa and eventually is excreted in the stool or is transported in the blood by transferrin primarily to the bone marrow for hemoglobin synthesis. The liver differs from the rest of the body, including the placenta, in that its capacity for iron uptake is unlimited [10, 11]. This first-pass effect is chiefly responsible for the decrease in plasma iron concentration after ingestion. These concepts support early iron concentration determination – 4–6 h after ingestion – as being useful after overdose, followed by the use of clinical parameters to predict prognosis after 8–12 h.

Pharmacokinetics of Iron
<i>Volume of distribution:</i> preparation dependent
<i>Protein binding:</i> 99%
<i>Mechanisms of clearance:</i> renal, fecal, skin desquamation
<i>Active metabolites:</i> none
<i>Method to enhance clearance:</i> deferoxamine

Table 1 Iron content of common preparations

Preparation	Elemental iron (%)
Ferrous gluconate	12
Ferrous sulfate ^a	20
Ferric chloride ^a	20
Ferrous chloride	28
Ferrous fumarate	33

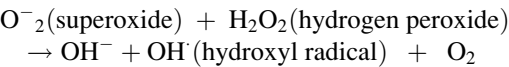
^aHydrated

Total iron body stores are approximately 3–4 g in adults, with 70% distributed in hemoglobin in the ferrous (Fe²⁺) state. It is also present in ferritin and hemosiderin, which are stored in the liver, spleen, and bone marrow. About 1–2 mg of iron is eliminated daily through urinary and fecal excretion and skin desquamation. The usually recommended daily allowance of iron is 10 mg in men, 18 mg in women, and 30–60 mg in women during pregnancy and lactation.

The amount of elemental iron ingested is the key factor in predicting the severity of toxicity. Common preparations contain various percentages of elemental iron (Table 1). Although 20 mg/kg of elemental iron or less may result in gastric upset, potentially severe toxicity may follow ingestions of 40–60 mg/kg, and potentially lethal doses range from 200–250 mg/kg [12]. In toddlers, doses of 1.0 g of elemental iron have been reported to be fatal [13, 14].

Pathophysiology

Iron, an essential element for bodily functions, must come from exogenous sources. It functions as a catalyst for the Haber–Weiss reaction resulting in the generation of a highly reactive hydroxyl radical:



Iron-induced lipid peroxidation, resulting from the production of these free radicals, is the primary mechanism of iron poisoning [15, 16]. These free radicals induce local injury, most notably in locations of high iron concentrations, such

as the intestine and liver. The primary intracellular target of toxicity is the mitochondria, resulting in destruction of cristae and loss of respiratory enzyme activity in a manner that is consistent with suppression of cellular respiration, without uncoupling oxidative phosphorylation [17, 18]. Iron primarily affects the gastrointestinal (GI) tract, liver, cardiovascular system, and acid–base status of the poisoned patient. Because of the high metabolic activity of the heart, the myocardial mitochondria are particularly vulnerable to the toxic effects of iron poisoning.

Gastrointestinal

The initial GI symptoms after iron overdose are due to a direct local irritant effect. With large ingestions, free radical-induced lipid peroxidation causes secondary injury to the GI tract. There is a significant risk of hemorrhage and ulcerative damage from segmental gut infarction in children and adults [19]. Because of this damage, there is a concern for emerging GI bleeding during the first 48–72 h after ingestion. Delayed effects, classically stricture formation, may occur weeks after exposure. Gastric outlet obstruction occurring 2–4 weeks post exposure is a consequence of healing and scarring of the gut. A high index of suspicion for gastric outlet obstruction exists in patients who have continual vomiting 2–3 weeks after the exposure incident or an onset of emesis after a symptom-free period [20]. Although pyloric injury is most common, lesions may occur at any location in the gut [19].

Hepatic

Characteristic hemorrhagic hepatic periportal necrosis has been described in autopsy reports of patients who died from iron poisoning and in experimental animal models [21]. Other reports indicate similar damage in patients and animal models [22]. After absorption, iron is transported to the liver via the portal vein, where carrier-mediated uptake into zone 1 acinar cells eventually becomes overwhelmed. Microscopic

observations indicate that hepatic mitochondrial injury within zone 1 is the primary location and mechanism of toxicity [23]. Because liver cell regeneration is a zone 1 function, injury to this region is of particular significance. After this injury, acute hepatic failure with elevated hepatic transaminases and serum ammonia concentrations, jaundice, steatosis, and hepatic coma may occur [24].

Coagulopathy

Coagulopathy resulting from severe iron poisoning is characteristically biphasic [25]. A dose-related reversible coagulopathy has been demonstrated in a canine model and in humans [25]. This condition results from a transient, early, dose-dependent depression of coagulation factors V, VII, IX, and X, causing a prolongation of the partial thromboplastin time [25]. An *in vitro* study revealed that free iron may inhibit the formation of thrombin and subsequently thrombin's ability to form fibrin from fibrinogen [26]. This early coagulopathy may subside as iron levels decrease; however, severe poisoning may result in a second phase (2–7 days postingestion) of progressive dysfunction of coagulation secondary to hepatotoxicity.

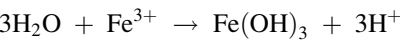
Cardiovascular

Circulatory shock is the most common cause of death after severe iron poisoning. In addition to hypovolemia resulting from GI volume loss and hemorrhage, an early distributive shock has been shown in animal models [27, 28]. The myocardium has high metabolic activity, and acute iron-induced cardiotoxicity may be mediated by free radical generation [29]. In addition to interference with mitochondrial adenosine triphosphate production, membrane lipid peroxidation may interfere directly with slow-channel calcium exchange or the activity of the sarcoplasmic reticulum [30]. Diminished myocardial contractility is an important component of the pathogenesis of iron-induced shock [31]. Cardiac failure may

occur 1 to several days after a major iron overdose [32]. The pathophysiology of shock resulting from iron overdose is therefore multifactorial.

Metabolic

Metabolic acidosis is a prominent feature of iron poisoning. As discussed earlier, circulatory shock is one pathophysiologic mechanism responsible for this metabolic acidosis. Acidosis also may occur, however, in the absence of cardiovascular instability [33]. As described previously, iron poisoning suppresses cellular respiration. A principal mechanism by which iron causes a metabolic acidosis occurs, however, after absorption of a quantity of iron that exceeds the binding capacity of transferrin. When unbound iron is present, its hydrolysis liberates three unbuffered protons from each ferric ion [34]:



Other Pathophysiologic Effects

Altered mental status may occur after large ingestions and is presumably multifactorial and related to the factors described earlier. Although no major direct toxicity is clinically apparent and relevant to the central nervous system, kidney, lung, and spleen, autopsy studies have revealed elevated iron concentrations in these organ systems and in the stomach, liver, and small intestine [35].

Clinical Presentation and Life-Threatening Complications

Classically, iron poisoning is described as occurring in five clinical stages (Table 2). Not all patients manifest this “textbook” presentation after overdose, however, and there is the potential for considerable temporal variability and overlap among these stages. The severity and stage of a particular patient’s poisoning should be determined by his or her individual clinical evaluation, not simply by the number of hours postingestion.

Table 2 Stages of iron poisoning

Stage	Typical
I – Gastrointestinal	30 min–6 h
II – Quiescent	2–8 h
III – Shock	2–48 h
IV – Hepatotoxicity	12–24 h
V – Gut obstruction	1–7 weeks

Stage I (the GI stage) of poisoning is encountered almost universally in all patients after significant iron ingestion. Epigastric pain, nausea, vomiting, and diarrhea typically occur immediately after ingestion in cases of overdose [36]. Hypotension, pallor, and lethargy often occur, resulting from vasodilation, intravascular volume loss, gastroenteritis, hematemesis, melena, or hematochezia secondary to the local effects of iron on the gut mucosa. Metabolic acidosis may occur at this stage. If acidosis is significant, blood volume loss occurs, resulting in circulatory shock, and the patient may progress directly into stage III.

Stage II is the time period associated with iron poisoning that is described as the latent or *quiescent* phase. During this interval, which may begin several hours postingestion, the patient is in transition between the resolution of direct GI signs and symptoms and the appearance of overt systemic toxicity. This often-described quiescent phase may reflect failure to recognize ongoing clinical toxicity. The patient may have fewer overt GI manifestations during this time, lulling the clinician into an underestimation of the true seriousness of the ingestion [12]. During this apparently clinically benign period, however, patients may have a worsening metabolic acidosis if volume resuscitation is not sufficient to restore adequate tissue perfusion. Patients who progress through stage I with resolution of clinical manifestations and without development of a metabolic acidosis are unlikely to develop more serious systemic iron toxicity.

Stage III, the shock stage of iron toxicity, is defined by evidence of insufficient tissue perfusion and shock and typically becomes manifest at least several hours after ingestion. Most deaths due to iron poisoning occur in this stage. Multiple

organ dysfunction as a result of cellular toxicity and inadequate perfusion may result in hypotension, tachycardia, altered mental status, seizures, coma, worsening metabolic acidosis, renal failure, hepatic dysfunction, coagulopathy, myocardial depression, pulmonary edema, and mesenteric ischemia [37]. Hepatotoxicity often is evident during stage III; however, this may also occur without concomitant shock.

Stage IV (hepatotoxicity) is not a universal finding in iron-poisoned patients [38]. The onset of this stage typically occurs 12–24 h post-ingestion but may occur 2–3 days after overdose [24]. Hepatic dysfunction is a poor prognostic sign when present [25], with hemorrhage secondary to coagulopathy often contributing to patient demise [25].

The hallmark of stage V is gastric outlet obstruction; however, fortunately this stage rarely occurs [12]. Local mucosal injury may lead to development of stricture formation several weeks postingestion [19]. Although the classic site of obstruction is the pylorus, segmental injury may occur along the length of the gut [19]. The diagnosis of gastric outlet obstruction should be considered in patients with persistent vomiting, achlorhydria, abdominal pain, and distention more than 1 week postingestion.

Iron poisoning may present in any of the abovementioned discrete stages, may skip specific stages, or may reflect overlap between or among different stages. The stages of toxicity are used as a guide to the conceptualization of the natural course of iron poisoning rather than as a consistently predictable sequence of events.

Diagnosis

The diagnosis of iron toxicity may be evident based on a history of ingestion and corresponding signs of iron toxicity. Any pediatric ingestion over 40 mg/kg (or 6.5 ml syrup/kg) should be assessed for iron toxicity. GI symptoms are present within 1 hr of ingestion in virtually all patients with significant iron ingestions [39]. Tachycardia may also be an early sign of iron toxicity. If no history of iron ingestion is

offered, however, the differential diagnosis includes other medical and surgical reasons for the varied manifestations of iron poisoning. Other poisonings to consider include those involving mercuric chloride, salicylates, pesticides, arsenic, and colchicine.

All patients with known or suspected iron overdose should receive an X-ray of the abdomen to evaluate for radiopaque tablets [40, 41]. Large overdoses of tablets can be visualized in the GI tract, helping to verify historical features and guide management with GI decontamination. If the patient ingested a liquid preparation, the abdominal film typically is unrevealing [41]. Pediatric multivitamins containing iron have such a low iron content that X-rays after ingestion of these also typically are negative [42]. Clinically significant poisoning after ingestion of iron-containing multivitamins is virtually nonexistent [43]. Negative abdominal plain films after iron ingestion also may be explained by dissolution of an ingested solid formulation; this is especially true in patients who present late after ingestion.

We recommend that a serum iron concentration be obtained on presentation and then every 1–2 h to monitor the symptomatic patient further. When a clear downward trend of serum iron concentrations is established, it is no longer necessary to follow this parameter. Iron concentrations less than 500 µg/dL (<90 µmol/L) at 4–6 h postingestion typically are not associated with significant systemic toxicity [44, 45]. Systemic toxicity often is seen with iron concentrations of 500–1000 µg/dL (90–180 µmol/L), with levels greater than 1000 µg/dL (>180 µmol/L) being associated with severe life-threatening illness.

A high anion gap metabolic acidosis accompanying an elevated lactate concentration should be assumed to be an indication of serious toxicity from iron ingestion [37] and the need for chelation therapy. Because of the possibility of hemorrhage and multiple-organ toxicity, a complete blood count, hepatic and renal function tests, electrolytes, and coagulation profile should be obtained. The presence of hemorrhage or anemia should prompt preparation for possible blood product replacement.

Historically, other laboratory findings, such as leukocytosis (white blood cell count $>15,000/\text{mm}^3$) and hyperglycemia (serum glucose $>150 \text{ mg/dL}$ [8.25 mmol/L]), were used as indices of severity of iron poisoning [46]. These parameters have not been shown to be sensitive predictors of toxicity, however [44, 47]. Likewise, a serum iron concentration greater than the total iron-binding capacity, previously considered an indication for chelation therapy, has not been found to be a reliable index of toxicity and no longer is recommended [44, 48, 49].

Indications for ICU Admission in Iron Poisoning

Significant acidemia (arterial pH < 7.3)

Shock/neurodynamic compromise

Altered mental status

Gastrointestinal hemorrhage

Serum iron concentration $>500 \text{ }\mu\text{g/dL}$ ($90 \text{ }\mu\text{mol/L}$)

Radiologic evidence of a significant gastrointestinal burden of iron ($>50 \text{ mg}$ of elemental iron/kg)

Deferoxamine administration

Significant hepatic dysfunction

Treatment

Patients with significant iron ingestions or severe systemic toxicity warrant monitoring in the intensive care unit. Secure intravenous access, fluid volume replacement, oxygen supplementation, cardiac monitoring, and airway and ventilatory support are essential to the initial management of the critically iron-poisoned patient. Bedside ultrasound of the heart and inferior vena cava or even a Swan–Ganz catheter may be indicated for monitoring of hemodynamic parameters during treatment and to differentiate between cardiogenic and distributive shock.

Limiting the absorption of ingested iron should be considered during initial management. Gastric lavage is an alternative form of gastric emptying. This procedure also has serious risks, has not proved to change outcome after iron ingestion, and should be considered only in life-threatening ingestions presenting within 1 h [50, 52]. Even in these circumstances, the efficacy of gastric lavage is questionable. Activated charcoal has not been shown to be effective in adsorbing iron [53]. Consideration of activated charcoal is appropriate when coingestion of noniron products has occurred. However, activated charcoal has not been shown to alter the outcome in poisoned patients. It may decrease drug absorption if given within 1 hr of ingestion.

The mainstay of GI decontamination for iron poisoning generally is considered to be whole-bowel irrigation [54, 55] (Grade III evidence). This procedure has not been shown, however, to alter the clinical course or outcome of iron-poisoned patients [54]. Whole-bowel irrigation theoretically is important only in patients with abdominal radiographs revealing substantial numbers of radiopaque iron tablets. Whole-bowel irrigation is reviewed in ► [Chap. 3, “Therapeutic Approach to the Critically Poisoned Patient.”](#) Although whole-bowel irrigation usually is limited to several hours of administration, one case report of multiple iron tablet persistence in the gut described a 5-day course of whole-bowel irrigation [56]. This case also may be taken as evidence, however, of the lack of efficacy of this technique. Subsequent abdominal X-rays can help guide the clearance of iron from the gut.

Gastroenterologic or surgical consultation may be warranted if a concretion or bezoar is shown or suspected; this is unusual, however. Concretions may be present when iron levels continue to rise. Usually there is a downward trend toward clearing by 6–24 h postingestion. Several authors reported successful gastrotomy and removal of massive amounts of iron tablets not amenable to removal by less invasive measures [57–61]. Clinical evidence of bowel obstruction may indicate intestinal necrosis. Lifesaving small-bowel resection was performed 24 h after presentation in a patient with a distended abdomen and signs of peritonitis [62].

Other attempts at reducing iron absorption from the gut have been undertaken without success. Oral bicarbonate, phosphate, and magnesium hydroxide have been used with the idea that if they formed insoluble complexes with iron, this would decrease absorption. Except for one canine study, data from in vitro and in vivo studies do not support bicarbonate or phosphate use, and these treatments may result in severe electrolyte imbalances [63–66]. Animal and human volunteer studies revealed a reduction in iron absorption after the administration of magnesium hydroxide; however, it does not affect absorption in humans after large overdoses of iron [67–69]. At present, there are insufficient data to support routine use of these modalities in human iron poisoning. Oral deferoxamine was shown in one prospective human study to reduce GI absorption of ferrous sulfate when mixed as a slurry with activated charcoal. Ferrioxamine, the deferoxamine–iron complex, has been shown to be lethal in animals after it is absorbed, but ferrioxamine absorption is reduced when activated charcoal is coadministered with deferoxamine [70, 71]. Because of the concerns about the toxicity of ferrioxamine, oral deferoxamine is not recommended.

Iron-induced hepatotoxicity should be regarded as a marker of severe toxicity. Because the periportal area is most affected, iron-induced hepatotoxicity portends a much poorer overall prognosis than similar insults caused by other toxicants [22]. In light of this, hepatic monitoring and treatment of organ failure or coagulopathy are indicated. Profound liver dysfunction warrants surgical consultation for possible transplantation. Correction of electrolyte and glucose abnormalities also may be crucial to patient outcome.

Hemodialysis should be used on a supportive basis for acute renal failure, usually developing in response to circulatory shock. Iron is not amenable to hemodialysis, even though the iron–deferoxamine complex can be cleared in this manner [72, 73].

Deferoxamine, derived from *Streptomyces pilosus*, is the specific chelator of choice for iron

poisoning. After complexing with free iron (iron not found in hemoglobin, myoglobin, ferritin, or transferrin), it forms ferrioxamine, which is excreted in the urine [3]. Deferoxamine also has been shown to promote clearance of intracellular iron effectively. Ferrioxamine produces a reddish-brown or “vin rose” appearance to the urine [74]. Deferoxamine challenge tests have been used in the past as a marker of iron excretion, as indicated by this urine color change. This test no longer is recommended; however, it is one may observe a urine sample before treatment and follow the course of color change during chelation. A total of 100 mg of deferoxamine mesylate chelates only approximately 8.5 mg of ferric iron. Although the use of deferoxamine in severe iron poisoning is considered the standard of care, there are no published controlled studies that show a change in outcome with this treatment [75, 76] (Grade III evidence).

Deferoxamine treatment should be administered as early as possible after poisoning. Although not formally validated, the data reviewed earlier in this chapter that suggest logical indications for deferoxamine treatment are indications of moderate-to-severe systemic toxicity, such as shock, GI bleeding, lethargy, and central nervous system depression. Metabolic acidosis is a reliable marker of cellular iron toxicity [37] and therefore should be considered to be an indication for initiating treatment. There is no rationale for withholding chelation while waiting for a serum iron concentration in significantly poisoned patients. An iron level 4–6 h postingestion of equal to or greater than 500 µg/dL (≥ 90 µmol/L) also is considered to be an indication for treatment [44, 45] (Grade III recommendation). After 12 h, the serum iron concentration is of no practical significance because the systemic burden has been distributed from the vascular compartment into tissues.

Recommendations for deferoxamine dosing are based primarily on case reports and have been established arbitrarily [76]. The intravenous route of administration is preferred. Intramuscular administration was used previously for less severe poisoning, but it is not reliable. Titration of the intravenous infusion up to a rate of 15 mg/kg/h

should be initiated while the patient is carefully monitored for adverse effects, including rate-related hypotension [77, 78]. Histamine release may underlie the hypotension and the flushing and urticaria that may be observed during deferoxamine infusion [78]. Administration of deferoxamine at even higher rates has been shown to be safe in ill patients and in patients on long-term hemodialysis [79]. There have been recommendations to administer less than 6–8 g/day even though 16 g/day has been given without concomitant side effects [80]. It is vital to maintain adequate intravenous fluid volume replacement during deferoxamine therapy to protect against the development of acute renal failure [81]. Finally, continuous infusions for greater than 24 h have been reported to be associated with adult respiratory distress syndrome; however, this interpretation is confounded by the presence of adult respiratory distress syndrome in severe iron poisoning, even in untreated cases [82–84]. A reasonable end point of therapy is cessation of anion gap metabolic acidosis and resolution of systemic toxicity. Because the deferoxamine–iron complex acts as a siderophore for the growth of *Yersinia enterocolitica*, sepsis after chelation therapy is a risk, and appropriate antimicrobial therapy should be initiated if high-grade fever, diarrhea, or signs of peritonitis develop. Appropriate antibiotics include aminoglycosides, trimethoprim–sulfamethoxazole, third-generation cephalosporins, doxycycline, or fluoroquinolones. If abscesses occur, they will require surgical drainage. Chelation therapy should not be suspended during antibiotic therapy [85–87]. It is important to determine serum iron concentrations by atomic absorption spectroscopy in deferoxamine-treated patients because deferoxamine interferes with most other routine assays.

Criteria for ICU Discharge in Iron Poisoning

Absence of acidemia or other systemic disorders (e.g., coagulopathy)
Hemodynamic stability
Clear sensorium
Declining serum iron concentrations

Special Populations

Pregnant Patients

Iron overdose has occurred with relative frequency in pregnant patients [88]. There is no proven teratogenic risk of deferoxamine therapy during pregnancy, and fetal loss may occur as a result of severe maternal iron toxicity. Similar to trauma and many other diseases of pregnant women, the goals are to stabilize and treat the mother, which stabilizes and treats the fetus. The approach to a pregnant patient is no different from that for any other patient; other than that if the fetus is potentially viable, it should be monitored for distress. Although spontaneous abortion, preterm delivery, and malformations are potential sequelae of treatment in severe iron poisoning, several cases reported successful use of deferoxamine in pregnancy [89–92]. Whole-bowel irrigation has been used successfully in the first trimester to treat an iron overdose [93]. One report described a postnatal fatality in a 30-year-old woman who was treated with deferoxamine 1 day after ingestion and successfully delivered a healthy infant 2 weeks before experiencing lethal multiple organ dysfunction [94]. The placenta serves as the fetus's barrier to systemic iron overload and associated toxicity. This concept is supported in an ovine model [11]. Deferoxamine may cross the placenta when the mother is treated for toxicity [89]. Harm to the fetus from deferoxamine use in pregnancy is referenced [11, 91] yet not supported by the actual evidence. Cases describe first-trimester use of deferoxamine in women with chronic overload without subsequent fetal abnormalities [95, 96]. Based on this deferoxamine therapy should not be withheld out of concern for the fetus. Appropriately treating the mother is tantamount to treating the fetus.

Parenteral Iron Infusions

Intravenous iron therapy is indicated in patients who (1) are hemodialysis dependent with iron

deficiency anemia, (2) have gastrointestinal mal-
adies such as Crohn's disease or a history of
gastric resection or bypass, or (3) are losing iron
from blood sources at higher rates than oral iron
can be tolerated. While isolated parenteral iron
toxicity requiring deferoxamine therapy is not
reported, iron infusions can result in infusion
reactions. Infusion reactions are considered
hypersensitivity reactions and patients at risk
include previous reactions, rapid infusion
rates, multiple drug reactions, severe atopy, and
possibly severe inflammatory diseases [97].
There exists controversy whether or not
these reactions are always true IgE mediated in
all cases. Iron dextran has historically thought to
be linked to anaphylactoid reactions compared
to iron gluconate and sucrose [98]. Complement
activation-related pseudo-allergy triggered
by iron nanoparticles is probably a more frequent
pathogenetic mechanism in acute reactions
to current formulations of intravenous iron
than is an immunological IgE-mediated
response [97].

Management of these reactions is therefore
recognition and discontinuation of the infusion.
Current consensus would still recommend intra-
venous fluids and corticosteroids for moderate
reactions and potentially supplemental oxygen,
epinephrine, and a nebulized beta-2 agonist for
more severe reactions [99].

Common Errors in Iron Poisoning

Withholding deferoxamine in an ill
patient while waiting for a serum iron
concentration

Withholding deferoxamine in a pregnant
patient who meets criteria for treatment

Assessing a patient in stage II of toxicity as
improved or fully recovered

Relying on leukocytosis and hyperglyce-
mia to predict prognosis or guide therapy

Using total iron-binding capacity or a chela-
tion challenge test to indicate need for
deferoxamine

Administering deferoxamine to patients
who exhibit only direct gastrointestinal toxicity

Key Points in Iron Poisoning

1. Estimate total iron ingested based on the elemental dose and not the weight of the salt.
2. Serum iron concentrations beyond 12 h after ingestion are of no benefit.
3. The end point of deferoxamine therapy is guided best by clinical stability of the patient and cessation of acidemia.
4. Fluid hydration is crucial during deferoxamine administration to help prevent acute renal failure.
5. Pregnant patients are approached in the same way and aggressively as nonpregnant patients.

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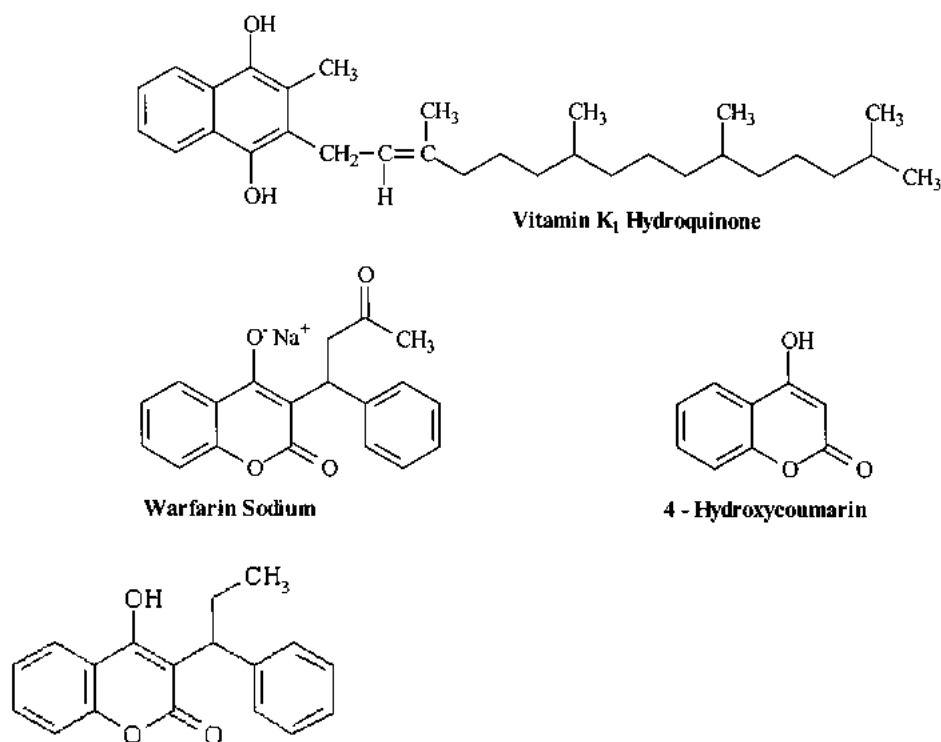
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In the 1920s, a hemorrhagic disorder of cattle feeding on spoiled clover silage was recognized. Studies of “sweet clover disease” led to the isolation in 1939 of dicumarol (bishydroxycoumarin), the first oral anticoagulant drug. A more potent synthetic derivative, 3-(α -acetonylbenzyl)-4-hydroxycoumarin, was produced in 1948 and named warfarin, after the Wisconsin Alumni Research Foundation. Warfarin initially was used mostly as a rodenticide because of concerns of unacceptable toxicity. Then in 1951, an army inductee uneventfully survived a massive overdose of a warfarin rodenticide. Warfarin also was used to treat President Eisenhower after a heart attack in 1955, contributing to its general acceptance as a therapeutic drug. Although not used in the United States, phenprocoumon (Fig. 1) and acenocoumarol are used in other parts of the world. These three drugs are 4-hydroxycoumarin derivatives with nonpolar carbon substituents at the 3 position. Indane-1,3-dione oral anticoagulants are available but are used infrequently therapeutically. Many rat populations have become resistant to warfarin, leading to the use of “superwarfarins” (see ► Chap. 95, “Rodenticides”) since the 1970s. These rodenticides have higher potencies and considerably longer half-lives than warfarin and the other therapeutic vitamin K antagonists (VKA).

Recently, several novel oral anticoagulants (NOACs) have been developed. These include direct activated factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) and the direct

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Phenprocoumon

Fig. 1 Chemical structures of oral anticoagulant compounds

thrombin (II) inhibitor dabigatran. These anticoagulants are prescribed with fixed dosing and do not need regular monitoring. They are marketed to have improved characteristics including less food and drug interactions, faster onset of action, and shorter half-lives of elimination.

Pharmacokinetics

The pharmacokinetics of available oral anticoagulants are listed in Table 1 [1–6]. S-Warfarin, the more potent enantiomer, undergoes metabolism by cytochrome P-450 2C9 (CYP2C9), with an elimination half-life ranging from 0.5 to 3 days. CYP2C9 and vitamin K epoxide reductase subunit 1 polymorphisms explain the variation in half-life and individual sensitivities to warfarin doses

required to reach therapeutic anticoagulation [1, 2]. Apixaban, rivaroxaban, and edoxaban are substrates of p-glycoprotein; edoxaban and dabigatran have active metabolites. Most of the NOACs are primarily renally eliminated.

Pathophysiology

Vitamin K Antagonists

Warfarin and other vitamin K antagonists interfere with the production of functional clotting factors. The vitamin K-dependent factors (factors II, VII, IX, and X and the anticoagulant factors protein C and protein S) undergo post-translational γ -carboxylation at several glutamate residues, necessary for binding calcium

Table 1 Pharmacokinetics of oral anticoagulants

Vitamin K antagonists					
	Tmax (hrs)	Protein binding (%)	Volume of distribution	Metabolism	Mechanism of elimination, half-life (hrs)
Warfarin	2–8	99	0.14 L/kg	CYP2C9	Renal, 0.5–3 days
Direct Xa inhibitors					
Apixaban	1.5–4	87	21–61 L	CYP3A4	Fecal/renal, 6.8–12
Edoxaban	1–2	55	107 L	Minimal hepatic	Bile/renal, 5.5–10.5
Rivaroxaban	2–4	92–95	50 L	Hepatic	Hepatic/renal, 5–11
Direct thrombin (IIa) inhibitor					
Dabigatran	1–6	35	50–70 L	Hepatic	Renal, 12–17

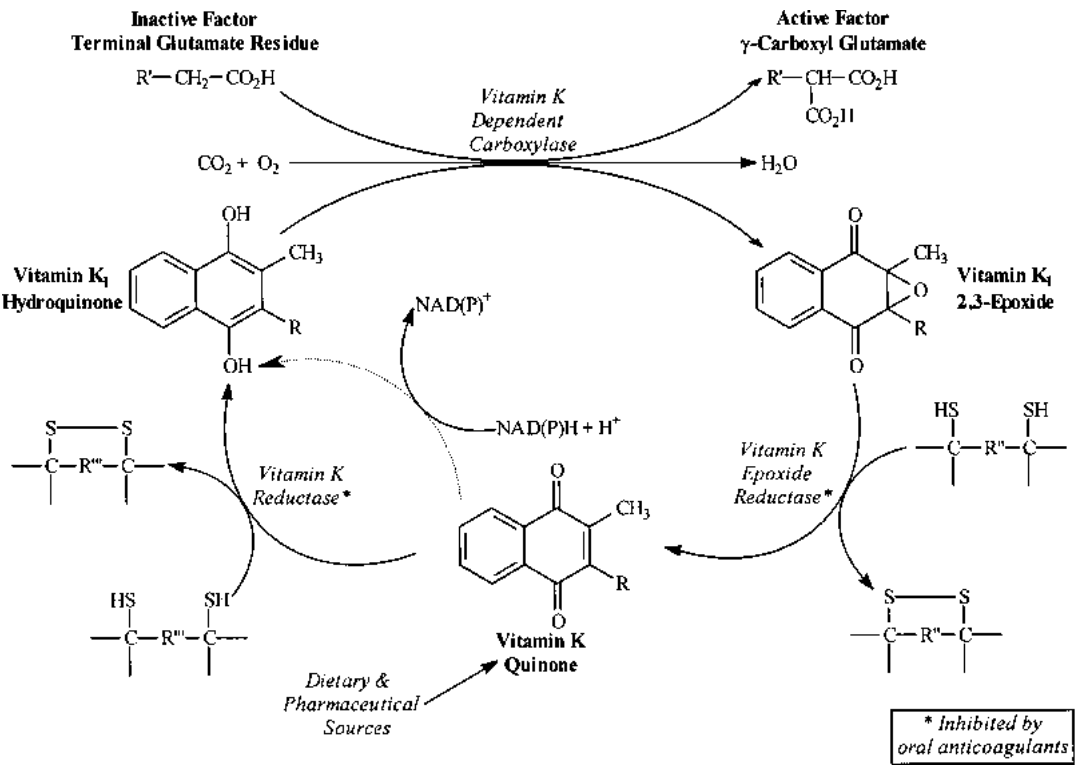


Fig. 2 Mechanism of action of the oral anticoagulants

ions involved in establishing a functional clotting cascade. This carboxylation step oxidizes the fully reduced, active vitamin K₁ (vitamin K hydroquinone) to vitamin K₁ 2,3-epoxide (Fig. 2). Regenerating the active form of vitamin K occurs continuously in normal subjects. The epoxide first is reduced to a quinone, then to the

hydroquinone; both of these reducing steps are inhibited by warfarin. Supplemental vitamin K₁ can be administered and is metabolized to the hydroquinone form in a reduced nicotinamide adenine dinucleotide phosphate-dependent step not inhibited by anticoagulants, resulting in active clotting factor synthesis. In the presence

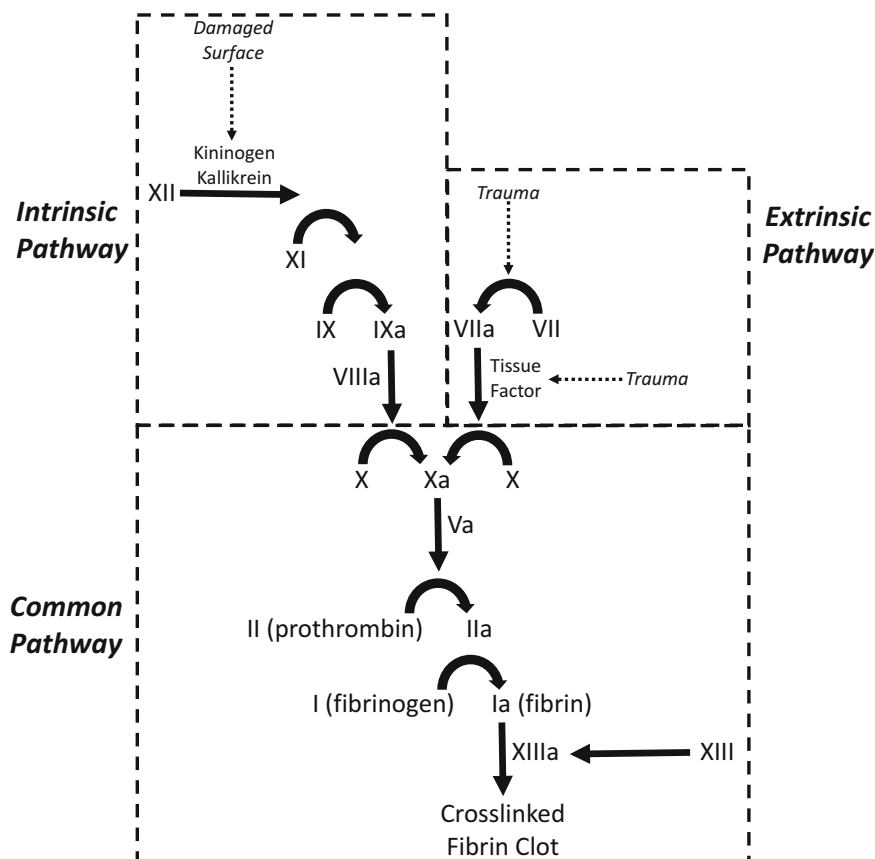


Fig. 3 Coagulation cascade (a = active form)

of warfarin, however, the inactive, epoxide form of vitamin K accumulates and cannot be reduced to the active form.

Novel Oral Anticoagulants

Unlike warfarin, which interferes with coagulation factor production, the NOACs disrupt clotting further down the coagulation cascade, primarily interfering with thrombus formation. Apixaban, edoxaban, and rivaroxaban selectively inhibit activated clotting factor Xa, decreasing activation of prothrombin to thrombin. Prothrombinase activity is also inhibited. Dabigatran and its active metabolites, acyl glucuronides, are competitive direct inhibitors of thrombin, inhibiting both free and clot-bound thrombin as well as thrombin-induced platelet aggregation (Fig. 3).

Clinical Presentation, Diagnosis, and Treatment

Vitamin K Antagonists

Chronic Toxicity

Most articles about warfarin “overdose” actually refer to chronic, often asymptomatic, supratherapeutic dosing and not to acute, intentional ingestions. As expected, the worse the coagulopathy, the higher the risk. In all patients taking warfarin for therapeutic purposes, the overall frequency of bleeding is 7.6 to 16.5 events per 100 patient-years, and frequency of major or life-threatening bleeds is 1.3 to 2.7 events per 100 patient years. The risk of an acute bleeding event within a 48-h period increases from 1 in 4000, for an international

normalized ratio (INR) between 2 and 2.9, to 1 in 100, for an INR of 7 or greater [7]. Gastrointestinal bleeding is the most common type, whereas intracranial bleeding carries the highest risk of mortality.

Indications for ICU Admission in All Oral**Anticoagulant Poisoning**

Oral anticoagulant-induced coagulopathy associated with

Intracranial hemorrhage

Gastrointestinal hemorrhage

Other clinically significant bleeding

Intentional overdose of oral anticoagulant drugs

The ideal management of chronic warfarin toxicity is unclear because most studies have been retrospective, have been of poor quality, and have had interstudy variance in treatment groups and doses. Notwithstanding these limitations, the American College of Chest Physicians (ACCP) has published consensus treatment guidelines [8, 9]. Over the last several years, similar guidelines have recommended conservative treatment of overanticoagulated patients, with less reliance on active interventions in stable patients [10]. However, compliance with these guidelines are varied [11].

According to ACCP guidelines, in the absence of clinically significant bleeding, patients with an INR less than 5 should have warfarin withheld and resumed when a therapeutic INR is reached. For INR values of 5–9, warfarin is held for one or two doses and resumed when a therapeutic INR is achieved or warfarin is held for one dose and 1 to 2.5 mg vitamin K₁ (phytonadione) is given orally. When an INR is greater than 9, warfarin is held and the patient is given 3–5 mg of vitamin K₁ orally. Twenty-four hours after vitamin K₁ is given by any route to patients with asymptomatic coagulopathy after chronic, therapeutic dosing, the reduction in INR is comparable: 47–86% for oral administration, 25–67% for subcutaneous administration, 40–75% for intravenous administration versus only 21–42% for simply discontinuing warfarin [12]. At 48 h, INR

reduction was similar for vitamin K doses greater than 2 mg for both oral and intravenous administration [13].

The American College of Chest Physicians recommendations are more aggressive when rapid reversal of coagulopathy is indicated. These recommendations specify that if surgery is planned and the INR is between 5 and 9, warfarin should be held and the patient given 2–4 mg of vitamin K₁ orally about 24 h before the procedure. Additional vitamin K₁, 1–2 mg orally, may be given if necessary. If the INR is greater than 20 or the patient is experiencing serious bleeding, vitamin K₁, 10 mg, should be given by slow intravenous infusion and may be repeated every 12 h as needed. If immediate reversal of coagulopathy is indicated (e.g., intracranial bleed, hemodynamically significant gastrointestinal hemorrhage), intravenous infusion of four-factor prothrombin complex concentrate or fresh frozen plasma is indicated. Warfarin resistance can be induced by administering excessive vitamin K₁, and patients may require heparinization temporarily if continued therapeutic anticoagulation is desired.

Criteria for ICU Discharge in Oral VKA Poisoning

Absence of clinically significant bleeding

Laboratory values stable for at least 12 (preferably 24) hours

Prothrombin time/international normalized ratio

Hemoglobin

Acute Overdose

In the absence of a positive or suggestive history, evidence supporting the diagnosis of warfarin overdose is summarized in Table 2. Since warfarin is not detected by most commonly used urine or plasma drug screens, elevations in prothrombin times should be a significant clue. However, peak elevations in prothrombin times will be delayed after acute overdose [14]. Patients not chronically anticoagulated typically exhibit a rise in the INR more than 12 h after ingestion, earliest

Table 2 Diagnostic clues to oral VKA overdose

Prolongation of prothrombin time out of proportion to activated partial thromboplastin time (both may be unmeasurable in severe overdoses)
Coagulopathy that responds, at least temporarily, to vitamin K ₁
Selective decreased activity of vitamin K-dependent factors – factors II, VII, IX, and X; protein C; and protein S (antigenic levels should be normal)

at 16 h [15]. Treatment of warfarin toxicity should be easier than for the anticoagulant rodenticides, mostly owing to their shorter half-lives. Patients who have intentionally ingested long-acting superwarfarins may require doses of vitamin K of 100 mg for as long as 6 months [16] (Grade III recommendation). In contrast, most patients with acute warfarin overdose require less than 1 week of therapy [17].

Reported treatments for acute warfarin overdose are varied. An asymptomatic toddler who ingested 45 to 50 mg warfarin sodium 20 min earlier was treated with activated charcoal and daily prothrombin time monitoring [14]. When the prothrombin time increased from 11.8 s (baseline) to 18 s on day 3, the toddler was given 2.5 mg of intramuscular vitamin K₁ daily for 3 days. It is debatable whether this treatment was necessary, because no bleeding complications occurred. Administering vitamin K when not clinically indicated may impair the ability to accurately follow the degree of anticoagulation. Adults with acute VKA overdoses typically present after coagulopathy has developed. Various coagulation products in addition to vitamin K have been used when urgent/emergent warfarin reversal is needed. A man presenting with bruising, gingival bleeding, and hematuria 1 day after ingesting 2000 mg of warfarin and injecting 250,000 units of heparin subcutaneously was treated successfully with intravenous prothrombin complex concentrate and several 20-mg intravenous doses of vitamin K [18]. Other cases of acute warfarin overdose have been managed with infusions of fresh frozen plasma, which seems especially helpful in cases in which maintaining therapeutic anticoagulation

is desirable [19]. A comparison of outcomes in patients requiring urgent warfarin reversal found that four-factor PCC had a faster reversal with lower red blood cell transfusion requirements and fewer adverse events than frozen plasma [20]. (Grade II-3 evidence)

Oral activated charcoal can be considered in patients presenting within an hour after acute warfarin ingestion based on the theoretical possibility of reducing drug absorption. While this treatment may decrease warfarin absorption, there are no data indicating that such therapy alters outcome in these patients. Acute gastrointestinal bleeding is a relative contraindication to charcoal because it may obscure endoscopic evaluation. Oral cholestyramine may increase clearance by interrupting enterohepatic circulation (Grade III evidence). Cholestyramine (4 g three times a day) reduced the half-life of single-dose intravenous warfarin from 1.98 ± 0.48 days to 1.34 ± 0.46 days ($P < 0.001$) in human volunteers [21]. In a case report of oral warfarin overdose, cholestyramine (4 g four times a day) decreased warfarin elimination half-life from 53 h to 33 h [22]. While it may decrease elimination half-life and can be considered for treatment after acute overdose, it has not been shown to decrease bleeding risk or decrease hospital length of stay.

Key Points in the Management of Acute VKA Overdose

1. Prothrombin time peaks in 0.5–4.5 days – do not be falsely reassured by minimal prothrombin time prolongation early after ingestion.
2. Gastrointestinal decontamination with activated charcoal or cholestyramine may be beneficial.
3. Vitamin K orally or intravenously reverses coagulopathy; dosing every 4–8 h may be required (in contrast to treating excessive coagulopathy after therapeutic doses).
4. Four-factor prothrombin complex concentrates (50 IU/kg), if unavailable then Fresh frozen plasma (15 mL/kg), should be used to treat potentially life-threatening bleeding – may need to be repeated.

Novel Oral Anticoagulants

Acute overdoses of NOACs are rarely reported and clinical experience is limited. In a review of dabigatran exposures reported to regional poison centers, severe outcomes from dabigatran exposures were not common, occurring in approximately 5% of cases [23]. Another single poison center review of dabigatran and rivaroxaban exposures demonstrated acute massive self-harm ingestions can lead to abnormal coagulation studies but only mild bleeding. Low-dose ingestions and pediatric ingestions were unlikely to lead to adverse effects, and significant hemorrhage only occurred in chronic therapeutic dosing [24]. A meta-analysis evaluated risk factors for bleeding with NOACs and identified that the highest risk factors were age and concomitant use of antiplatelet drug therapy [25]. Additionally, renal impairment in elderly patients has been identified as a risk factor for bleeding on dabigatran [26]. Reported adverse effects to many of the NOACs are GI upset, gastritis, and gastrointestinal bleeding. Dabigatran contains tartaric acid which can lead to dyspepsia and gastritis. Initial clinical trials of direct Xa inhibitors and thrombin inhibitors demonstrated dabigatran had an increased risk for GI bleeding when compared to warfarin (overall RR of 1.28, CI 1.05–1.56) [27]. Conversely, subsequent retrospective cohort reviews did not find an increased risk of GI bleed except in patients over 65 years of age, renal or cardiovascular comorbidities, previous *H. pylori* infections, alcohol use, antiplatelet therapy, and digoxin use [28, 29].

Although there are many pro-hemostatic products available in the event of an acute hemorrhage, unfortunately none of them have clearly been shown to completely reverse anticoagulation or change morbidity or mortality associated from a bleed attributed to the NOACs.

Direct Xa Inhibitors

Unlike warfarin, there are no readily available commercial laboratory coagulation values that can accurately assess the degree of anticoagulation for the NOACs. For most direct Xa inhibitors, partial thromboplastin time (PTT)

will not be significantly affected or will have variability between assays. Prothrombin time (PT) can be used as a qualitative measurement for rivaroxaban and the other Xa inhibitors but poorly reflects the intensity of anticoagulation [27]. Chromogenic antifactor Xa assays were initially designed for indirect, antithrombin-dependent factor Xa inhibitors (heparins) but is the best available quantitative measurement for direct Xa inhibitors [30–32]. However, unlike low-molecular weight heparins, chromogenic antifactor Xa assays may be difficult to clinically interpret as therapeutic ranges for direct Xa inhibitors have not been established for all assays.

Activated charcoal can be considered in recent acute ingestions but, similar to warfarin, may interfere with endoscopy if needed for a gastrointestinal bleed. Activated charcoal decreased the elimination half-life of apixaban from 13.4 h to 5 h when administered at 2 or 6 h post dose [33]. In both activated and nonactivated four-factor PCC and factor VII-corrected coagulation parameters in healthy human subjects who received therapeutic doses of rivaroxaban, but did not reduce blood loss in rabbit models with apixaban or rivaroxaban (there is limited human data for apixaban and edoxaban) [34–41], cryoprecipitate, fresh frozen plasma, or vitamin K are unlikely to have clinical benefit and have not shown to have significant reversal. Despite renal clearance, apixaban and rivaroxaban are highly protein bound and are unlikely to have significant clearance via hemodialysis. Edoxaban is also not amenable to dialysis.

Direct Thrombin Inhibitors

Direct thrombin inhibitors will not significantly change PT and international normalized ratio (INR). Dabigatran will affect activated PTT (aPTT) values, but this will plateau at concentrations ≥ 200 ng/ml, or 1.4–1.8 times normal [42]. Thus, aPTT will have poor correlation with a high degree of anticoagulation but could potentially be used as a qualitative measure. Ecarin clotting time (ECT) and dilute thrombin time (dTT), or hemocot thrombin inhibitor assay, are

the best coagulation parameters to evaluate the anticoagulation effects of dabigatran [42]. ECT is an assay for assessing the effect of direct thrombin inhibition and can be used to concentrations less than 300 ng/ml. Thrombin time (TT) measures the polymerization of fibrinogen to fibrin in the presence of thrombin. Since TT was demonstrated to be too sensitive, dilute TT has been used to quantify the anticoagulation effects of dabigatran. Similar to chromogenic factor Xa assays, ECT and dTT are not readily available at many institutions.

Similar to warfarin and direct Xa inhibitors, activated charcoal can be considered in the setting of an acute ingestion but may have limited clinical utility outside of a recent acute ingestion since it is rapidly absorbed and may interfere with endoscopy in the setting of a gastrointestinal bleed. Activated four-factor PCC and factor VII appeared to achieve the best reversal of coagulation parameters (exogenous thrombin potential and lag time) in humans and have also demonstrated reduced bleeding time, but not blood loss, in animals models [41, 43] (Grade III evidence). No significant change in INR and aPTT was noted after fresh frozen plasma or vitamin K. With characteristics including small molecular size, low protein binding, and significant renal clearance, dabigatran is amendable to conventional hemodialysis and continuous veno-venous hemodiafiltration [44–47]. Case reports of patients with end-stage renal disease on hemodialysis demonstrated clearance of over 60% after 2–4 h [44–46]. Redistribution after hemodialysis has also been described [47]. Despite being amendable to extracorporeal removal, the use of these measures may not be practical. The amount of time to prepare a patient for extracorporeal therapy, in addition to placing a dialysis catheter, can be difficult in a patient with acute life-threatening hemorrhage from dabigatran. Extracorporeal therapy may be considered as an adjunct therapy in a significant bleed, large ingestion, or in the setting of renal failure; however, this should not delay more immediate treatment measures for acute hemorrhage.

Key Points in the Management of Acute NOAC Overdose

1. Chromogenic antifactor Xa assay is the best available quantitative measurement for direct Xa inhibitors.
2. Ecarin clotting time (ECT) or dilute thrombin time (dTT) is the most sensitive coagulation parameter for direct thrombin inhibitors.
3. Gastrointestinal decontamination with activated charcoal may be beneficial.
4. Activated four-factor Prothrombin complex concentrates (50 IU/kg) or activated Factor VII should be used to treat potentially life-threatening bleeding.
5. Idarucimab can be used to treat moderate bleeding from dabigatran.
6. Extracorporeal therapy may be considered as an adjunct therapy in dabigatran toxicity in the setting of significant bleed, large ingestion, or renal failure

Future Antidotes for NOACs

With inconsistent results from readily available pro-hemostatic blood products, specific antidotes are being developed for NOACs and are under clinical trials [48]. Andexanet-alfa is a Fab antibody fragment which is a truncated form of an enzymatically inactive factor Xa and binds and reverses the anticoagulant action of the factor Xa inhibitors. Animal models demonstrate reduced bleeding, and phase I/II studies show correction of laboratory coagulation parameters [49, 50]. Aripazine is another reversal agent originally developed as a reversal agent for heparin and fondaparinux that has shown to have some activity against factor Xa inhibitors and direct thrombin inhibitors. However, it is unclear if it truly reverses the anticoagulant or acts as a procoagulant [41]. Idarucizumab is a recently FDA-approved antibody for reversal of bleeding from dabigatran and is discussed in Anticoagulation Reversal Agents [51, 52].

Anticoagulation Reversal Agents

Vitamin K₁

Vitamin K₁ is an antidote for warfarin toxicity, although it does not reverse enzyme inhibition in the vitamin K cycle (see Fig. 2). Rather, supplemental vitamin K₁ bypasses the inhibited enzymes, allowing for production of active clotting factors. Vitamin K₁ may be administered orally, subcutaneously, or intravenously. The optimal dose and route of vitamin K₁ has not been established [12]. The intravenous route is most predictable but occasionally is associated with anaphylactoid reactions; intravenous vitamin K₁ should be given at a rate not exceeding 5 mg/min, although some have suggested 1 mg/min. [31]

Regardless of route, vitamin K₁ does not have immediate effects, and significant bleeding can be treated with blood products. In massive acute warfarin overdose, three to five daily doses of vitamin K₁ may be necessary, owing to the latter's short plasma half-life [53]. With chronic warfarin toxicity, a single dose often is sufficient.

Common Errors in the Management of Acute Oral Anticoagulant Overdose

Relying on negative urine drug screen to exclude ingestion

Failing to recognize that the coagulopathy may not peak for several days for VKA

Giving only a single dose of vitamin K₁ when some patients require vitamin K₁ doses several times daily

Relying on conventional coagulation measures (PT, INR, PTT) to evaluate the degree of anticoagulation from NOACs.

Coagulation Factors

Patients with life-threatening bleeding require rapid reversal of coagulopathy. Fresh frozen plasma (FFP) generally is administered at a dose of 15 mL/kg. Repeat dosing may be necessary

because coagulation factor half-lives are in the range of several hours. Because many patients receiving warfarin have underlying cardiopulmonary disease, fluid overload is a concern with repeat fresh frozen plasma dosing.

Coagulation factor concentrates also may be used. PCC contains either 3 factors (factors II, IX, and X with dosage based on factor IX content), 4 factors (II, VII, IX, and X), or 4 factors with activated factor VII. Doses of 12 IU/kg have been used in moderate coagulopathy, although 50 IU/kg has been given in the most serious cases, such as intracranial hemorrhage [53] (Grade III recommendation). If only the three-factor concentrate is used, an infusion of factor VII concentrate (25–30 IU/kg) or FFP may be added. Normal coagulation is achieved more rapidly with PCC infusion than with fresh frozen plasma [20, 54, 55] (Grade II-3 evidence). Maintenance therapy with supplemental vitamin K₁ still is necessary when using blood products for VKA because the effects are temporary. Activated factor VII was developed for the treatment of bleeding in hemophilia patients with inhibitors against factors VIII or IX but has been used to achieve hemostasis by activating the extrinsic pathway of the coagulation cascade.

Idarucizumab

Idarucizumab is an intravenous monoclonal antibody fragment available for the reversal of moderate bleeding from dabigatran [51, 52]. Clinical trials (RE-VERSE AD phase III multinational study) show idarucizumab normalized ECC and dTT in 89–98% of patients receiving dabigatran [51, 52] (Grade II-2 evidence). It is recommended to administer a fixed dose of 5 g (in the clinical trial 2.5 g given twice separated by no more than 15 min was used), which is expected to reverse all bound and unbound dabigatran for concentrations up to 99th percentile concentrations of patients enrolled in the Randomized Evaluation of Long-Term Anticoagulation Therapy (Re-LY) trial. It is a 1:1 binding, and the reversal is immediate and sustained for at least 12 h. The half-life of idarucizumab may be prolonged in patients with renal failure.

Drug Interactions with Oral Anticoagulants

Warfarin

As a result of several unfavorable pharmacologic properties of the VKAs, great potential exists for life-threatening interactions with other drugs and foods. First, the VKAs possess a narrow therapeutic index; small changes in drug dosing, metabolism, or distribution can alter coagulability radically. The coumarins are highly bound to serum albumin, and drugs competing for binding to this protein cause an increased free fraction, resulting in enhanced coagulopathy. Coumarin metabolism depends on the activity of several CYP enzymes. Agents that inhibit this metabolism may induce hemorrhage, whereas metabolism inducers may result in loss of effective anticoagulation. The R and S stereoisomers of warfarin are metabolized by different, but overlapping, sets of CYP isoenzymes. The more potent S-warfarin is metabolized primarily by CYP2C9 and to a lesser degree by CYP3A4; R-warfarin is metabolized primarily by CYP1A2 and by CYP3A4 and CYP2C19. Even when the aforementioned issues are tightly controlled, dietary intake of vitamin K can vary, making therapeutic dosing difficult.

Systematic review of reported warfarin-drug interactions found that the drugs listed in Table 3 were considered probable or highly probable to potentiate warfarin. Drugs considered probable or highly probable to reduce warfarin's action are listed in Table 4.

Acetaminophen's apparent potentiation of warfarin's effect has important potential clinical implications. Because of the antiplatelet effects of aspirin and other nonsteroidal anti-inflammatory drugs, physicians often recommend acetaminophen for patients taking warfarin. A few patients taking both of these drugs develop prolonged prothrombin times unaccounted for by warfarin alone. A potential mechanism for this interaction is acetaminophen competitively inhibiting warfarin metabolism or vitamin K carboxylase [1].

Several drugs impair vitamin K metabolism even in the absence of VKAs. Drugs with such a

Table 3 Drugs likely to have clinically significant interactions with warfarin: agents likely to cause potentiation

Acetaminophen
Amiodarone
Anabolic steroids
Aspirin
Chloral hydrate
Cimetidine
Ciprofloxacin
Clofibrate
Co-trimoxazole
Dextropropoxyphene
Disulfiram
Erythromycin
Ethanol (if liver disease is present)
Fluconazole
Influenza vaccines
Isoniazid
Itraconazole
Metronidazole
Miconazole
Omeprazole
Phenylbutazone
Phenytoin
Piroxicam
Propafenone
Propranolol
Quinidine
Simvastatin
Sulfipyrazole
Tamoxifen
Tetracycline

Table 4 Drugs likely to have clinically significant interactions with warfarin: agents likely to cause lessening of warfarin's effect

Barbiturates
Carbamazepine
Chlordiazepoxide
Cholestyramine
Diets or enteral feeds high in vitamin K content (including green leafy vegetables, avocados, and green tea) [13]
Griseofulvin
Nafcillin
Rifampin
Sucralfate

warfarin-like effect include cephalosporin antibiotics with *N*-methyl-thiotetrazole side chains (cefamandole, moxalactam, cefoperazone, cefazolin, cefazedone) and salicylates. Aspirin may induce bleeding with an additive effect to that of warfarin and by a synergistic effect through platelet inhibition.

Novel Oral Anticoagulants

A marketed advantage of therapeutic use of NOACs compared with VKAs is fewer drug interactions; however, drug interactions are not completely absent. Rivaroxaban and apixaban are substrates for p-glycoprotein and CYP3A4 [3, 5]. Thus concomitant use of CYP 3A4 inducers or inhibitors can affect plasma concentrations such as HIV protease inhibitors, azole antifungal agents, macrolide antibiotics, rifampin, phenytoin, St. John's wort, and carbamazepine. Dabigatran and edoxaban are also substrates for p-glycoprotein, thus inducers such as rifampin and St John's wort can decrease dabigatran concentrations [4, 6]. P-glycoprotein inhibitors such as amiodarone, cyclosporine, verapamil, and antifungals may increase plasma dabigatran and edoxaban concentrations.

Nonhemorrhagic Complications of VKA

VKAs are associated with several adverse effects unrelated to their therapeutic effect. Nonhemorrhagic complications include warfarin skin necrosis, the "purple toes syndrome," hepatitis, and warfarin embryopathy.

Warfarin Skin Necrosis

Skin necrosis occurs in 1 in 10,000 of patients taking VKAs, with a female:male ratio of 1:4 [56]. Most reported cases have occurred in association with warfarin, although it may occur with any of the coumarin-derived VKAs. The usual presentation is the rapid development of painful,

well-localized hemorrhagic or erythematous skin lesions 3–5 days after initiating VKA therapy (Fig. 4). Occasionally, these lesions are heralded by paresthesias or a pressure-like sensation and poorly demarcated erythema. The lesions become edematous, producing a peau d'orange effect, and may develop petechiae and hemorrhagic bullae. The affected areas develop full-thickness skin necrosis, form eschars, and eventually slough. Small lesions can heal by granulation, but larger lesions usually require surgical débridement, skin grafting, or amputation, depending on their extent.

Warfarin skin necrosis occurs more commonly in obese, middle-aged women, with the preponderance of lesions found on the skin of the breast, buttock, and thigh [56]. Other risk factors include perimenopausal, viral infections, hepatic disease and drug interactions. Patients with protein C or protein S deficiencies and patients receiving large oral loading doses also are at higher risk [55]. These associations suggest that the high-risk population is already prone to thrombosis and that the early hypercoagulable state occurring with oral anticoagulants (due to decreased protein C and S activities) may precipitate localized thrombosis.

Although late treatment clearly consists of wound care and surgical intervention, early treatment before completed skin necrosis is not so obvious. Cessation of warfarin is the mainstay of treatment. If anticoagulation is necessary, substitution of heparin or low-molecular-weight heparins for anticoagulation is recommended [56]. Occasionally, vitamin K is used to reverse the anticoagulation of warfarin. Prostacyclin may be effective (grade III evidence), and patients with protein C deficiency may benefit from infusion of protein C concentrate; however, this can be cost prohibitive [57–59] (Grade III evidence). Even with optimal medical treatment, surgical intervention ultimately is required in about half of patients [56].

Purple Toes Syndrome

The purple toes syndrome is a rare complication of VKA therapy (Fig. 5). Patients can develop



Fig. 4 Coumarin-induced skin necrosis: The patient on the *left* had a deep vein thrombosis, while the patient on the *right* had rheumatic mitral stenosis with atrial fibrillation

(Courtesy of Herbert L. Fred and Hendrick A van Dijk under a Creative Commons license)

purplish discoloration of the plantar surfaces and sides of the toes, usually within 3–8 weeks of initiation of therapy. These lesions are painful and tender, blanch with pressure, and fade with leg elevation. Several cases with biopsy or autopsy specimens show an association with cholesterol microemboli. The purple toes syndrome may represent a sentinel event, presaging further emboli from atherosclerotic lesions, possibly from VKA interference with the healing of ulcerated atheromatous plaques. Other cases of warfarin-related cholesterol embolization (without purple toes) have responded to withdrawal of the offending drug. Consideration should be given to withdrawing VKAs when the purple toes syndrome occurs [60].

Hepatitis

Rare cases of drug-induced hepatitis have been reported with therapeutic dosing of warfarin, phenprocoumon, and acenocoumarol. Hepatocellular injury mimicking a viral hepatitis has been described, occurring within several months of

initiating therapy; less commonly, a cholestatic pattern is evident. In some patients with phenprocoumon-induced hepatitis, the substitution of warfarin has resulted in recurrent hepatitis, suggesting cross-reactivity between these agents. This cross-reactivity is not the rule, because other patients with phenprocoumon-induced hepatitis have been treated successfully with either acenocoumarol or warfarin [61].

Special Populations

Pregnant Patients

Pregnancy generally is considered a contraindication to warfarin therapy owing to teratogenic effects. The US Food and Drug Administration has categorized warfarin as pregnancy class X. Intrauterine exposure has resulted in the fetal warfarin syndrome, characterized by nasal/midface hypoplasia, bone stippling of the epiphyses (evident on plain radiographs), optic atrophy, and mental retardation [62]. Warfarin crosses the placenta, but its mechanism of teratogenesis is



Fig. 5 Purple Toes Syndrome (Image courtesy of Dr. Stephan Moll, University of North Carolina, Chapel Hill, NC, USA)

unclear. Hemorrhage into cartilage with subsequent scarring and calcification has been postulated as causing bone stippling, but this mechanism does not explain adequately the other observed abnormalities [62]. Roughly one sixth of pregnancies with warfarin exposure result in an infant with fetal warfarin syndrome, and another one sixth result in stillbirths or spontaneous abortions; the remaining two thirds result in apparently normal newborns [63]. Heparin usually is substituted for warfarin in pregnant women requiring anticoagulation, although one third of these cases still result in prematurity or stillbirth [18]. Apixaban has no well-controlled studies in pregnant women and classified as pregnancy class B. In animal models, apixaban was not associated with increased risk for fetal malformations but increased risk of bleeding [64]. There are also no well-controlled studies in pregnancy or reported fetal malformations for edoxaban, rivaroxaban, and dabigatran and are all pregnancy class C. There were 10 pregnancies reported in the edoxaban clinical trials (HOKUSAI VTE), outcomes were 6 live births, 3 elective abortions, and

1 spontaneous abortion [65]. Inadvertent rivaroxaban exposure during pregnancy did not lead to increased malformation risk [66]. Although evidence is limited, NOACs are not currently recommended for use in pregnancy [67].

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Toxicologic events related to therapeutic administration of thrombolytics, heparins, and antiplatelet drugs are far more common than accidental or intentional overdoses. This chapter focuses on the adverse effects of these agents most commonly encountered by intensivists – in particular, bleeding and heparin-induced thrombocytopenia.

Thrombolytic Therapy

Thrombolytic therapy is indicated in the treatment of acute myocardial infarction, hemodynamically significant pulmonary embolism, hyperacute stroke, and acute peripheral arterial occlusive disease as well as to facilitate the drainage of inflammatory pleurisies. Agents in clinical use include streptokinase (SK), urokinase (UK), alteplase (t-PA), reteplase, and tenecteplase.

Pathophysiology

The hematologic effects of thrombolytic agents may be divided into two phases. In the first phase, drug action results in the cleavage of the arginine₅₆₀-valine₅₆₁ bond of the inactive zymogen plasminogen; this produces a molecule of plasmin, which may be free in the plasma or fibrin-associated. Fibrin-associated plasmin is protected from neutralization by alpha-antiplasmin. In the second phase, plasmin

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catalyzed proteolysis of cross-linked fibrin present in clots, the desired therapeutic effect of thrombolytic agents, but also an undesired cause of bleeding complications. Alteplase, reteplase, and tenecteplase display high binding affinity for freshly formed thrombus and, therefore, are relatively selective in activating plasminogen and promoting thrombolysis at the site of clot formation. SK has less specificity and generates both free and fibrinogen-associated plasmin, leading to systemic plasminogen activation. Plasmin catalyzes proteolysis of cross-linked fibrin present in clots. This is the mechanism behind the therapeutic effect of thrombolytic agents and the main cause of bleeding complications.

The duration of plasminogen activation is relatively brief; the half-lives of thrombolytic agents are 6 min for alteplase, 20 min for SK and UK, and 90 min for tenecteplase [1, 2]. In general, circulating plasminogen activator is cleared from the circulation within 6 h of discontinuation, regardless of the thrombolytic agent administered [1, 3, 4].

Plasmin is a nonspecific serine protease. Circulating fibrinogen, factor V, factor VIII, and other coagulation-related proteins besides fibrin are also depleted by plasmin. This is true of all thrombolytics, but particularly SK, because it activates plasminogen systemically. Therefore, after plasminogen activation ceases, a significant anticoagulated state persists due to depletion of multiple coagulation factors. Some have referred to this second phase as the “lytic state,” although this is a misnomer, since lysis of fibrin occurs predominantly in the phase of plasminogen activation [5]. Complete hemostatic recovery from this “second phase” of thrombolytic effect may take 48 h or longer [3, 5–7].

Hypofibrinogenemia is an important characteristic of the second phase. Cleavage of fibrinogen into fibrin is the final common pathway by which clots form, and fibrinogen is essential to platelet aggregation. Fibrinogen concentrations less than 100 mg/dL (≈ 3 $\mu\text{mol/L}$) are common after thrombolytic therapy [3, 6, 8] and are inadequate for normal hemostasis in patients with congenital hypofibrinogenemia and in surgical patients [9, 10]. Intracranial hemorrhage after thrombolytic

therapy has been shown to be related to reduction of plasma fibrinogen by >200 mg/dL (≈ 6 $\mu\text{mol/L}$) [11]. Fibrinogen proteolysis is agent specific and is more severe after administration of SK than after use of t-Pa [4]. Fibrinogen concentrations may take 48 h to normalize after administration of thrombolytics unless it is replaced [6]. Fibrinogen degradation by plasmin results in the accumulation of fragments X, Y, and D which have been shown to exhibit potent anticoagulant effects [12] and to weaken newly formed clot [13]. Factors V and VIII also reach levels that are inadequate for hemostasis in many patients receiving thrombolytic agents. Minimally acceptable levels for factor V and factor VIII (<10 – 30% activity) generally have been based on studies of patients with isolated factor deficiencies [14]. Because thrombolysis involves multiple additional hemostatic defects, it is possible that higher levels are necessary in these patients to control bleeding.

Plasminogen activation also results in platelet dysfunction. Plasmin has been shown to inhibit platelet release of thromboxane B_2 , which recruits other platelets to sites of vascular injury [15]. Plasmin also cleaves platelet glycoprotein Ib [16] and glycoprotein IIb/IIIa [17] – essential for platelet adherence and aggregation. In our experience, inhibition of platelet function commonly is overlooked by physicians treating patients with bleeding complications resulting from thrombolytic therapy.

Clinical Presentation and Life-Threatening Complications

The most common systemic adverse event associated with thrombolytic therapy is hemorrhage, typically associated with vascular access sites or the GI tract [4]. Bleeding in unusual anatomical locations can be particularly life-threatening. Hemothorax and hemomediastinum have been reported in patients receiving thrombolytic agents after undergoing cardiopulmonary resuscitation [18]. Diffuse pulmonary hemorrhage [19] and localized hematoma of the airway [20] can be life-threatening in the absence of exsanguination. But the most immediately life-threatening

hemorrhagic complication of thrombolytic therapy is intracranial hemorrhage (ICH).

The risk for ICH is highest in patients receiving thrombolytics for stroke (6–9%) [21–25], but the risk also is significant in patients with acute myocardial infarction (0.3–0.6%) [26–29] and pulmonary embolism (1.2%) [30, 31]. ICH is typically lobar and usually presents within 24 h of the initiation of thrombolytic therapy. Presenting symptoms, in order of frequency, include decreased level of consciousness, focal neurologic deficits, vomiting, seizure, and headache [32]. Mortality is approximately 50% [33].

Treatment

Bleeding complications of thrombolytic therapy can be minimized by excluding high-risk patients, especially among those with acute stroke. The administration of t-Pa to patients with mass effect or edema on brain computed tomography (CT) has been associated with a 31% rate of ICH, and administration later than 6 h after onset of stroke has been associated with a rate of 53% [34, 35]. Bleeding also may be prevented by avoiding vascular procedures that are unnecessary or in locations that are difficult to compress adequately, such as the subclavian vein.

There are no randomized controlled trials to guide therapy of bleeding complications related to thrombolytics, and suggested treatment, below, represents Level III evidence. Most published data on treatment of pharmacologically associated intracranial hemorrhage relate to oral anticoagulants and cannot be confidently extrapolated to postthrombolytic ICH [2, 36, 37]. Treatment of postlytic bleeding usually includes administration of cryoprecipitate, fresh frozen plasma, and platelets, but these have not clearly been proven to alter the natural course of bleeding [36, 38]. The following serves as a rational (if unproven) approach based on the underlying pathogenesis.

Treatment is initiated with cryoprecipitate and fresh frozen plasma (FFP) administered rapidly to replace clotting factors depleted by plasmin. The standard unit of cryoprecipitate provides a

minimum of 150 mg and an average of 250 mg of fibrinogen. In addition, it contains 80 U of factor VIII. The volume of distribution is equal to the plasma volume – approximately 3200 mL in a 70-kg patient. Intravenous infusion of 10 U of cryoprecipitate increases the fibrinogen concentration by approximately 75 mg/dL (≈ 2.2 $\mu\text{mol/L}$) and the factor VIII level by 30%. Some have suggested that higher doses of cryoprecipitate should be considered in patients with intracranial hemorrhage [36].

FFP contains 180–300 U of factor V per unit. In a 70-kg patient, 6 U of FFP would be required to increase the factor V level by 30%, but smaller doses often result in clinical hemostasis. Laboratory assessment of fibrinogen and factors V and VIII levels can be helpful in guiding therapy if initial transfusions of cryoprecipitate and FFP are unsuccessful. Several factors complicate the interpretation of results, however. If blood is drawn during the phase of plasminogen activation, proteolysis may proceed *in vitro*, falsely diminishing levels of coagulation factors as measured in the laboratory [39].

Platelet transfusion should be considered, especially if the bleeding time is abnormal or dilutional thrombocytopenia occurs as a complication of massive red blood cell transfusion. Theoretically, transfused platelets should function better than native platelets previously exposed to high levels of plasmin. In addition, platelet-bound factor V may help correct factor V deficiency. One unit of single-donor platelets usually provides adequate numbers of functioning platelets. A recent study showed that 0.4 mcg/kg intravenous desmopressin improves platelet function in patients with ICH associated with abnormal platelet function [40]. Although the patients in this study had not received thrombolytic therapy, the theoretical cost/benefit ratio of desmopressin seems acceptable.

Antifibrinolytic agents, aminocaproic acid or tranexamic acid, may be considered early in treatment if transfusion therapy fails to control bleeding. In the case of ICH, they should be considered up front, since their administration is likely to be faster than transfusion therapy, and the prognosis in ICH is likely to be dependent on how quickly bleeding can be controlled

[36, 38]. Aminocaproic acid is a lysine analogue that binds to lysine-binding sites on plasmin and plasminogen. Some have cautioned against the use of aminocaproic acid to control thrombolytic bleeding because of associations with life-threatening thrombotic complications, including stroke, myocardial infarction, limb gangrene, and renal cortical thrombosis [41]. Antifibrinolytic agents would not be expected to be beneficial when the initial phase of plasminogen activation is over (>6 h after infusion of a thrombolytic agent).

Some have suggested that prothrombin concentrate complex (PCC) could be considered in the management of thrombolytic-associated bleeding [36]. However, PCC contains predominantly vitamin-K dependent factors II, VII, IX, and X, and replacing these would be insufficient to re-establish postthrombolytic hemostasis in which fibrinogen, factor V, and factor VIII are depleted. A similar theoretical argument against the likelihood of efficacy would apply to the use of recombinant factor VIIa. Factor VIII inhibitor bypassing activity (FEIBA), otherwise known as activated PCC, might theoretically get around some of this by directly providing thrombin and activated Factor X; however, fibrinogen would still be required for hemostasis to succeed. We were unable to locate published reports of the use of PCC or rFVIIa in patients with postthrombolytic hemorrhage.

Treatment of Clinically Significant Bleeding Due to Thrombolytic Agents

- Cryoprecipitate (approximately 10 U) and
- Fresh frozen plasma (approximately 2–6 U)

If bleeding continues:

- Platelets (1 U single donor or 10 U random donor)

If bleeding continues and thrombolytics were administered within last 6 h:

- Consider aminocaproic acid (Amicar®)

Common Errors in the Diagnosis and Treatment of Complications of Thrombolytic Therapy

- Giving thrombolytics despite late presentations and contraindications
- Failure to recognize platelet dysfunction in patients who are bleeding after thrombolytic therapy

Several nonhemorrhagic adverse effects can occur with thrombolytics. Streptokinase is derived from cultures of group B Streptococci and can induce antibody formation. SK administration has been associated with fever, bronchospasm, anaphylactic reactions, and hypotension [42, 43] – the latter associated with activation of the kallikrein-bradykinin system. Anaphylactic shock, anaphylactoid reactions, and orolingual angioedema have been associated with t-PA [44, 45]. Anaphylaxis and anaphylactoid reactions are treated with fluid resuscitation, epinephrine, H₁ and H₂ receptor antagonists, and corticosteroids.

Unfractionated and Low-Molecular-Weight Heparins and Fondaparinux

Unfractionated heparin (UH) acts by binding to antithrombin and catalyzing the inactivation of thrombin (Factor II), factor Xa, and other clotting factors. Inactivation of thrombin requires a heparin chain length of at least 18 saccharides, and inactivation of factor Xa requires 5 saccharides. Low-molecular-weight heparins (LMWHs) have reduced antithrombin activity compared with UH. The antithrombotic activity of LMWH commonly is attributed to its antifactor Xa activity. The anti-Xa assay is the laboratory test most often used in monitoring and adjusting LMWH [46]. Fondaparinux is a synthetic pentasaccharide derived from the antithrombin binding site of heparin. It has specific anti-Xa, but no anti-IIa activity.

Heparins also have complicated effects on coagulation that are independent of interaction with antithrombin, and their relative importance is uncertain. Heparins (UH and LMWH) trigger

endothelial cell release of tissue factor pathway inhibitor [47–49]. Tissue factor pathway inhibitor is a serine protease inhibitor that blocks tissue factor/factor VIIa-dependent coagulation. Tissue factor pathway inhibitor release seems to account for a significant fraction of heparin's antithrombotic activity [50]. Heparins also interact with heparin cofactor II, which is a serine protease that is structurally similar to antithrombin but has specific antithrombin activity [51]. The antithrombin activity of LMWH might be clinically important, even though low antithrombin/anti-Xa activity previously was thought to be a theoretical advantage of LMWHs [52, 53]. Antithrombin activity can be measured by anti-IIa assays, although these are not typically clinically employed in North America.

Recognition of uncertainty concerning the mechanism of action of LMWH is important during attempts to use anti-Xa activity to guide clinical administration. Because LMWH does not produce isolated factor Xa inhibition, anti-Xa assays do not fully reflect clinical therapeutic or toxic effects [46]. In addition, the anti-Xa test has been reported to exhibit wide interassay variability [54, 55]. Several studies have failed to show a significant relationship between anti-Xa results and the therapeutic or adverse effects of LMWHs [56–58].

Clinical Presentation

Bleeding

The most common toxicological effect of heparin seen in the intensive care unit is bleeding. Rarely, bleeding occurs when single, inappropriately high doses of heparin are given in error. Patients have also received inadvertent heparin boluses when their heparin-loaded dialysis catheters were flushed before first removing the heparin. Pseudoheparin resistance has been reported, in which inappropriately high doses of heparin are erroneously given in order to achieve a “therapeutic” APTT. Elevated factor VIII levels in these patients artificially suppress prolongation of activated partial thromboplastin time (APTT),

leading to unnecessary administration of escalating heparin doses [59].

Most often, hemorrhagic complications occur during appropriate administration of heparin. Although bleeding often is attributed to “overanticoagulation” – defined by supratherapeutic APTT results – several large studies showed no correlation between bleeding and the APTT [60–63]. The most important risk factors for bleeding are patient-specific, such as underlying peptic ulcer disease or thrombocytopenia and procedural trauma.

The gastrointestinal and urinary tracts are the most common sites for heparin-induced bleeding. Approximately 50% of these patients have a discoverable underlying pathologic lesion [64]. Appropriate workup should not be neglected with the logic that the heparin administration alone is a sufficient explanation.

Retroperitoneal hemorrhage often presents with nonspecific findings that commonly are misdiagnosed initially. Patients may complain of back, hip, or thigh pain, and the initial decline in hemoglobin may not be dramatic. Radiation of the pain to the thigh associated with decreased quadriceps strength indicates compression of the femoral nerve [65]. Cullen's or Grey Turner's signs may be noted if sought-for. CT should be considered in any patient receiving heparin who has unexplained back or flank pain.

Rectus sheath hematomas are usually caused by bleeding from the inferior epigastric artery. They present as a painful abdominal mass. Careful examination usually shows the mass to be external to abdominal cavity in the abdominal wall [66]. One case series showed that delays in diagnosis of rectus sheath hematomas are common and seem to contribute to morbidity and mortality [67]. A rectus sheath hematoma may be misdiagnosed as a hernia and “reduced,” with catastrophic results. Rectus sheath hematomas may require embolization or surgical intervention.

Bilateral adrenal hemorrhage may present with nonspecific findings, including abdominal pain, nausea, fever, hypotension, tachycardia, hypoglycemia, and anemia. A cosyntropin stimulation test usually shows inability to produce serum cortisol

levels greater than 18 $\mu\text{g/dL}$ (>497 nmol/L). The hemorrhagic etiology of adrenal insufficiency can be demonstrated by CT [68].

Spinal epidural hematoma presents as severe, persistent back pain radiating in a dermatomal pattern. This condition can occur spontaneously or in association with lumbar puncture or epidural anesthesia. The concomitant use of prophylactic-dose LMWH and indwelling epidural analgesia has been recognized as a risk factor for this complication [69]. Neurologic findings, such as paraparesis, sensory loss, and urinary retention, are indications for urgent decompression.

The nonhemorrhagic toxicologic effects of heparin include hyperkalemia, skin necrosis, and osteoporosis [64]. These effects are not discussed in further detail here.

Treatment

The treatment of clinically severe bleeding related to heparin therapy includes heparin neutralization, supportive care, and transfusion. The effects of UH can be neutralized rapidly by an intravenous bolus of protamine sulfate (Level I evidence). Protamine is a cationic protein which strongly binds to (anionic) heparin. A dose of 1 mg of protamine sulfate neutralizes approximately 100 U of UH; thus, a patient who bleeds immediately after an intravenous bolus of 5000 U of UH requires 50 mg of protamine sulfate. When UH is given as an intravenous infusion, only heparin given during the preceding several hours needs to be included in the dose calculation because the half-life of intravenous UH is approximately 90 min. For instance, a patient receiving a continuous intravenous infusion of 1250 U/h requires approximately 20 mg of protamine sulfate. Neutralization of a subcutaneous dose of UH may require a prolonged infusion of protamine sulfate. The APTT can be used to confirm neutralization of UH [70].

The risk of severe adverse reactions from protamine, such as hypotension and bradycardia, can be minimized by administering protamine slowly (over 1–3 min) [71]. Development of antiprotamine

antibodies and increased risk for allergic reactions, including anaphylaxis, are associated with (1) previous administration of protamine-containing insulin (e.g., neutral protamine Hagedorn [NPH] Insulin), (2) vasectomy, and (3) allergic sensitivity to fish [70, 72, 73]. Patients at risk of protamine allergy can be pretreated effectively with corticosteroids and antihistamines. Recombinant activated factor VII (rFVIIa) has been used successfully to neutralize heparin when protamine reversal is incomplete [74].

Many other methods have been used to neutralize the effects of UH, including heparinase (Neutralase) [75], platelet factor 4 (PF4) [76], extracorporeal heparin removal devices [77], and synthetic protamine variants [78]. These therapies are not widely available.

There is no proven antidote for LMWH. Protamine neutralizes the antithrombin activity of LMWH but fails to completely neutralize anti-Xa activity [79–82]. Protamine-heparin binding is related to the molecular weight of the heparin [83], and it is theorized that failure of anti-Xa neutralization occurs because of reduced protamine binding to low-molecular-weight components [82, 84]. Others have suggested that plasma proteins inhibit protamine binding to LMWH [85].

The clinical significance of incomplete anti-Xa neutralization by protamine is unclear. Animal studies have shown a hemostatic benefit of protamine in microvascular bleeding models, despite persistent anti-Xa activity [86–88]. In a small case series, protamine failed to completely correct abnormal bleeding associated with LMWH in two of three patients [80]. There are no published clinical studies that show a beneficial effect of protamine on bleeding complications of LMWH. However, the package insert for enoxaparin suggests the following approach: if the LMWH heparin was given within 8 h, protamine sulfate may be given in a dose of 1 mg per 100 anti-Xa U of LMWH (1 mg of enoxaparin equals approximately 100 anti-Xa U). A second dose of 0.5 mg of protamine sulfate per 100 anti-Xa U may be administered if bleeding continues. The aforementioned recommendation for protamine's use for LMWH constitutes Level III evidence.

Neither protamine nor FFP transfusion will neutralize the antithrombotic action of fondaparinux. Studies have shown that recombinant activated factor VII (rFVIIa) can reverse laboratory evidence of the antithrombotic effect of fondaparinux, but evidence for clinical efficacy is only at the level of case reports [89–91]. A recent systematic literature review concluded that there is limited evidence to support the use of rFVIIa, (but not PCC or aPCC) in the treatment of life-threatening bleeding associated with pentasaccharide antithrombotic agents [92].

In some cases, surgical repair or endovascular intervention is warranted. Some data suggest surgical intervention is not beneficial in retroperitoneal hemorrhage [67].

Common Error in the Diagnosis and Treatment of Complications of Heparin Therapy

Delay in recognition of occult bleeding, including retroperitoneal hemorrhage, rectus sheath hematomas, and adrenal hemorrhage

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a unique pathologic syndrome characterized by onset of significant thrombocytopenia after the initiation of heparin therapy associated with the presence of thrombogenic antibodies and a high risk (50–80%) of venous and arterial thromboembolism [93–95]. Heparin-associated thrombocytopenia (HAT) and, also previously called, type 1 HIT, are confusing names for a nonpathogenic and nonimmune-mediated decreases in platelet counts that occur in 10–20% of patients in the first 1–2 weeks after heparin is commenced. Platelet counts usually remain $> 100 \times 10^9/L$, and importantly, HAT is not associated with any disease or thrombotic complication and should not be considered a disorder or toxicologic effect of heparin. The main danger these benign, heparin-associated drops in platelet counts produce is when patients experience side effects of drugs given erroneously to treat HIT.

Pathophysiology

The mechanism of HIT is complex and not fully understood, but platelet factor 4 (PF4) plays an important role. PF4 is normally released by activated platelets and neutralizes the antithrombotic effects of endothelial-bound heparans (heparin-like polysaccharides that line human endovascular endothelium) by competing there for binding with antithrombin. PF4 also binds to glycosaminoglycans on the surface of platelets and is chemotactic for neutrophils and monocytes [96]. When exogenous heparin is administered, PF4 dissociates from the endothelium and platelet surface and forms large PF4/heparin complexes [97]. These provoke generation of anti-PF4/heparin antibodies in potentially pathogenic quantities within 4 days after exposure [98–101]. Seventeen percent of patients receiving UH and 8% of patients receiving LMWH develop detectable titers of these antibodies [93, 102], although only 25% of these patients with antibodies develop clinical HIT [103, 104]. In patients who previously received heparin, anti-PF4/heparin antibodies may persist for months, causing immediate-onset HIT if heparin is later re-administered [105].

Anti-PF4/heparin IgG antibodies bind to PF4/heparin complexes on platelet surface and also to IgG-Fc receptors of adjacent platelets [98, 99]. In susceptible individuals, this aggregates and activates the platelets and causes further PF4 release in a pathogenic positive feedback loop [106, 107]. Thrombocytopenia is caused, in part, by platelet consumption as multifocal thrombi subsequently form. This explains a unique clinical aspect of HIT – all other forms of drug-induced autoimmune thrombocytopenia may have an increased risk of *bleeding*, but patients with HIT suffer venous and arterial thromboembolism.

Epidemiology, Clinical Presentation

The incidence of HIT is about ten-times higher in patients receiving UH thromboprophylaxis than in patients receiving LMWH thromboprophylaxis

(3% vs. 0.2%) [108]. But at therapeutic doses, this distinction is lost (1.5% vs. 1.2%) [109]. Even small quantities of UH used to flush intravenous catheters, or incorporated into the linings of intravascular catheters, have been reported to cause HIT [110, 111]. Patients admitted to medicine or surgery are at higher risk than those admitted to obstetrical or pediatric services [112] perhaps due to differences in underlying levels of platelet activation and PF4 release. One large study showed that HIT is very unusual in patients less than 40 year of age [109]. An increased risk for subsequent HIT can be recognized when the patient suffers an acute systemic reaction to heparin administration such as chills, rigors, fever, tachycardia, and dyspnea [113] or dermal plaques or necrosis at heparin injection sites [114]. Very rarely, HIT has been described in relation to fondaparinux administration [115].

Thrombocytopenia typically becomes apparent 5–14 days after the onset of heparin therapy, just as significant levels of anti-PF4/heparin antibodies become detectable. The platelet nadir is usually less than $150 \times 10^9/L$ but almost always higher than $20 \times 10^9/L$, and the median platelet count in one large study was $60 \times 10^9/L$ [95]. Approximately 10% of patients have thromboembolic events consistent with HIT, despite platelet counts greater than $150 \times 10^9/L$ [95]. These patients typically have had 30–50% decreases in platelet counts, albeit to levels greater than $150 \times 10^9/L$. Bleeding complications are unusual, even when thrombocytopenia is severe [116]. Thrombocytopenia can occur within 10 h of heparin initiation in patients who received heparin in the preceding 100 days [105] and can develop weeks to months after exposure to heparin in a rare subset of patients with “delayed-onset HIT.” [117]

Venous thromboembolism occurs in approximately 50% of patients with HIT, with an incidence rate of 5–10% per day [118, 119]. Progressive, recurrent, or bilateral lower extremity deep venous thromboses are seen in 50% of affected individuals, and pulmonary embolism is seen in 25% [116]. It may be difficult to recognize these as distinct signs of HIT in a patient receiving heparin who already has an established diagnosis of venous thromboembolism. Deep venous thromboses often occur at the

site of venous catheters. Rare forms of venous thromboembolism associated with HIT include bilateral adrenal hemorrhage and cerebral dural sinus thrombosis. HIT-associated deep venous thrombosis has progressed to venous limb gangrene in a subset of patients receiving warfarin. The gangrene apparently is triggered by warfarin-induced, acute protein C deficiency [120].

Arterial thrombosis also occurs with increased frequency. Among patients with HIT, aortic, or iliofemoral thrombosis resulting in acute limb ischemia occurs in 5–10%, stroke and myocardial infarction each occur in 3–5%, and spinal cord infarction has been reported [116]. Approximately 35% of patients with HIT who develop thromboembolic complications lose a limb or ultimately die [118, 119].

The clinical suspicion of HIT should be evaluated first by calculating the 4 T score *before* diagnostic tests are ordered, because diagnostic result interpretation is difficult when the pretest probability of disease is very low (unless Bayes’ theorem is explicitly applied). “4Ts” stand for four clinical and laboratory features that are each scored (zero through two points) in relation to how strongly they are predictive for the diagnosis of HIT: Thrombocytopenia, Timing of onset, Thrombosis, and *a*lTernative reasons for thrombocytopenia (see Table 1). The resulting score is well validated and allows stratification of patients with suspected HIT into three categories, representing pretest probability of HIT of approximately 1%, 10% and 50% (see Table 1) [121, 122].

Diagnosis

Previous studies have shown 45–84% of patients referred for laboratory testing are at low risk of HIT based on their 4 T score [123–126]. It could be argued that these patients should not have undergone diagnostic testing in the first place [127], since the prevalence of HIT in this population is likely less than 1% [121–124]. Lower prevalence (or pretest probability) leads to higher false positive rates, even when a diagnostic test with excellent operating characteristics is employed.

Table 1 “Four-Ts” (4Ts) clinical assessment for HIT

Clinical feature	Points assigned for each finding ^a	
	2 points	1 point
Thrombocytopenia	>50% drop with nadir $\geq 20 \times 10^9/L$	30–50% drop or nadir $10\text{--}20 \times 10^9/L$
Timing of platelet count fall	Clear onset in 5–10 days or Onset ≤ 1 day if prior heparin exposure in last 30 days	Unclear onset but consistent with onset in 5–10 days or Onset in ≤ 1 day w/prior heparin exposure 30–100 days previously
Thrombosis or other sequelae of HIT	Confirmed new thrombosis or Skin necrosis at injection site or Acute systemic reaction after IV unfractionated heparin bolus	Suspected new thrombosis or Progressive or recurrent thrombosis or Erythematous non-necrotizing skin lesions at injection sites
Alternative cause	None apparent	Possible but not definite alternative

^aZero points assigned in a category if criteria are not met – for instance, if the patient has a definite alternative cause for thrombocytopenia (e.g., s/p chemotherapy)

Probability of HIT based on 4Ts score:

0–3 points: Low probability of HIT (about 1%)

4–5 points: Intermediate probability (about 10%)

6–8 points: High probability (about 50%)

The diagnosis of HIT is optimally based on clinical criteria above *and* demonstration of heparin-dependent, platelet-activating immunoglobulin G [128]. Highly sensitive and specific washed platelet activation assays for detecting pathologic platelet-activating antibodies include the platelet ^{14}C serotonin-release assay (SRA) in North America and the heparin-induced platelet activation (HIPA) test in Europe. The SRA has been shown to have sensitivity and specificity greater than 98% and 95%, respectively [128]. It is considered sufficiently accurate that a strongly positive SRA result ($>50\%$ serotonin-release) can be used as a proxy for the clinico-pathological diagnosis of HIT in most clinical situations [93, 129]. However, the SRA is technically demanding

and available only at specialized testing centers. Consequently, many centers depend on commercial enzyme-linked immunosorbent assays designed to detect antibodies directed against platelet factor 4/heparin (anti-PF4/H ELISA) [130].

A positive ELISA test in a patient with intermediate or high probability of HIT by 4 T score is typically sufficient to make the diagnosis of HIT. But ELISA results can be difficult to interpret. The manufacturer of the ELISA test most commonly used in the USA (Gen-Probe GTI Diagnostics, Waukesha, WI, USA) defines a positive result as >0.4 optical density (OD) units based on analysis of anti-PF4/heparin antibody levels in populations of healthy volunteers not receiving heparin [131]. However, the presence of anti-PF4/heparin antibodies at this low threshold has poor specificity when used to diagnose HIT in patients receiving heparin [124, 132–134]. Although the sensitivity of the anti-PF4/H ELISA is as high as 99%, the specificity is reported to be 50% or less in clinical studies [123, 133] that use the manufacturer-recommended cutoff. One reason for the low specificity of the anti-PF4/H ELISA is that (unlike the SRA) only a minority of antibodies detected by ELISA have the pathogenic characteristics necessary to activate platelets and thus to trigger HIT [123]. Indeed, although 25–30% of patients referred for suspicion of HIT have elevated anti-PF4/H antibody levels by ELISA (>0.4 OD units), as few as 1–7% overall satisfy the full clinic-pathological diagnostic features of HIT [123, 124, 133]. The low specificity of the currently accepted cutoff for a positive anti-PF4/heparin ELISA tends to lead to clinical overdiagnosis of HIT [127].

Our published analysis suggests that a Bayesian approach to diagnosis of HIT, incorporating the 4 T score and stratified interpretation of the ELISA result as depicted in Table 2 below, is most likely to yield accurate decisions [132]. We have recently validated this approach at our center, although good bedside judgment might trump an algorithmic approach in some cases.

In summary, diagnostic tests should generally not be ordered unless the clinical picture is consistent with HIT (at least intermediate probability

Table 2 Optimized algorithm for interpreting anti-PF4/H ELISA results in patients suspected of having HIT

Pretest probability of HIT by 4 T score	ELISA result (OD)	Post-test probability of HIT (%) Based on		Reasonable clinical action
		IgG ELISA	Poly-spec. ELISA	
Low (0–3 points) <i><1% chance patient has HIT</i>	>2.00	51%	42%	Order SRA ^a
	1.50–1.99	11	7	
	0.60–1.49	1	1	HIT ruled out ^b
	<0.6	0	0	
Intermediate (4–5 points) <i>~10% chance patient has HIT</i>	>2.00	92	91	Treat HIT
	1.50–1.99	56	44	Order SRA ^a
	0.60–1.49	14	11	
	<0.6	0	0	HIT ruled out ^b
High (6–8 points) <i>~50% chance patient has HIT</i>	>2.00	99	99	Treat HIT
	1.50–1.99	92	87	
	0.60–1.49	59	54	Order SRA ^a
	<0.60	2	0	

^aMost patients undergoing SRA testing should be treated for HIT pending the result

^bAssumes that the pretest probability for HIT has not been altered substantially by subsequent clinical and/or laboratory finding

by 4 T score). A negative ELISA is good at ruling HIT out, but values of 0.4–0.8 OD, which are considered “positive” by the manufacturer, are actually diagnostically equivocal. When there is uncertainty about the diagnosis, an SRA is the gold standard.

Treatment

When HIT is reasonably suspected (4 T score indicating at least an intermediate risk of HIT), all heparin should be discontinued immediately pending confirmatory laboratory testing. Care should be taken to be sure that heparin flushes and heparin-coated intravenous catheters are not overlooked. Alternative antithrombotic therapy should be started immediately in patients with suspected HIT with thromboembolism, and in patients with laboratory-confirmed HIT, even in the absence of overt thromboembolic complications. LMWH consistently cross-reacts with existing heparin/platelet factor 4 antibodies and cannot be used in therapy of HIT due to UH [135].

Argatroban is a synthetic direct thrombin inhibitor and the only FDA-approved treatment

for the treatment of HIT in the general patient population. Two historically controlled trials showed a reduction in new thromboembolic events, limb amputation, and death in patients with HIT treated with argatroban, representing Level II evidence effectiveness [136, 137]. The initial infusion dose is 2 µg/kg/min, adjusted to attain an APTT value 1.5–3 times baseline, with a maximum of 100s. Dose reduction is recommended in patients with heart failure, and the drug should not be used in patients with significant liver dysfunction.

Platelet counts usually begin to improve within 48 h of heparin discontinuation and typically resolve within 2 weeks; however, thrombotic risk remains elevated for approximately 6 weeks due to persistence of circulating anti-PF4/heparin antibodies [94], requiring prolonged therapy even after platelet counts have completely recovered and even when no overt thromboembolic complications are recognized [138]. Therefore, after the platelet count has recovered (e.g., $>150 \times 10^9/L$), warfarin should be started and overlapped with argatroban for approximately 5 days [138]. Argatroban prolongs the prothrombin time, so during the overlap period, an INR greater than 4 usually is typically required to account for the additive actions of

argatroban and warfarin. The recommended duration of warfarin therapy for HIT is 4 weeks in the absence and 3–6 months in the presence of clinically recognized thromboembolism [138].

Bivalirudin and fondaparinux are possible alternatives to argatroban. Fondaparinux has several advantages – it is given as a single daily subcutaneous dose (7.5 mg for patients who weigh 50–100 kg and 10 mg for patients >100 kg), does not require monitoring, and is relatively inexpensive. Although fondaparinux belongs to the heparin family of antithrombotic agents, it does not appear to incite or crossreact with anti-PF4/heparin antibodies associated with HIT [139]. Its efficacy is supported by several small case series [140–143], but it is not FDA-approved for the treatment of HIT (Level III evidence). Fondaparinux is contraindicated in patients with creatinine clearance < 30 mL/min. Plasmapheresis has been rarely utilized in HIT in an attempt to reduce anti-PF4/H antibodies [144].

Common Errors in the Diagnosis and Treatment of Heparin-Induced Thrombocytopenia

- Failure to monitor for or consider the diagnosis
- Failure to stop all heparin immediately while the diagnosis is being confirmed
- Failure to recognize that the cross-reactivity between heparin and low-molecular-weight heparin is 100% in patients with heparin-induced thrombocytopenia

Antiplatelet Drugs

P2Y₁₂ Platelet Receptor Blockers

Ticlopidine, clopidogrel, prasugrel, and ticagrelor are antiplatelet agents that act by antagonizing P2Y₁₂ receptors on the surface of platelets. P2Y₁₂ is a G-coupled transmembrane receptor that activates platelets by decreasing intracellular cAMP. P2Y₁₂ receptor antagonists are indicated for secondary prevention of stroke, for elective percutaneous coronary intervention, and in acute myocardial infarction. Ticlopidine, clopidogrel,

and prasugrel are converted to active metabolites that covalently and irreversibly bind to P2Y₁₂ receptors, explaining inhibition of ADP-mediated platelet aggregation for the life of the platelet. Ticagrelor has no such metabolite and reversibly binds to P2Y₁₂ receptors, explaining a somewhat shorter duration of action after termination of therapy. Overall, patients who present with bleeding who have received a P2Y₁₂ receptor antagonist within approximately 10 days should be considered to have potentially significant platelet dysfunction. We have seen several episodes of life-threatening bleeding associated with these agents in patients who had undergone high-risk procedures, such as gynecologic-oncologic surgery, without withholding a P2Y₁₂ receptor antagonist for an adequate period of time for platelet function to recover.

If the bleeding is serious, platelet transfusion is warranted, even if the platelet count is normal. However, there are no controlled trials that have demonstrated changes in survival or decreased bleeding in patients taking these drugs, making the recommendation for platelet transfusion based on Level III evidence and in vitro studies on platelet function. In vitro studies demonstrate that ticagrelor's reversible binding to platelets allows it to inhibit donor platelet function, as well. Thus, as long as ticagrelor is still circulating, platelet transfusion would not be expected to be as effective in comparison with patients receiving ticlopidine, clopidogrel, or prasugrel. Effective reversal agents for P2Y₁₂ receptor antagonists are not currently available or well studied. Desmopressin has been shown to repair platelet aggregation inhibited by clopidogrel, in an animal model [145], but not repair platelet aggregation in the blood of subjects receiving ticagrelor [146]. rFVIIa has been shown to restore platelet aggregation and thrombin generation in ex vivo blood treated with prasugrel [147], and in blood from patients receiving aspirin/clopidogrel [147].

Thrombotic thrombocytopenic purpura (TTP) is one of the hematologic complications of this class of drugs that might present in the ICU. TTP is a life-threatening syndrome characterized by microangiopathic hemolytic anemia and thrombocytopenia sometimes in association with renal

insufficiency, fever, and central nervous system abnormalities. Laboratory findings consistent with the diagnosis of TTP include elevated lactate dehydrogenase; schistocytes on blood smear; and normal prothrombin time, partial thromboplastin time, and fibrin degradation products. No cases of ticlopidine-associated TTP were reported during phase III trials [148], but postmarketing surveillance has shown that TTP occurs in approximately 1/1600–1/5000 patients receiving ticlopidine. Mortality of TTP is 20–60% [148–150].

Ticlopidine seems to induce the formation of autoantibodies to von Willebrand factor metalloproteinase in patients who subsequently develop TTP; these antibodies reduce degradation of ultralarge von Willebrand factor multimers, increase binding of platelets to von Willebrand factor, and cause widespread microvascular thromboses [151]. Most patients with ticlopidine-associated TTP develop it within 3 months of initiating therapy [148], but a significant minority may develop delayed TTP. A nonrandomized study showed a reduction in mortality from 60% to 20% in patients with ticlopidine-associated TTP receiving plasma exchange [148]. Ticlopidine also has been associated with life-threatening neutropenia and aplastic anemia.

Clopidogrel is closely related chemically to ticlopidine and has largely replaced it in clinical use. TTP has been reported in association with its use, however [152]. Clopidogrel-associated TTP has occurred within the first 2 weeks of therapy and seems to respond to plasma exchange.

Glycoprotein IIb/IIIa Receptor Antagonists

The glycoprotein IIb/IIIa receptor plays a pivotal role in platelet aggregation. When activated by adhesion or agonist receptors, this integrin can bind soluble ligands, such as fibrinogen and von Willebrand factor that mediate platelet cohesion. A detailed review of this process is referenced [153]. Platelet aggregation is particularly important in the formation of arterial clots. Antagonists of the glycoprotein IIb/IIIa integrin

have been found to be efficacious in the therapy of acute coronary syndromes. The intravenous agents abciximab, eptifibatide, and tirofiban hydrochloride are in clinical use in the USA for patients with coronary artery disease.

The pharmacokinetic properties of these agents are important in the management of hematologic complications. Abciximab has the highest affinity for platelet binding and the slowest rate of dissociation. Although the plasma half-life is 26 min, the “biologic” half-life (recovery of platelet aggregation) is approximately 8 h. Platelet-associated abciximab can be detected for more than 14-day postinfusion [154]. Eptifibatide and tirofiban have lower platelet binding affinity and significantly faster dissociation kinetics. Their serum half-lives are approximately 2 h, and their biologic half-lives are less than 4 h [154]. After a dose of any of these agents, the bleeding time corrects more rapidly than does platelet aggregation [155] and is of little utility in the evaluation of bleeding complications [156]. It is possible that thromboelastography might be an option in this regard [157], but this is not clinically well studied.

Bleeding associated with glycoprotein IIb/IIIa antagonists occurs most commonly at the site of intravascular catheters in the groin. Although this bleeding is overt, the quantity of blood loss often is underestimated, particularly when bleeding from the femoral artery tracks up into the retroperitoneal space. We have seen several patients experience life-threatening hemodynamic compromise from groin hemorrhages that were rapidly clinically recognized but treated inadequately. Abciximab given within 12 h of emergent cardiac surgery has been associated with a significant increase in perioperative bleeding [158]. The risk of intracranial hemorrhage with glycoprotein IIb/IIIa antagonists is 0.07% – equal to the risk with heparin [159]. Diffuse alveolar hemorrhage has been reported by several authors [160, 161].

Manual compression of enlarging groin hematomas is often sufficient treatment, but in some cases consultation of interventional radiology or vascular surgery might be indicated, particularly when femoral artery pseudoaneurysm is present. Methods to repair hemostasis are agent specific.

The unbound fractions of eptifibatide and tirofiban typically are large enough to negate any benefit of platelet transfusion. Both of these agents undergo rapid renal clearance, with significant recovery of platelet function within 4 h [162]. Treatment of bleeding associated with these agents is often supportive. It is unclear whether either agent is dialyzable. In contrast, abciximab is almost entirely platelet bound in vivo, with little unbound drug to inhibit the function of transfused platelets. In addition, the antiplatelet effects of abciximab can last up to 48 h, making it much more likely that platelet transfusion might be beneficial [162].

Glycoprotein IIb/IIIa receptor antagonists are associated with severe thrombocytopenia that can occur within the first day of initial administration [163–166]. Thrombocytopenia in this situation is associated with severe bleeding complications, myocardial infarction, and death [164, 167, 168]. It has been hypothesized that binding of glycoprotein IIb/IIIa receptor by these drugs might expose a “ligand-induced” neoepitope on the platelet surface, similar to epitopes associated with platelet senescence and to which some patients already have preexisting antibodies [169].

The first step in evaluating thrombocytopenia due to glycoprotein IIb/IIIa receptor antagonist is to rule out pseudothrombocytopenia by repeating the platelet count in a tube anticoagulated with sodium citrate rather than EDTA. If pseudothrombocytopenia is ruled out, glycoprotein IIb/IIIa inhibitors be discontinued when the platelet count decreases to less than $100 \times 10^9/L$ [169]. HIT should be considered in the differential diagnosis, but is usually clinically distinguishable because it typically does not occur as rapidly or cause as severe thrombocytopenia ($<30 \times 10^9/L$) as is commonly associated with glycoprotein IIb/IIIa inhibitors. Platelet transfusion should be considered if the patient is bleeding, the platelet count decreases to less than $20 \times 10^9/L$, or an emergency invasive procedure is needed [169]. Platelet count recovery typically occurs within 5 days after discontinuation of eptifibatide and tirofiban and within 2 weeks after abciximab [170, 171].

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Part XII

Medications: Miscellaneous

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This is an update of the chapter originally written by
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Antidiabetic agents include insulin and nine classes of oral drugs:

1. Sulfonylureas
2. Meglitinides
3. Biguanides
4. Glitazones
5. α -glucosidase inhibitors
6. Glucagon-like peptide-1 (GLP-1) agonists
7. Dipeptidyl-peptidase-4 (DPP-4) inhibitors
8. Amylin analogs
9. Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors)

Although they may have other effects, antidiabetic agents are used primarily for the treatment of hyperglycemia, the cardinal feature of all forms of diabetes mellitus and the consequence of overproduction and underuse of glucose due to underlying insulin deficiency (low levels of circulating insulin) and insulin resistance (decreased tissue responsiveness to insulin). Insulin therapy provides exogenous hormone, sulfonylureas and meglitinides enhance endogenous insulin secretion, biguanides and glitazones enhance the tissue insulin activity, α -glucosidase inhibitors reduce the intestinal absorption of carbohydrates. More recent antidiabetic agents, GLP-1 agonists, DPP-4 inhibitors, and amylin analogs, affect glycemic control primarily by slowing gastric emptying, decreasing postprandial glucagon production, and overall decreasing food intake. SGLT2 inhibitors, however, are a new class which blocks reabsorption of glucose in the kidneys, thereby increasing glucose excretion in the urine. Insulin, sulfonylureas, and meglitinides can cause hypoglycemia and are classified as hypoglycemic agents. Biguanides, glitazones, α -glucosidase inhibitors, GLP-1 agonists, DPP-4 inhibitors, amylin analogs, and SGLT2 inhibitors do not on their own cause hypoglycemia and are characterized as antihyperglycemic agents. However, they can potentiate the action of hypoglycemic agents and precipitate hypoglycemia when added to a therapeutic regimen that includes hypoglycemic agents. Biguanide exposure also has been associated with the development of lactic acidosis.

Chemistry and Pharmacokinetics

Insulin

Insulin is a protein hormone that is related structurally to the somatomedins or insulin-like growth factors, which act as paracrine modulators [1, 2]. It consists of two chains of amino acids linked by disulfide bonds and is synthesized by β cells of pancreatic islets of Langerhans. These cells first produce a single long chain of amino acid known as *preproinsulin*. After entering the rough endoplasmic reticulum, an end portion of preproinsulin is cleaved off to form proinsulin (Fig. 1). Proinsulin then spontaneously folds on itself as disulfide bonds are established between the two ends. It subsequently is packaged in vesicles and transported to the Golgi complex. Here, proinsulin is repackaged in secretory granules along with enzymes that convert it to a double-stranded insulin molecule by cleaving a connecting segment or C peptide from the fold or midportion of proinsulin. Insulin stored in granules complexes with zinc to produce insulin hexamers, a concentrated crystalline form of insulin. This process facilitates the conversion of proinsulin to insulin. Although C peptide has no known biologic activity, equimolar amounts of insulin and C peptide are produced from the cleavage of proinsulin and released into the circulation from secretory granules (along with small quantities of proinsulin).

Insulin for therapeutic use originally was obtained by extracting it from pork or beef pancreas, with doses and concentrations expressed in units of insulin based on bioassay in rabbits. In 1921, Banting and Best were the first to use such an extract to treat a human patient successfully. Pork and beef insulins, which differ from human insulin by one (pork) and three (beef) amino acids, and mixtures of these insulins are still available. Human insulin, now more widely used, is prepared by enzymatic modification of pork insulin or produced by strains of *Escherichia coli* or *Saccharomyces cerevisiae* using recombinant DNA technology. Insulin lispro is a recombinant DNA-derived human insulin analogue. Insulin doses still are expressed in bioassay units, but

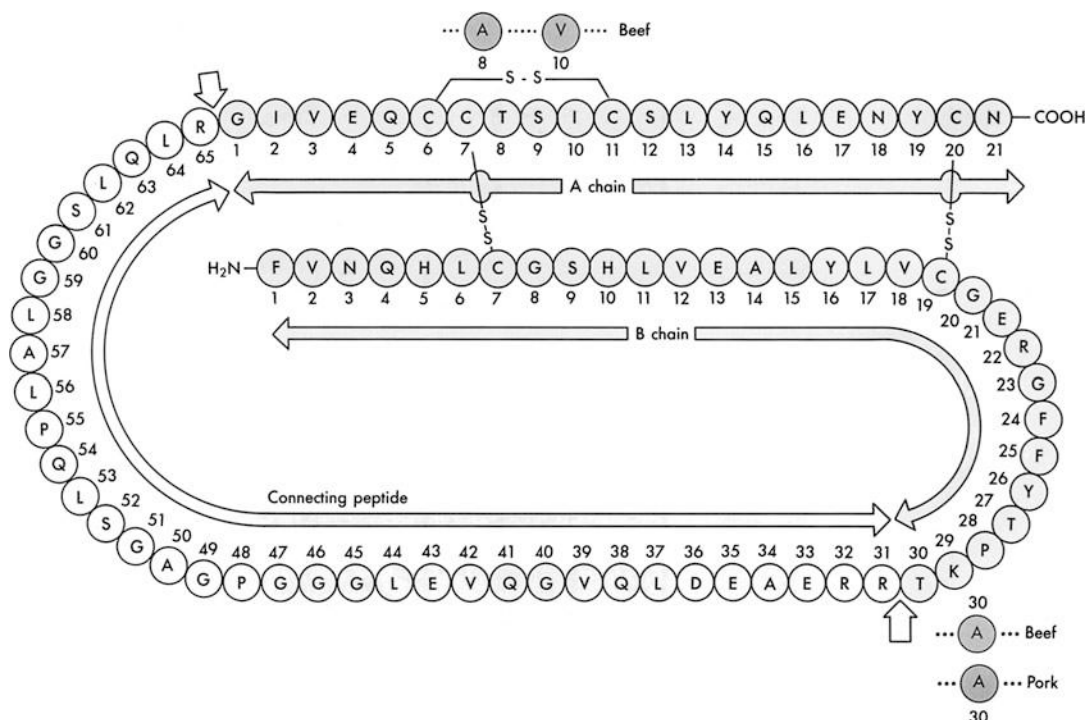


Fig. 1 Amino acid sequence of human proinsulin. When the connecting peptide is removed (the portion between the arrows), the remaining primary structure is that of insulin. Amino acid substitutions in the sequence for pork insulin and beef insulin also are noted (From Lawrence JC: Insulin

and oral hypoglycemic agents. In Brody TM, Larner J, Minneman KP [eds]: *Human Pharmacology: Molecular to Clinical*, 3rd ed. St. Louis, Mosby, 1998, p 549, with permission)

solutions and suspensions now have been standardized to concentrations of 100 U/mL. This standardization is also true for fixed combinations, such as those containing 70/30 U/mL and 50/50 U/mL of regular and NPH (isophane) insulin (e.g., Humulin, Novolin). As with endogenously stored insulin, exogenous preparations often consist of hexameric insulin complexed with zinc.

Insulin must be given parenterally, usually by subcutaneous injection, although an inhaled form of insulin (Afrezza) was approved by the US Food and Drug Administration in 2014 [1–4] (US brand names are given as examples. These may be similar or different in other countries.). Therapeutic subcutaneous doses range from 0.2 to 2.5 U/kg/day. After absorption (or secretion), hexameric insulin dissociates and circulates in the blood as the more biologically active free

monomer. It is distributed in extracellular fluid, has a volume of distribution of about 0.4 L/kg, and is minimally bound to plasma proteins. Elimination occurs by liver, kidney, and muscle metabolism, with a half-life of 5–9 min after intravenous injection. The half-life is prolonged in patients with antiinsulin antibodies, patients with renal failure, and, to a lesser extent, patients with hepatic disease. The duration of effect of insulin after subcutaneous administration is much longer (hours to days). More importantly, it depends on the insulin formulation. Differences in the duration of action after subcutaneous administration reflect differences in the rate of dissolution and absorption (not metabolism) of insulin preparations, and these differences affect times of onset and peak effect and apparent half-life. Regular insulin is the only preparation that can be given

intravenously. By this route, its action begins in minutes, peaks within 0.5 h, and lasts 2–3 h.

Under fasting conditions, the pancreas secretes about 1 U (40 µg [7 nmol]) of insulin per hour in nondiabetics, resulting in an average serum insulin level of about 12 µU/mL (0.5 ng/mL [84 pmol/L]) by radioimmunoassay. After ingestion of a meal, insulin levels in nondiabetics average about twice this amount. Normally, about 10% of the immunoreactive insulin level is due to the presence of proinsulin, with normal levels of the latter being 36–126 ng/mL (4–14 pmol/L). Because proinsulin has a longer half-life than insulin (about 17 min), a slightly higher fraction is seen in non-insulin dependent diabetes. A much higher fraction of proinsulin (20–80%) is seen in patients with insulinomas because of abnormal processing of this peptide by these tumors. Also, because proinsulin has only about $1/50$ the biologic activity of insulin, the effective insulin level is actually lower than that determined by radioimmunoassay. Similarly, because C peptide has a longer half-life than insulin (about 30 min), serum concentrations of this protein (also measured by radioimmunoassay) are higher than serum concentrations of insulin (1–4 ng/mL [500–2000 pmol/L]). Lower insulin and C peptide concentrations may be seen in untreated insulin-dependent diabetics who are insulin deficient, and higher concentrations may be seen in non-insulin dependent diabetics (treated and untreated) who are insulin resistant. Serum insulin concentrations may be many times higher in insulin-dependent diabetics treated with nonhuman insulin because they rapidly develop antibodies capable of binding large amounts of exogenous insulin in the plasma, and radioimmunoassays measure total rather than free immunoreactive insulin (unless a preliminary separation step is employed) (Table 1).

Sulfonylureas

The sulfonylureas (substituted arylsulfonylureas) are related structurally to sulfonamide antibiotics (Fig. 2) [1–3]. Agents in current use differ in potency with the newer or second-generation

Table 1 Classification and pharmacodynamics of insulin preparations^a

Classification/ preparation	Onset (h)	Peak (h)	Duration of action (h)
Rapid acting			
Lispro	0.25–0.5	0.5–2.5	3–6
Regular (crystalline)	0.3–1	1–5	5–10
Intermediate acting			
Lente	1–3	6–14	16–24
NPH (isophane)	1–2	6–14	16–24
Long acting			
Ultralente	4–6	8–20	24–36

^aAfter subcutaneous administration

analogues, being about 100 times more potent than the first-generation agents. They also differ in half-life and duration of action but are similar in terms of their high (>90%) plasma protein binding, primarily to albumin, and low (0.1–0.2 L/kg) volumes of distribution. Atypically, and for unclear reasons, their duration of action does not correlate with half-life [5].

Sulfonylureas are well absorbed from the gastrointestinal tract with bioavailabilities of 80% or greater. Food can decrease their absorption and bioavailability. Antihyperglycemic effects typically begin within 1 h and peak in 2–6 h, with first-generation agents having a longer time to peak effect than second-generation agents. The coadministration of other drugs that are highly protein bound (e.g., oral anticoagulants, phenytoin, salicylates and nonsteroidal antiinflammatory agents, sulfonamides) can displace sulfonylureas from binding sites and enhance their effects (and vice versa). These agents are eliminated by hepatic metabolism (to a variety of active and inactive metabolites) and renal excretion (along with their metabolites). Hepatic or renal insufficiency can prolong their half-lives. The renal elimination of chlorpropamide is increased in alkaline urine and decreased in acidic urine. Because all sulfonylureas are weak acids with pK_a values of about 5, the urinary excretion of other agents also is likely to be dependent on urinary pH. Chlorpropamide, which has relatively

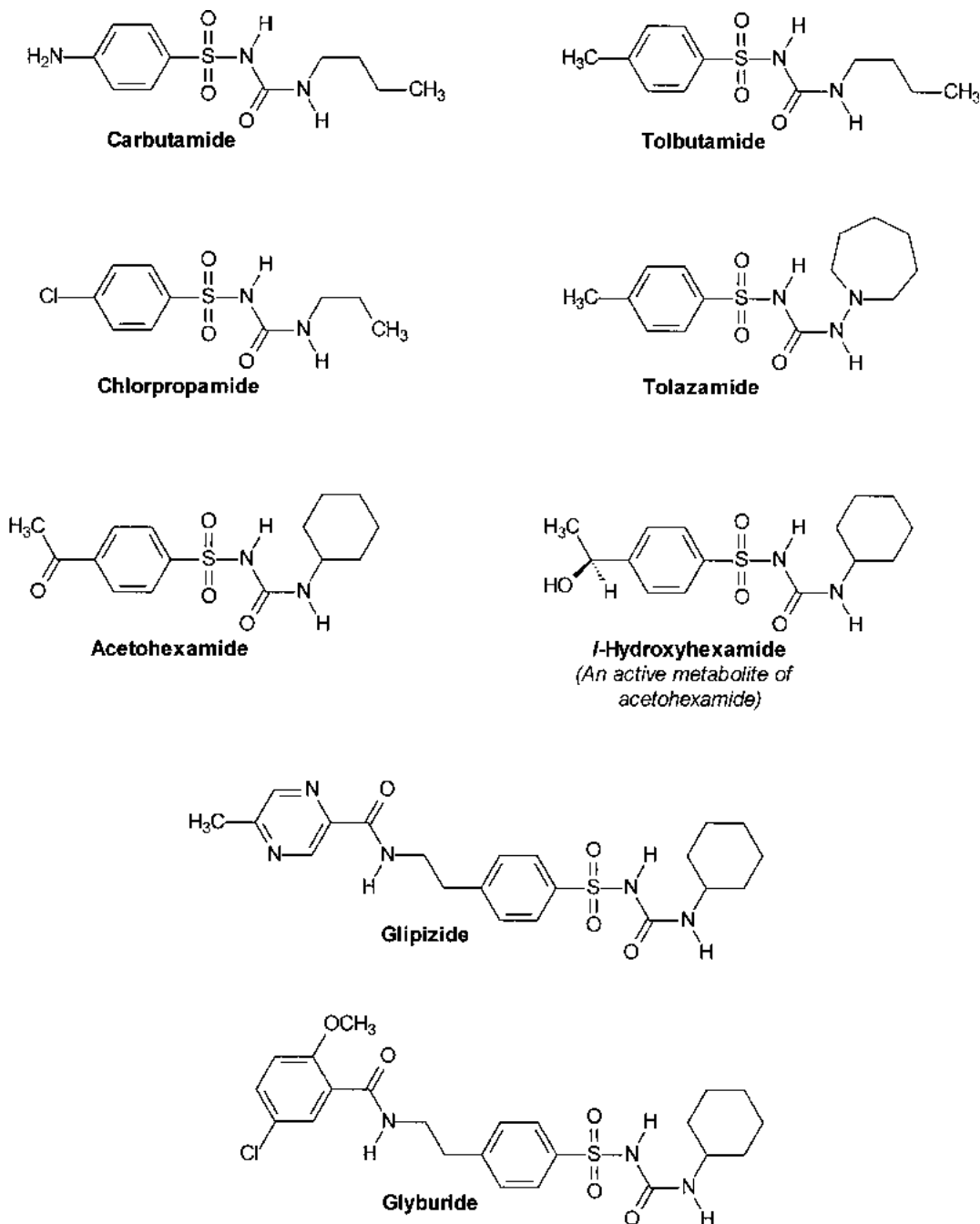


Fig. 2 Chemical structures of sulfonylurea hypoglycemic agents

greater renal elimination, and acetohexamide, glyburide, and tolazamide, which have active metabolites, are more likely than other agents to cause hypoglycemia in patients with renal failure (Table 2).

Meglitinides

Meglitinides are analogues of the nonsulfonylurea moiety of glyburide [6, 7]. Repaglinide (Prandin) and nateglinide (Starlix) are the only agents in this

Table 2 Selected pharmacokinetics and pharmacodynamics of sulfonylureas

	Usual dose (mg/day)	Half-life (h)	Duration of action (h)
First-generation agents			
acetohexamide (Dymelor)	500–750 ^a	1.4 (0.8–2.4)	12–24
Chlorpropamide (Diabinese)	250–500 ^b	36 (25–60)	24–72
Tolazamide (Tolinase)	100–1000 ^a	7 (5–11)	10–24
Tolbutamide (Orinase)	1000–2000 ^a	7 (4–25)	6–24
Second-generation agents			
Glimepiride (Amaryl)	1–4 ^b	5 (2–8)	24+
Glipizide (Glucotrol)	10–20 ^a	2.8 (1.1–3.7)	12–24
Glyburide ^c (DiaBeta, Glynase, Micronase)	3–20 ^b	1.6 (0.7–3)	24
Gliclazide (Diamicon)	40–240 ^b	12–20	24

^aOnce a day or divided^bOnce a day^cAlso known as glibenclamide

class currently available in the USA. The recommended dose is 0.5–4 mg for repaglinide and 60–120 mg for nateglinide two to four times a day before or with meals. These agents are well absorbed orally and are highly (>98%) bound to plasma proteins, primarily albumin. They have relatively low volumes of distribution (about 0.4 L/kg) and are eliminated by hepatic metabolism, with renal excretion of inactive metabolites. Half-lives are about 1.5 h. Their elimination may be impaired in patients with hepatic or renal insufficiency. Because cytochrome P-450 enzymes, CYP3A4 in particular, are partly responsible for their metabolism, the coadministration of drugs that induce CYP3A4 (e.g., barbiturates, carbamazepine, rifampin, pioglitazone) or inhibit CYP3A4 (e.g., azole antifungals, calcium channel blockers, cimetidine, human immunodeficiency virus protease inhibitors, macrolide antibiotics, oral contraceptives) could potentially decrease or increase the effect of meglitinides, respectively.

Biguanides

Biguanides (diguanydes) are derivatives of guanidine [1–3, 8]. Above-ground parts of the flowering plant *Galega officinalis* (Goat's rue, French lilac, Italian fitch) contain the guanidine analogues galegine and 4-hydroxygalegine. This plant was used in medieval Europe for the treatment of diabetes and is still available as an herbal

medicine, primarily used as a diuretic and secondarily as supportive therapy in diabetes. Metformin (Glucophage) is the only biguanide prescription medication currently available in the USA. It has been in clinical use in Europe since 1970 but was withdrawn from most markets in 1977 along with the related agent phenformin because use of the latter was associated with a low but unacceptable incidence of fatal lactic acidosis. Although this complication also can occur during metformin therapy, it is extremely rare and much less common than it is with phenformin. Metformin was reintroduced in Europe in the late 1980s and approved for use in the USA in 1995.

Metformin is absorbed slowly and incompletely from the gastrointestinal tract. It does not bind to plasma proteins and has a volume of distribution of 3.7 L/kg. It is eliminated by urinary excretion and to a lesser extent in the feces as unchanged drug. The usual therapeutic dose is 500 or 850 mg, taken during or after meals; doses generally should not exceed 2550 mg/day. Sustained-release formulations (e.g., Glucophage XR) are also available for once- or twice-daily dosing (e.g., 2000 mg once a day or 1000 mg twice a day). Bioavailability is about 50%. Antihyperglycemic effects begin about 1 h after ingestion and persist for 12 h (longer with sustained-release formulations). The half-life averages 4–8 h and is prolonged in patients with renal impairment. Renal insufficiency decreases the volume of distribution and increases peak

plasma drug levels and the risk of toxicity. For these reasons, metformin is contraindicated in patients with renal disease or dysfunction and in patients who have conditions that predispose to renal impairment, such as congestive heart failure, dehydration, sepsis, and shock. It also is recommended that therapy be discontinued when performing radiographic imaging with intravenous iodinated contrast material, which can cause renal failure (particularly in diabetics), and not be resumed until postprocedure renal function is determined to be normal. Because metformin undergoes proximal tubular secretion and glomerular filtration, its renal clearance is about 3.5 times that of creatinine. Cimetidine and possibly other drugs that undergo renal tubular secretion, such as amiloride, digoxin, morphine, quinidine, procainamide, triamterene, trimethoprim, and vancomycin, can compete with metformin for proximal tubular transport and increase its plasma level.

Thiazolidinediones

Thiazolidinediones (glitazones) currently available in many countries are pioglitazone (Actos) and rosiglitazone (Avandia) [3]. Lobeglitazone has very limited availability worldwide. Troglitazone (Rezulin), the first widely used thiazolidinedione, was introduced in the USA in 1997 but removed from the market in March 2000 because of potentially fatal idiosyncratic liver toxicity associated with its use. The risk of this toxicity seems to be much less with pioglitazone and rosiglitazone.

Therapeutic doses are 15–45 mg/day for pioglitazone and 2–8 mg/day for rosiglitazone. Both drugs are well absorbed from the gastrointestinal tract, are highly (>99%) bound to plasma proteins (primarily albumin), have relatively small volumes of distribution (0.3–0.6 L/kg), and are eliminated by hepatic metabolism. Half-lives are approximately 3 h, and there is renal excretion of active and inactive metabolites. Pioglitazone, but not rosiglitazone, is metabolized by CYP3A4 and could be subject to interactions with drugs that are metabolized by or inhibit this enzyme (see under section “[Meglitinides](#)”).

α -Glucosidase Inhibitors

α -Glucosidase inhibitors currently available in the USA include acarbose (Precose) and miglitol (Glyset) [3]. Therapeutic doses of acarbose and miglitol are 25–100 mg three times a day given with meals. Acarbose, an oligosaccharide, has limited systemic absorption and is eliminated by metabolism within the gut, primarily by intestinal bacteria but also by digestive enzymes. Miglitol, a monosaccharide derivative, is well absorbed after oral administration. It has negligible protein binding, has a small volume of distribution (0.18 L/kg), and is eliminated by renal excretion of unchanged drug. Although its elimination may be impaired in patients with renal insufficiency, absorption does not contribute to its therapeutic effect (see later), and dosage adjustments are unnecessary in these patients.

Glucagon-Like Peptide-1 Agonists

Available glucagon-like peptide-1 (GLP-1) agonists in the USA include exenatide (Byetta), liraglutide (Victoza), albiglutide (Tanzeum), and dulaglutide (Trulicity). These medications are only available as subcutaneous injections. Exenatide is a synthetic formulation of exendin-4, which is found in Gila monster (*Heloderma suspectum*) saliva. This naturally occurring substance shares 53% of its sequence with GLP-1 [9]. However, unlike GLP-1, these agonists are resistant to degradation by dipeptidyl peptidase 4 (DPP-4), making them useful clinically. Exenatide should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min). Liraglutide, albiglutide, and dulaglutide are long-acting GLP-1 agonists, where liraglutide is dosed once daily and others are dosed once weekly. These also have structural modifications to prevent degradation by DPP-4 and to prolong half-lives. There is little experience with using these medications in patients with severe renal impairment. Cases of acute pancreatitis have been reported in patients on GLP-1 agonists. The evidence at this time is inconclusive, but these medications should be used with

Table 3 Dosing and half-lives of GLP-1 agonists

	Usual dose	Half-life (h)
Exenatide IR ^a	5–10 mcg	2.4
Exenatide ER ^b	2 mg	336
Liraglutide ^c	0.6–1.8 mg	13
Albiglutide ^b	30–50 mg	120
Dulaglutide ^b	0.75–1.5 mg	120

^aTwice daily

^bOnce weekly

^cOnce daily

caution in patients who have a history of pancreatitis and should be discontinued if patients should develop acute pancreatitis during use [10] (Table 3).

Dipeptidyl Peptidase-4 Inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors available in the USA include sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina). Vildagliptin, trelagliptin, and anagliptin are approved in some other countries. The DPP-4 inhibitors are taken orally and are generally readily absorbed. Therapeutic doses are 100 mg/day for sitagliptin, 2.5–5 mg/day for saxagliptin, 5 mg/day for linagliptin, and 25 mg/day for alogliptin. Peak plasma concentrations are within 1–3 h. With the exception of linagliptin, which is 70–80% protein bound, protein binding is generally low. The volumes of distribution for the DPP-4 inhibitors are modest for sitagliptin, saxagliptin, and alogliptin (about 150–500 L) but larger for linagliptin (1000–3000 L). All of the DPP-4 inhibitors are recommended as once daily administrations; however, the drugs differ in half-lives and durations of action. The terminal half-lives of alogliptin and sitagliptin are 21 and 12 h, respectively, and their duration of effect approximates this. Saxagliptin, however, has a much longer duration of effect than its half-life of 2.5–3 h would suggest. Linagliptin has a long terminal half-life as well (>100 h); however, accumulation has not been shown clinically. All of the DPP-4 inhibitors except linagliptin are

renally excreted. Linagliptin is eliminated enterohepatically and therefore is the only DPP-4 inhibitor that is safe in renal impairment [11, 12].

Amylin Analogs

Pramlintide is the only amylin analog available and is marketed under the trade name of SymlinPen. As its name suggests, it is available only as a subcutaneous injection and is to be used in conjunction with prandial insulin [13]. Dosing differs depending on whether a patient has type 1 or type 2 diabetes mellitus (30–60 mcg or 60–120 mcg, respectively) and is to be injected immediately prior to major meals. Bioavailability is approximately 30–40%. Time to peak plasma is 20 min, and the half-life is 50 min following single injection. Pramlintide is approximately 60% protein bound and is eliminated renally. No dosage adjustments are suggested for patients with renal failure, but pramlintide has not been studied in patients with end-stage renal disease [14].

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2 Inhibitors)

Currently available SGLT2 inhibitors include canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance). These medications are taken orally once daily. Therapeutic doses are 50–300 mg/day for canagliflozin, 5–10 mg/day for dapagliflozin, and 10–25 mg/day for empagliflozin. Canagliflozin is 65% bioavailable, whereas dapagliflozin about 80% bioavailable. All of the SGLT2 inhibitors are highly protein bound (86% for empagliflozin, where canagliflozin and dapagliflozin are 99% and 91%, respectively). For all of the SGLT2 inhibitors, peak plasma is within 1–2 h and the half-life is about 13 h. SGLT2 inhibitors are either excreted unchanged in the urine or feces or glucuronidated to inactive metabolites, which are then eliminated in feces or urine. 33% of canagliflozin is excreted in the urine. Dapagliflozin and empagliflozin have a higher percentage of

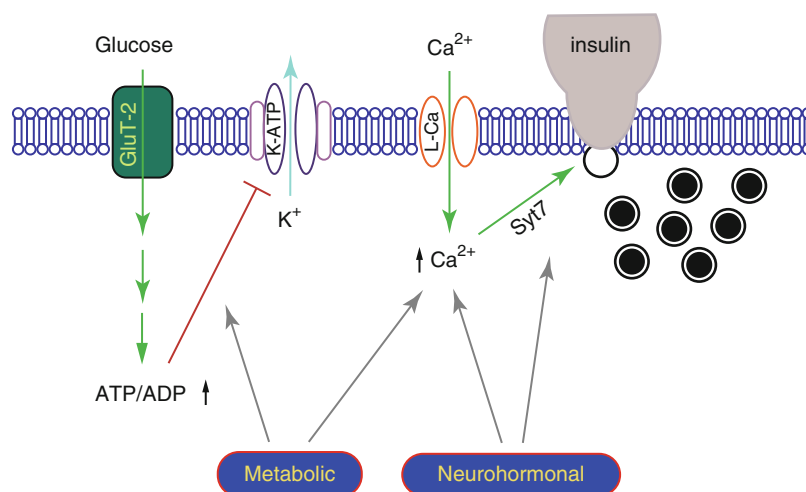


Fig. 3 Cellular and molecular regulation of insulin secretion. The cellular events leading to insulin secretion start with a rise in blood glucose level, which quickly leads to glucose uptake into pancreatic β -cells. Glucose in the cells then undergoes glycolysis and TCA cycle to produce ATP, resulting in an increased ATP/ADP ratio and consequent closure of K_{ATP} -channels. Membrane depolarization from K_{ATP} -channel closure opens L-type calcium channels, allowing calcium influx into the cells and the rise in

intracellular calcium levels. Calcium, mediated at least in part by synaptotagmin-7, then triggers insulin granule exocytosis and the release of insulin into blood. Many of the steps leading to insulin secretion are regulated by metabolic and neurohormonal signals. *GluT-2* glucose transporter 2, *TCA* tricarboxylic acid cycle, *Syt7* synaptotagmin-7, *K-ATP* ATP-sensitive potassium channel, *L-Ca* L-type calcium channel (From Shahidul Islam M [ed]: Calcium Signaling, Springer, 2012, with permission)

urinary excretion (75% and 54%, respectively) and therefore are not recommended for use if GFR is <60 L/min for dapagliflozin and <45 L/min for empagliflozin [15–17].

Pathophysiology

Insulin

In an individual with a normally functioning pancreas, endogenous insulin secretion (i.e., the exocytosis of secretory granules from pancreatic β cells) depends primarily on and is inversely related to the blood glucose concentration [1, 2]. It is influenced to a lesser degree by other nutrients, gastrointestinal hormones, and the autonomic nervous system. Increases in plasma glucose, amino acid, fatty acid, and ketone concentrations; the release of gastrointestinal inhibitory peptide, glucagon-like peptide-1, enteroglucagon, cholecystokinin, gastrin, gastrin-releasing peptide, secretin, and vasoactive intestinal peptide; and vagal stimulation, all of

which occur after the ingestion of glucose or other foods, promote insulin secretion. β_2 -Adrenergic receptor stimulation enhances insulin secretion, whereas α_2 -adrenergic receptor stimulation inhibits it. Hormonal and vagal effects explain why oral glucose is a more potent stimulant of insulin secretion than intravenous glucose is.

Insulin secretion ultimately is triggered by a rise in the intracellular concentration of calcium in response to the generation of adenosine triphosphate (ATP), primarily by the oxidation of glucose but also by the metabolism of other nutrients. It is thought that ATP binds to and blocks the pore-forming unit of ATP-sensitive and voltage-sensitive potassium channels in β -cell membranes. This activity inhibits potassium efflux, with consequent membrane depolarization leading to activation of voltage-sensitive calcium channels and the influx of calcium. Hormones and adrenergic receptors seem to potentiate or antagonize the action of glucose by stimulating or inhibiting adenylyl cyclase, increasing or decreasing intracellular cyclic adenosine monophosphate and calcium concentrations (Fig. 3).

Insulin lowers the serum glucose concentration by facilitating glucose uptake by the liver, myocardium, skeletal muscle, and adipose tissue and by inhibiting hepatic gluconeogenesis and glycogenolysis. Glucose enters cells by diffusion that is facilitated by a family of at least six distinct membrane glycoproteins that are known as glucose transporters (GLUT). Insulin stimulates glucose uptake by promoting the translocation of intracellular vesicles that contain GLUT (subtypes 1 and 4) to the cell membrane and by enhancing the synthesis of GLUT4. It first binds to insulin receptors, membrane glycoproteins that are ligand-activated tyrosine kinases, with consequent enzyme activation. The intervening cascade of events is not well characterized. Other actions of insulin are mediated, at least in part, by its ability to bind and stimulate insulin-like growth factor (IGF) receptors, particularly IGF-1 (also called *somatomedin C receptors*).

In excessive doses, insulin can cause hypoglycemia. Hypoglycemia inhibits endogenous insulin secretion and stimulates the secretion of a variety of counterregulatory hormones, most notably glucagon but also cortisol, epinephrine, estrogens, growth hormone (somatotropin), norepinephrine, somatostatin, and thyroid hormones. Epinephrine and norepinephrine contribute to the autonomic (sympathetic nervous system) symptoms of hypoglycemia (see later), and glucagon may be responsible for the Somogyi phenomenon (morning hyperglycemia after an episode of nocturnal hypoglycemia). Other counterregulatory hormones seem to have only a permissive role during recovery from hypoglycemia. Central nervous system manifestations of hypoglycemia are due to decreased cellular metabolism resulting from the lack of glucose (neuroglycopenia), an essential, and nearly exclusive, energy substrate for brain tissue, which is unable to synthesize glucose.

Sulfonylureas

Sulfonylureas enhance the secretion of insulin in response to increases in blood glucose [1–3] (Fig. 4). They bind to a distinct “sulfonylurea

receptor” site associated with ATP-sensitive and voltage-sensitive potassium channels on the β -cell membrane with consequent blocking of these channels, inhibition of potassium efflux, membrane depolarization, calcium influx, and insulin secretion. Extrapankreatic effects (e.g., decreased hepatic gluconeogenesis and insulin clearance, increased peripheral insulin sensitivity, stimulation of somatostatin secretion, and suppression of glucagon secretion) are thought to be clinically insignificant. Toxic effects are secondary to hyperinsulinemic hypoglycemia.

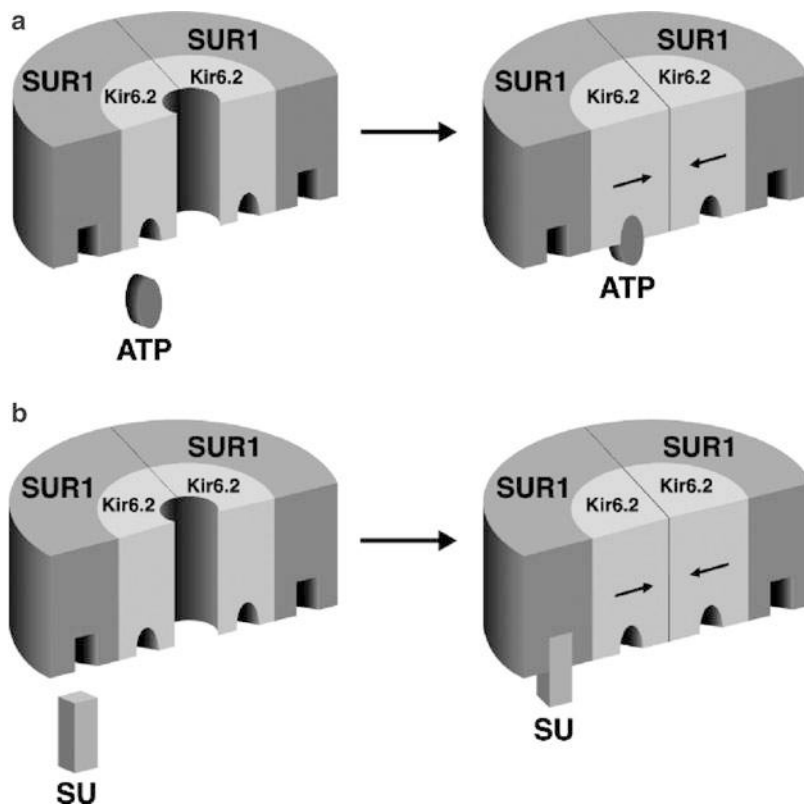
Meglitinides

Similar to the sulfonylureas, these agents bind to receptors on the β -cell membrane with consequent blocking of potassium channels, membrane depolarization, opening of calcium channels, and insulin secretion in response to increases in blood glucose [5, 6]. Toxic effects are due primarily to hyperinsulinemia and subsequent hypoglycemia.

Biguanides

Antihyperglycemic effects are due to enhanced peripheral glucose uptake and inhibition of hepatic gluconeogenesis [1–3, 8]. Metformin promotes glucose uptake by increasing the binding of insulin to its receptor and by increasing the synthesis and intracellular translocation of glucose transporters, such as GLUT-1 (also known as SLC2A1). It also enhances the tyrosine kinase activity of insulin receptors, promoting the uptake of glucose by skeletal muscle. Despite being used clinically for many years, the exact mechanism of action is not yet fully understood. Newer evidence suggests that metformin also inhibits complex I in the mitochondrial electron transport chain and that by lowering ATP levels in the mitochondria, AMP accumulates, thus disrupting the activity of enzymes in gluconeogenesis pathway, and inhibiting the body’s response to glucagon [18]. Although insulin (endogenous or exogenous) is required for metformin to be

Fig. 4 Closure of the pancreatic β -cell type K_{ATP} channel by ATP and sulfonylurea. Increased ATP caused by glucose metabolism closes the K_{ATP} channel by binding to the Kir6.2 subunit (a). Sulfonylureas close the channel by binding to the SUR1 subunit (b). The SUR2 subunit has binding sites for benzamide-derivatives in addition to sulfonylureas (SU). Although there are four binding sites for the ATP molecule and four binding sites for the sulfonylurea molecule in each channel complex, occupation of only one of these sites by ATP or sulfonylurea is sufficient to close the channel (Offermanns S and Rosenthal W [eds]: Encyclopedic Reference of Molecular Pharmacology, Springer, 2004, with permission)



effective, insulin levels are not affected, and hypoglycemia does not occur with metformin monotherapy or overdose.

Metformin associated lactic acidosis has also been fairly poorly understood, but now thought to be secondary to inhibition of complex I of the respiratory chain in addition to likely inhibiting various enzymes in the entry point from the glycolysis pathway in the citric acid cycle [19]. Higher metformin doses (as in overdose) and renal insufficiency are risk factors for development of this disorder. Therefore, any drugs which have potential to compromise renal function may precipitate this condition (aminoglycosides, iodinated radiographic contrast material, for example). In addition, medications which inhibit the organic cation transporter-2 (including cetirizine, trimethoprim) in the proximal tubules of the kidney may inhibit metformin secretion, causing build up of the drug and thereby precipitating lactic acidosis.

Thiazolidinediones

Thiazolidinediones primarily act by decreasing insulin resistance in adipose tissue, liver, and skeletal muscle, potentiating the effects of hypoglycemic agents [3, 20, 21]. They also decrease hepatic gluconeogenesis and have favorable effects on other risk factors for cardiovascular disease (e.g., blood pressure, fibrinolysis, lipid profile). However, there is ongoing concern that thiazolidinediones increase risk of heart failure, fracture, and weight gain. Stimulation of peroxisome proliferator-activated receptors, primarily the gamma subtype, which enhances the transcription of insulin-responsive genes involved in the control of glucose transport, use, and production (and in the regulation of fatty acid metabolism), is the underlying mechanism. Because thiazolidinediones enhance the effects of insulin, insulin and C peptide plasma concentrations are reduced, and hypoglycemia is not expected to occur with

monotherapy or overdose. Liver toxicity has been reported in therapeutic doses of rosiglitazone, troglitazone, and pioglitazone.

α -Glucosidase Inhibitors

α -Glucosidase inhibitors competitively and reversibly inhibit membrane-bound α -glucosidase, glucoamylase, maltase, and sucrase, enzymes that hydrolyze oligosaccharides (dextrins, maltose, maltotriose, and sucrose) to glucose in the brush border of the small intestine. This activity delays and partially decreases the absorption of glucose [3]. Acarbose also inhibits pancreatic α -amylase, which hydrolyzes ingested polysaccharides, such as amylose and amylopectin, or starch, to oligosaccharides. Although neither agent significantly inhibits lactase, the resultant malabsorption of nonlactose carbohydrates can result in gastrointestinal symptoms that are identical to those of lactase deficiency. Taken alone, α -glucosidase inhibitors do not cause hypoglycemia. Acarbose has been linked to elevated serum aminotransferase concentrations, which resolve upon discontinuation of the medication. Overdose of these medications would be expected to cause gastrointestinal upset, such as abdominal pain, bloating, diarrhea, and cramping.

GLP-1 Agonists and DPP-4 Inhibitors

GLP-1 is an incretin hormone, which is released from gastrointestinal L-type cells in response to an oral glucose load [10]. This hormone promotes insulin release from the pancreatic islet cells. In addition to insulin release, the hormone also delays gastric emptying, decreases food intake, improves insulin sensitivity, decreases postprandial glucagon secretion, and promotes synthesis of insulin (Fig. 5). GLP-1 is metabolized very quickly and is therefore therapeutically ineffective. GLP-1 agonists, however, are resistant to degradation. DPP-4 inhibitors and GLP-1 agonists have similar effects on blood glucose, as DPP-4 is responsible for degradation of GLP-1. The GLP-1 agonists and DPP-4 inhibitors are not expected to cause hypoglycemia as monotherapy

in therapeutic doses. These agents are not well studied in overdose and therefore information regarding acute overdose is limited to case reports. Report of an overdose of 90 μ g of exenatide did not result in hypoglycemia [22]. However, accidental administration of 10 times the normal dose of exenatide in a phase III clinical trial did result in hypoglycemia [23]. The actual glucose concentration is not reported. There are also reports of hypoglycemia associated with neteglinide and repaglinide overdose [24]. A recent review on clinical effects of exposures to DPP-4 inhibitors showed a rare incidence of clinically significant hypoglycemia in both intentional and accidental exposures [25].

Amylin Analogs

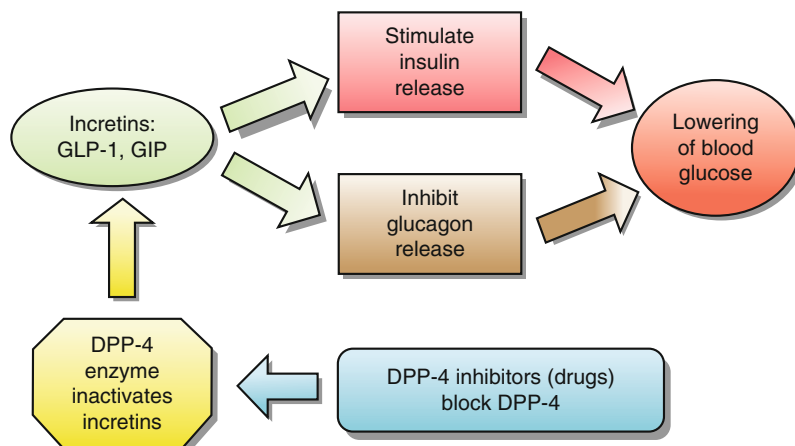
Pramlintide is an injectable synthetic amylin analog. Amylin is a 37 amino acid peptide, which is stored in pancreatic beta cells and released with insulin. Amylin and insulin have complementary effects, which is why pramlintide is used in conjunction with insulin therapy. Amylin works to regulate postprandial glucose serum concentrations by promoting satiety, delaying gastric emptying, and decreasing postprandial glucagon release [13, 26]. As this medication is added to insulin therapy, patients are at risk for hypoglycemia even with therapeutic doses, especially in the first 4 weeks of instituting therapy [27].

SGLT-2 Inhibitors

Sodium glucose cotransporter 2 inhibitors decrease plasma glucose by enhancing renal glucose excretion. About 90% of glucose is reabsorbed in the renal proximal tubules by SGLT2. The remaining 10% is then reabsorbed in the distal tubules by SGLT1. By inhibiting SGLT2, plasma glucose is decreased by increasing glucose in urine. Hypoglycemic episodes in conjunction with other antidiabetic agents have been reported. There is evidence that use of these medications increases risk of urinary tract infections as well as fungal vaginal infections.

Fig. 5 Physiology of DPP-4 inhibitors

(Courtesy of Wikipedia under Creative Commons)



Some of these infections have been life threatening [28, 29]. Many cases have been reported of patients taking prescribed doses of SGLT2 inhibitors and subsequently develop ketoacidosis with only mildly elevated plasma glucose. One case reported a patient on canagliflozin who presented with hypernatremia and hypercalcemia, likely from osmotic diuresis and subsequent dehydration [30]. The US Food and Drug Administration issued safety alerts in 2015 warning of the risks of ketoacidosis, urinary infections, and fractures (secondary to decreased bone mineral density) in patients taking SGLT2 inhibitors [31, 32].

Clinical Presentation

Hypoglycemia

Hypoglycemia, the hallmark of poisoning by insulin, sulfonylureas, and meglitinides, may result from therapeutic doses of these agents in nondiabetics and excessive doses in diabetics [33–36]. Accidental poisoning may occur after therapeutic dosing in individuals with diabetes who miss a meal or eat at a time that does not correspond to that of peak drug effects; increase their dose of a hypoglycemic agent or physical activity; change agents, formulations, or brands; or have another antidiabetic drug added to their therapeutic regimen. Agents without intrinsic hypoglycemic activity also can precipitate hypoglycemia when added to existing antidiabetic

therapy (Table 4). Predisposing factors include congestive heart failure; renal insufficiency; malignancy; sepsis; and conditions associated with limited glycogen reserves, such as extremes of age, malnutrition, and advanced liver disease [37].

Accidental poisoning also may result from dispensing errors (wrong drug or wrong dose). Poor handwriting and sound-alike drug names (e.g., chlorpropamide/chloroquine/chlorpromazine, Diabinese/Diamox, Tolinase/Tolactin) are responsible for some medication errors. Neonatal hypoglycemia can result from maternal drug exposure. As for all other agents, poisoning can occur in young children as a consequence of accidental ingestion, an innocent exploratory behavior in this age group.

Nonaccidental self-poisoning usually occurs in depressed, suicidal individuals but also may be encountered in individuals with factitious disorder. Factitious hypoglycemia can involve anyone who has access to hypoglycemic agents, such as diabetics, relatives of diabetics, and health care workers [38]. Difficult-to-diagnose but rare presentations of antidiabetic agent poisoning include attempted homicide and factitious disorder imposed on another [39]. A puncture wound, boggy skin, skin discoloration, and tenderness may be noted at the site of an insulin injection [40].

Autonomic manifestations of hypoglycemia include anxiety, diaphoresis, hunger, nausea and vomiting, palpitations and tachycardia,

Table 4 Agents that can cause hypoglycemia^a

Agent	Mechanism
Akee fruit (unripe)	Inhibition of gluconeogenesis by hypoglycin
	A toxin
Anabolic steroids	Enhanced peripheral insulin effect
ACE inhibitors	Inhibition of catecholamine release/effects
β_2 -agonists	Enhanced insulin secretion
β -blockers	Inhibition of catecholamine effects
Bromocriptine	Inhibition of growth hormone secretion/catecholamine effects
Calcium	Enhanced insulin secretion
Clofibrate	Enhanced peripheral insulin effect
Disopyramide	Unknown
Ethanol	Inhibition of gluconeogenesis
Lidocaine	Unknown
Lithium	Unknown
NSAIDs ^b	Unknown
Para-aminobenzoic acid	Unknown
Pentamidine	Destruction of pancreatic β cells with release of insulin
Propoxyphene	Unknown
PNU	Destruction of pancreatic β cells with release of insulin
Quinidine/quinine	Enhanced insulin secretion
Salicylates ^b	Enhanced insulin secretion and peripheral insulin effect
Streptozocin	Destruction of pancreatic β cells with release of insulin
Sulfonamides ^b	Unknown

ACE angiotensin-converting enzyme, NSAIDs nonsteroidal antiinflammatory drugs, PNU N-3-pyridylmethyl-N'-p-nitrophenylurea, Vacor

^aOther agents, implicated on the basis of isolated case reports, include chlorpromazine, cocaine, haloperidol, orphenadrine, para-aminosalicylic acid, sulfapyrazone, and valproate

^bThese and other highly protein-bound agents, such as warfarin and phenytoin, also can enhance the effect of sulfonylureas by decreasing the protein binding of sulfonylureas

tachypnea, paresthesias, tremors, and peripheral vasoconstriction with pallor and widening of the pulse pressure [33–36, 41–45]. As mentioned previously, multiple bioamines can be heightened or activated in the setting, such as norepinephrine and epinephrine. The absence of autonomic findings does not preclude a diagnosis of

hypoglycemia, however, particularly in patients who are taking medications with sympatholytic activity, such as β -blockers, clonidine, and prazosin, and in patients with long-standing diabetes who may have impaired autonomic function and counterregulatory hormone responses.

Tachydysrhythmias, primarily atrial fibrillation and premature atrial and ventricular beats but also atrial flutter; supraventricular, junctional, and ventricular tachycardia (monomorphic and polymorphic); and ventricular fibrillation have been reported [46, 47]. Electrocardiographic manifestations also include T-wave flattening and increases in the QT interval and QT dispersion [48]. ST segment depression also has been described [49]. Repolarization effects seem to be common yet subtle and often go unrecognized. These effects are thought to promote tachydysrhythmias and, similar to other autonomic effects, ultimately result from the action of counterregulatory hormones (primarily epinephrine) [50]. Tachydysrhythmias may be responsible for many cases of sudden, unexplained death in diabetics, particularly patients with early autonomic neuropathy, which results in sympathetic hyperactivity [51]. Bradycardia and heart block also can occur, but bradydysrhythmias seem to be much less common than tachydysrhythmias [52]. Both fetal bradycardia and tachycardia have been attributed to maternal hypoglycemia [41, 53]. Hypoglycemia also has been associated with congestive heart failure, worsening heart failure, and sudden death in patients with heart failure, but in most cases, it is not clear that a causal relationship exists [37, 54].

Prolonged (>1 h) hypoglycemia may lead to hypothermia [55, 56]. Neonates and infants also seem to be particularly susceptible to hypothermia. Less commonly, sympathetic hyperactivity secondary to hypoglycemia may cause hyperthermia. Other complications include respiratory failure and adult respiratory distress syndrome [57]. Cyanosis and respiratory failure have been noted in newborns and infants. Metabolic abnormalities commonly associated with hypoglycemia include hypokalemia; hypomagnesemia; hypophosphatemia [58]; and, rarely, hyponatremia, hypocalcemia, and metabolic acidosis. Serum insulin concentrations are always inappropriately high.

Neuroglycopenia initially causes impaired cognitive function manifested as altered affect, perception, and personality; difficulty with calculations, concentration, memory, and speech; and delirium [33–36, 41–45]. Ataxia, blurred vision, dizziness, fatigue, headache, generalized weakness, and malaise also may be noted. Neonates, infants, and young children may exhibit irritability and feeding problems. If neuroglycopenia persists, progressive deterioration in the level of consciousness occurs, with manifestations ranging from agitation and seizures to lethargy and coma, with or without focal findings [59–62]. Seizures may be single or recurrent and focal or generalized. Both brief and prolonged postictal periods have been described. Coma may be associated with decerebrate posturing, but brainstem reflexes, such as oculocephalic, oculovestibular, and pupillary reflexes, are usually preserved. Hemiplegia, with or without coma, and choreoathetosis also can occur. With prompt treatment, complete recovery is expected, but prolonged neuroglycopenia may result in permanent neurologic damage (e.g., cognitive dysfunction, cranial nerve palsies, cerebral infarction, coma, recurrent seizures, or death).

The time of onset and duration of hypoglycemia depend on the agent and dose involved. They also depend on the baseline glucose and the presence or absence of insulin antibodies and insulin resistance, with insulin-dependent diabetics tending to be less susceptible than nondiabetics to a given dose. Hypoglycemia after usual or slightly greater doses of insulin would be expected to begin around the time of peak effect of a therapeutic dose (see Table 4) [58]. Because insulin typically is administered in the morning and late afternoon or evening, hypoglycemia most commonly occurs between noon and supertime (from the morning dose) and during the late night or early morning hours (from the afternoon/evening dose). Larger doses likely would result in an earlier onset. Delayed onset of hypoglycemia also has been reported (23 h for regular insulin, 30 h for NPH insulin, and 44 h for Lente insulin) [63]. The duration of action seems to be dose related, with persistent or recurrent hypoglycemia lasting up to 6 days after massive insulin overdose

[64]. Although serum insulin concentrations do not seem to correlate with the severity of hypoglycemia, they do correlate with its duration, with hypoglycemia persisting until insulin concentrations return to normal [64, 65].

The incidence of hypoglycemia during sulfonylurea therapy seems to be related to the half-life of the agent involved, occurring more frequently with agents that have longer half-lives. In this setting, hypoglycemia most commonly occurs in the afternoon. In children with accidental sulfonylurea ingestions, the time of onset of hypoglycemia ranges from 0.5–16 h, with 50% occurring within 2 h and 96% occurring within 8 h, and a single tablet is potentially toxic [66, 67]. Data based on dispensing errors indicate that therapeutic doses also are potentially toxic in nondiabetic adults, but hypoglycemia sometimes may not occur until after the second or third dose. A single or extra therapeutic dose is unlikely to cause hypoglycemia in an adult diabetic. Although patients with intentional overdose often present with hypoglycemia long after ingestion (up to 48 h) [68], the maximal interval between ingestion and symptom onset in these patients is unclear. The duration of hypoglycemia seems to be dose related and typically ranges from hours to several days, although a case lasting 27 days has been reported [69].

Metformin Associated Lactic Acidosis

Metformin associated lactic acidosis may occur acutely after large intentional overdose in adults [70–73]. More commonly, this complication occurs when a therapeutic dose is increased or patients on long-term therapy develop conditions that decrease drug or lactate metabolism or increase lactate production (as in severe illness or sudden decrease in GFR) [19, 74–76]. In these settings, onset typically is insidious. Symptoms are nonspecific and include anorexia, lethargy, nausea, vomiting, diarrhea, thirst, and abdominal pain. Hyperpnea and signs of dehydration, hypoxia, or shock may be present. Laboratory evaluation reveals an increased anion gap metabolic acidosis with elevated plasma lactate

(>5 mEq [or mmol]/L) [74]. Ketosis (of unclear origin) may or may not be present [75, 77]. Mortality of this condition is certainly improving but still quite high and reported to be about 50% [78].

Diagnostic Considerations

Although a blood glucose concentration of less than 70 mg/dL (3.9 mmol/L) is considered low, clinical hypoglycemia requires the presence of symptoms. Whipple's triad [43–46, 79] for the diagnosis of hypoglycemia consists of low blood glucose, symptoms of hypoglycemia, and improvement after glucose administration. There are situations of clinical hypoglycemia, however, in which these criteria are not met, including the empirical administration of glucose when a blood sample cannot be obtained and failure to respond to glucose because irreversible neurologic damage has occurred. Patients with serious sulfonylurea toxicity may also not respond to intravenous glucose therapy alone [68, 80].

Signs and symptoms of hypoglycemia usually occur when the serum glucose level decreases to 40–45 mg/dL (2.2–2.5 mmol/L), but there is substantial individual variation. Although autonomic manifestations typically precede manifestations of neuroglycopenia, diabetics with autonomic neuropathy may be asymptomatic until symptoms of neuroglycopenia develop. Women tend to be asymptomatic at lower blood glucose concentrations than men, and children tend to be asymptomatic at lower values than adults. Symptoms are more likely to occur when glucose concentrations decrease rapidly or by a large amount and depend on the baseline glucose value. Symptoms can occur in diabetics with normal or even elevated glucose levels if they are accustomed to a higher baseline level and experience a rapid decline in their glucose concentrations. Conversely, when glucose levels slowly decline, such as with prolonged fasting, symptoms may be absent despite glucose levels of 20–30 mg/dL (1.1–1.6 mmol/L) [81] because high levels of free fatty acids and ketone bodies provide alternative energy substrate.

Table 5 Medical conditions that can cause hypoglycemia

Decreased glucose availability
Decreased glucose absorption: diarrhea, malabsorption syndromes
Decreased glucose intake: fasting, acute or chronic malnutrition due to illness or starvation, vomiting
Inability to synthesize glucose: inborn errors of metabolism (gluconeogenic enzyme deficiency)
Inability to synthesize, store, or metabolize glycogen: inborn errors of metabolism (glycogen synthesis and glycogenolysis enzyme deficiency, glycogen storage diseases), liver disease (especially acute hepatic failure, Reye's syndrome), end-stage renal failure
Increased glucose utilization
Deficiency of counterregulatory hormones: adrenal, pancreatic, pituitary, and thyroid disease
Increased insulin activity or secretion: insulin antibodies with insulin-like activity (pseudohyperinsulinemia), pancreatic β -cell adenoma (insulinoma) or ductal overgrowth (neonatal nesidioblastosis), reactive hypoglycemia (dumping syndrome, postprandial)
Increased metabolic demands: fever/sepsis, large tumor loads, pregnancy
Lack of alternative energy sources: decreased fat stores (malnutrition), inability to metabolize or mobilize fat (carnitine deficiency)

The differential diagnosis of hypoglycemia includes nonantidiabetic drug exposure (see Table 4) [34–36], a variety of medical conditions (Table 5), and antidiabetic agent poisoning. Direct inspection of all prescribed pills and independent confirmation of their identity by imprint code may disclose a medication error. Failure of the blood glucose concentration to normalize after intravenous glucose administration is usually a consequence of severe sulfonylurea poisoning [68, 81]. The presence of low birth weight and other metabolic abnormalities (e.g., high lactate acidemia or high free fatty acid levels, ketosis) in a neonate suggests an inborn error of metabolism [82]. Although virtually any neurologic manifestation, including focal findings, is consistent with a diagnosis of hypoglycemia, failure of the dysfunction to respond to normalization of the blood glucose concentration should prompt evaluation (e.g., computed tomography scan, lumbar puncture) for conditions such as central nervous system infarction, infection, or hemorrhage.

After clinical evaluation, if the cause of hypoglycemia is not apparent, measurement of serum insulin, C peptide, and proinsulin levels and toxicology testing may be helpful [37]. To interpret hormone levels properly, samples must be obtained at the time of hypoglycemia. Insulin secretion normally is suppressed and insulin and C peptide levels are low when hypoglycemia is present. When hypoglycemia is due to exogenous insulin or to oral hypoglycemics and other agents and conditions that enhance endogenous insulin secretion (see Tables 4 and 5), however, serum insulin concentrations are elevated. Except with exogenous insulin exposure, C peptide also is elevated. An alternative, more sophisticated approach is to determine the molar ratio of insulin to C peptide [83]. Because C peptide has a longer half-life than insulin, this ratio is less than 1, unless exogenous insulin has been administered. This relationship seems to hold for patients with renal failure, who may have abnormally high baseline levels of insulin and C peptide, but not for diabetics who have insulin antibodies, which can elevate insulin levels falsely. Diabetics with insulin antibodies who have insulin-like activity (i.e., autoimmune hypoglycemia) have low C peptide levels, whereas diabetics with insulin antibodies who lack such activity (e.g., diabetics with insulin resistance) have elevated C peptide levels [84].

Proinsulin levels also are elevated when hypoglycemia is due to enhanced endogenous insulin secretion [85]. Insulinomas can be differentiated from other causes by the presence of an increased ratio of proinsulin to insulin. Although sulfonyleurea overdose also can produce these findings, proinsulin levels are not nearly as high as they are with insulinomas. An inappropriately low level of IGF-1 binding protein [86] and exaggerated insulin [87] and glycemic (>30 mg/dL increase in blood glucose level) [88] responses to glucagon also are seen in patients with endogenous hyperinsulinemia.

Detection of oral hypoglycemic agents and measurement of insulin concentration require sophisticated laboratory methods and therefore are not routinely available. For the laboratory investigation of potential antidiabetic agent

poisoning, it is advisable to consult with laboratory personnel to determine the appropriate specimen (blood or urine) and test for detecting or measuring the suspected agent or agents involved.

Treatment

Hypoglycemia

Although standard life-support measures sometimes may be required, increasing the blood glucose level is often all that is necessary when hypoglycemia is the underlying cause of physiologic derangement. This is the rationale for performing a rapid bedside glucose determination or empirically administering glucose in patients with altered mental status, the hallmark of neuroglycopenia. Supportive care also should include correction of fluid and electrolyte abnormalities.

Indications for ICU Admission in Antidiabetic Agent Poisoning

Patients with unstable vital signs or unstable cardiac rhythm and evidence of myocardial ischemia or acute infarction associated with hypoglycemia

Patients with neurologic dysfunction that persists despite normalization of the blood glucose and for those with significant acidemia owing to metformin poisoning

Note:

ICU admission is not routinely indicated for the monitoring of asymptomatic patients with a history of antidiabetic agent overdose and the monitoring and treatment of those with reversible hypoglycemia, but it may be necessary if continuous observation, frequent blood testing for glucose and other analytes, and therapy for hypoglycemia cannot be provided elsewhere.

Cardiac monitoring is not routinely necessary for patients who are asymptomatic or have reversible hypoglycemia, but it may be appropriate for those with underlying cardiovascular disease.

The preferred treatment for hypoglycemia is sucrose or dextrose (D-glucose). (Grade II-1 recommendation) Dextrose can be given orally to patients who are awake and cooperative. Chewable 4-g tablets and gels containing 15 g of dextrose are available. The usual adult dose is 10–20 g. Alternatively, candy or a cup of fruit juice with several teaspoons of added sugar can be given [89]. Table sugar (sucrose) may not be effective, however, for patients taking α -glucosidase inhibitors. Oral glucose solutions should not be given to patients who lack adequate protective airway reflexes.

Intravenous dextrose is necessary for patients who cannot take it orally. Dextrose is available in a variety of formulations, with 50-mL ampoules of 10%, 25%, and 50% solutions (i.e., D10, D25, and D50) containing 5, 12.5, and 25 g of dextrose, respectively, being the most common. The 50% solution can be used in adults and children, but lower concentrations are recommended for infants and neonates. The goal of therapy is to increase the serum glucose to normal levels (70–110 mg/dL [3.9–6.1 mmol/L]). Care should be taken not to overtreat because hyperglycemia stimulates endogenous insulin secretion and promotes recurrent hypoglycemia. This phenomenon of rebound hyperinsulinemia after glucose administration, which has been well documented in sulfonylurea poisoning [68], also seems to occur after insulin overdose [90]. It can lead to a vicious cycle of alternating hyperglycemia and hypoglycemia, making treatment unduly complicated. In addition, there are wide individual variations in the magnitude of rise in serum glucose in response to a given dose of intravenous dextrose [91, 92]. Except in prolonged neuroglycopenia resulting in permanent brain damage and in severe sulfonylurea poisoning, return to normal mental status can be expected to occur rapidly (within seconds to minutes of dextrose administration). If this does not occur either prolonged hypoglycemia has been present or there is an unrelated cause for the hypoglycemia.

It is important that proper functioning of the intravenous line be confirmed before administering intravenous dextrose because these solutions

are extremely hypertonic (2525 mOsm/L for D50) and can cause tissue necrosis if extravasation occurs. They also can cause vein irritation, with pain, phlebitis, and venous thrombosis. Rapid administration also can cause hyperosmolality and consequent central nervous system dysfunction. For these reasons, slow injection is preferred. Other potential complications include fluid overload, hypokalemia, hypophosphatemia, and hypomagnesemia. In patients who are at high risk for Wernicke's encephalopathy (e.g., alcoholics and malnourished patients), concomitant administration of intravenous thiamine is prudent.

If an intravenous line cannot readily be established, intramuscular or subcutaneous glucagon, 1 mg for adults and children weighing more than 20 kg and 0.5 mg for children weighing less than 20 kg, can be given [1–3, 93]. (Grade I recommendation) Glucagon increases serum glucose by enhancing glycogenolysis. Clinical effects are slower in onset than they are with intravenous dextrose, with return to normal mental status occurring in 5–20 min. [94] Glucagon may be ineffective if hepatic stores of glycogen are diminished (e.g., in malnourished patients). Because effects may be transient, supplemental glucose should be given subsequently. Glucagon, like glucose, stimulates insulin secretion and can promote recurrent hypoglycemia, especially in the context of sulfonylurea ingestion or insulinoma [95]. Vomiting is a relatively common side effect.

Patients who respond to dextrose or glucagon then should be fed a meal. Diabetics with therapeutic misadventures involving insulin or an antihyperglycemic agent are unlikely to experience recurrent hypoglycemia and can be discharged, provided that they can monitor their blood glucose at home and have a responsible third party stay with them. Medication dosage adjustment also may be necessary. Patients with intentional insulin overdose and intentional or unintentional oral hypoglycemic agent exposure are at risk for delayed or recurrent hypoglycemia and require prolonged and frequent or continuous clinical monitoring with hourly blood glucose determinations, which generally can be

accomplished only in an emergency, intermediate, or intensive care unit setting. Little is known about GLP-1 agonist, DPP-4 inhibitor, pramlintide, and SGLT2 inhibitor overdose. For this reason, it is suggested to admit these patients until more data can be gathered.

Recurrent hypoglycemia can be treated initially with an intravenous bolus of dextrose as described earlier. If needed, a continuous infusion of D₁₀W also can be used, starting at a basal glucose requirement rate of about 0.1 g/kg/h or 1 mL/kg/h and adjusted upward as necessary [91]. However, in sulfonylurea overdose specifically, this therapy may not be successful as most of these patients will have intact pancreatic function. In these patients, after a glucose bolus is administered, insulin is secreted, contributing to another hypoglycemic episode. Therefore, after the initial IV bolus of dextrose for symptomatic sulfonylurea overdose, treatment with octreotide (Sandostatin) is expected to be more effective than dextrose infusions [96]. (Grade I recommendation)

Octreotide is a synthetic analogue of the naturally occurring pituitary gland hormone somatostatin [1, 3]. Similar to somatostatin, it regulates the function of the pituitary gland, pancreas, and intestine by inhibiting the secretion of insulin, glucagon, and other hormones from these organs (see ► Chap. 156, “Octreotide” for greater detail of the clinical pharmacology of this agent). To treat oral hypoglycemic poisoning, octreotide usually is given subcutaneously in a dose of 50 µg every 6 h. Continuous infusions also have been used. When used in this setting, no significant side effects have been reported.

Diazoxide is a vasodilator antihypertensive agent that is related structurally to thiazide diuretics and has also been used for oral hypoglycemic overdose [1, 3]. Tachycardia and orthostatic hypotension are common with diazoxide use. The other main side effect of diazoxide, sodium and water retention, could add to the free water effects of dextrose therapy.

Octreotide was found to be superior to diazoxide in preventing hypoglycemia in glipizide-poisoned volunteers. It was so effective

that some subjects did not even require supplemental glucose. Given the efficacy of octreotide and side effect profile of diazoxide, octreotide has replaced diazoxide therapy in acute oral hypoglycemic overdose. In the same study, dextrose requirements were shown to be similar when treated with diazoxide or dextrose infusion alone and both treatment arms measured high levels of insulin in the poisoned patients. Therefore, with the limited evidence available, it is not recommended that diazoxide be used when octreotide is unavailable as it is likely similarly efficacious to dextrose infusion and has unwanted side effects [80, 97].

When a second episode of hypoglycemia occurs, more episodes are likely. Because the risk of recurrence and the duration of risk are variable and unpredictable, however, the optimal duration of insulin secretion inhibitor therapy is unknown. One approach is an initial treatment period of 24 h followed by close monitoring for hypoglycemia for another 12–24 h, because delayed recurrence of hypoglycemia has been reported after such therapy [97, 98]. Should another episode of hypoglycemia occur, reinstitution of treatment for an additional 24 h should be considered.

Measures to prevent drug absorption and enhance drug elimination also should be considered. Gastric decontamination measures may be appropriate for acute oral overdoses involving hypoglycemic agents and metformin. Activated charcoal adsorbs sulfonylureas [99]. However, there are no data indicating that activated charcoal administration alters the outcome in these patients. It is unlikely that activated charcoal will have a significant effect on drug absorption if given greater than 1 hour post-ingestion [100]. Surgical excision of tissue from the site of injection of insulin overdose has been reported [101, 102], but the efficacy of this intervention is anecdotal, and the necessity of performing it remains questionable due to the inherent risks and invasiveness of such a procedure. Urinary alkalization will enhance the elimination of chlorpropamide [103]. Therefore, it should be

considered in order to shorten time-course of poisoning. This exceedingly rare event should be done so with proper supportive care and treatment of hypoglycemia as above [104].

Metformin-Associated Lactic Acidosis

The treatment of metformin poisoning is primarily supportive [19, 73, 75]. Intravenous saline can be given to correct dehydration, with caution not to cause fluid overload in patients with decreased urinary output. Intravenous saline also should enhance the elimination of metformin, but the efficacy of inducing diuresis for this purpose, although theoretically attractive, has not been proven. Hemodialysis is indicated for refractory acidosis. It also is effective in removing lactate, pyruvate, and ketones and as supportive therapy for uremia. Recently published workgroup recommendations outline indications for extracorporeal treatment, which are as follows: lactate concentration greater than 20 mmol/L, pH less than or equal to 7.0, shock, failure of standard supportive measures, and decreased level of consciousness. The group goes on to recommend that extracorporeal treatment be continued until the lactate concentration is less than 3 mmol/L and pH greater than 7.35. Intermittent hemodialysis is recommended initially, but continuous renal replacement therapies may be considered if hemodialysis is unavailable [19, 71, 105, 106]. (Grade III evidence)

Criteria for ICU Discharge in Antidiabetic Agent Poisoning

Normal vital signs, normal cardiac rhythm, and no sign of hypoglycemia-induced cardiac ischemia

Resolution or stabilization of hypoglycemia-induced neurologic dysfunction

In the case of metformin, resolution of the metabolic acidosis

Common Errors in Antidiabetic Agent Poisoning

Failure to consider the possibility of occult exposure to antidiabetic agents or their surreptitious use in patients with unexplained hypoglycemia, particularly those who are health care workers or relatives of diabetics

Failure to include exposure to nonantidiabetic drugs and potential drug interactions in the differential diagnosis of hypoglycemia

Failure to appreciate that a blood glucose level less than 70 mg/dL (3.9 mmol/L), while statistically abnormal, is not sufficient to make a diagnosis of hypoglycemia; that there is substantial individual variability in the glucose level at which signs and symptoms of hypoglycemia develop; that an abnormally low blood sugar may be seen in asymptomatic individuals, particularly women and children; that some individuals, especially diabetics, may exhibit signs and symptoms of hypoglycemia at normal or even elevated blood glucose levels; and that the administration of glucose solely on the basis of an abnormally low blood glucose level is unnecessary and will obscure the diagnosis of antidiabetic agent poisoning

Failure to appreciate that sulfonylurea-induced hypoglycemia may be delayed in onset and prolonged in duration and that an extended period of observation is required for patients with unintended or excessive exposure to such agents

Failure to appreciate that the oral administration of table sugar and complex carbohydrates may not be effective in treating hypoglycemia in patients taking alpha-glucosidase inhibitors

Failure to appreciate that overzealous treatment of hypoglycemia resulting in hyperglycemia will stimulate insulin secretion and can promote recurrent hypoglycemia, particularly in patients with sulfonylurea poisoning

Key Points in Antidiabetic Agent Poisoning

1. Hypoglycemia, the hallmark of antidiabetic agent poisoning, can result from exposure to hypoglycemic agents, which cause hyperinsulinemia either directly (exogenous insulin) or indirectly by enhancing endogenous insulin release (sulfonylureas, meglitinides, GLP-1 agonists, DPP-4 inhibitors) or to antihyperglycemic agents, which do not cause hypoglycemia when taken alone but which enhance the tissue action of insulin (biguanides and thiazolidinediones) or prevent the intestinal absorption of carbohydrates (alpha-glucosidase inhibitors) and thus potentiate the effect of hypoglycemic agents.
2. Signs and symptoms of hypoglycemia are due to central nervous system dysfunction resulting from the lack of essential energy substrate (neuroglycopenia) and autonomic dysfunction (sympathetic hyperactivity) caused by the effects of counter-regulatory hormones, primarily epinephrine.
3. The magnitude of increase in blood glucose that occurs in response to exogenous glucose administration, the preferred treatment for hypoglycemia, is variable and unpredictable, making it difficult to avoid causing hyperglycemia, a phenomenon that occurs most commonly, but not exclusively, in sulfonylurea poisoning.
4. The administration of octreotide, which inhibits endogenous insulin secretion, can prevent rebound hyperinsulinemia and decrease the incidence of recurrent hypoglycemia resulting from glucose therapy in patients with sulfonylurea-induced hypoglycemia.
5. Metformin, by inhibiting complex I of the mitochondrial electron transport chain, can cause lactic acidosis following acute overdose and under conditions of reduced drug elimination or increased lactate production. Therapy is primarily supportive, with extracorporeal elimination being reserved for refractory acidosis.

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Microtubules are present in all eukaryotic cells. They are responsible for movement of vesicles within cells, motion of cilia and flagella, and chromosome separation in mitosis. In neurons, microtubules serve as tracks for protein particles and organelles that move up and down the axon. They also can direct proteins for repair of cellular injury. Antitubulin agents, including colchicine, vincristine, vinblastine, and podophyllin, inhibit the construction of microtubules, which accounts for the therapeutic and the toxic actions of these agents.

Colchicine

Colchicine is an alkaloid derived from *Colchicum autumnale*, a member of the family Liliaceae [1], and from *Gloriosa superba* (glory lilly) [2, 3]. *C. autumnale* is a perennial plant that is known commonly as *autumn crocus*, *wild saffron*, *meadow saffron*, *naked lady*, *naked boy*, and *son before the father*. This plant is indigenous to temperate areas of Europe, Asia, and America. It is unusual because it flowers after the long, lanceolate leaves wither back and fall off (hence the “son before the father”). All parts of the plant contain colchicine, but the highest concentration is in the bulb, which is rooted underground [1]. Accidental and intentional ingestion of *Colchicum autumnale* has led to fatal poisoning despite supportive measures [4, 5]. Intentional ingestion of *Gloriosa superba* has also been reported to result in

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significant toxicity that is indistinguishable from poisoning with colchicine [6].

Colchicine has been used since the sixth century A.D., when it was introduced by Alexander of Tralles as a treatment for gout. It is said that Benjamin Franklin also used colchicine as a remedy for his gouty arthritis and possibly introduced it into the United States [1, 7]. Purified colchicine later was isolated from *C. autumnale* tubers in 1820 by Syng Dorsey and became widely known as a treatment for gouty arthritis [2].

In 2009, the US Food and Drug Administration (FDA) approved oral colchicine for the treatment of gouty arthritis, preventing gout attacks, and managing familial Mediterranean fever [8]. Previously, oral colchicine had been used for many years in the United States as an unapproved drug without FDA-approved prescribing information, dosage recommendations, or drug interactions. Over the years, colchicine has also been advocated for pseudogout, sarcoidosis [9], scleroderma [10], amyloidosis [11], Behçet's disease [12, 13], psoriasis [14], systemic sclerosis [15], Paget's disease, condyloma acuminatum [16], brown recluse spider envenomation [17], alcoholic cirrhosis [18], primary biliary cirrhosis [19], Sweet's syndrome [20], and low back pain [21, 22].

Despite being available since the 1950s, the FDA withdrew marketing approval for IV colchicine after numerous deaths were associated with its use were reported. In fact, 20 adult deaths were reported between 1983 and 2000 after IV administration of colchicine [23]. In addition, in 2007 a compounding error lead to 3 deaths in the US states of Washington and Oregon after patients received IV colchicine for back pain at an alternative medicine clinic [24, 25].

Biochemistry and Pharmacokinetics

Colchicine has a complex structure (Fig. 1). Tropolones have a hydrogen ion, which resonates between an oxygen and methyl group. Wallace [26] identified five colchicine analogues. It was found that one analogue lacked a tropolone structure; that particular analogue failed to have antiinflammatory activity (Table 1).

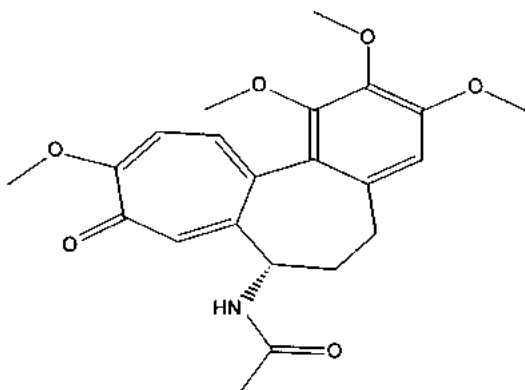


Fig. 1 Chemical structure of colchicine

Table 1 Colchicine pharmacokinetics [27]

Time to peak concentration	0.5–3 h
Bioavailability	25–50%
Protein binding	10–50%
Volume of distribution	2–12 L/kg
Mean elimination half-life	4.4–16 h therapeutic use 11–32 h in overdose
Hepatic metabolism	CYP 3A4
Lowest reported lethal dose	7 mg
High fatality rate	>0.5 mg/kg

The kinetics of colchicine are variably reported, but the most frequently cited observations regarding absorption from the gastrointestinal tract show the occurrence of a peak plasma concentration in 30 min to 3 h. Approximately 10–50% of the drug is protein bound, and its volume of distribution is estimated to be 2–12 L/kg. This information allows for an understanding of the limited efficacy of hemodialysis as a means of enhancing drug clearance. The major route of elimination of colchicine is through hepatic metabolism and biliary excretion. Colchicine undergoes extensive first-pass metabolism, which explains its decreased bioavailability of 25–50%. It is believed that enterohepatic recirculation may prolong exposure of the intestinal mucosa to colchicine [1]. Twenty percent of unchanged drug is excreted in the urine [28]. In the setting of preexisting renal or hepatic impairment, these elimination percentages may change. Thus, patients with impaired hepatic or renal

function are at significant risk for toxicity even on conventional dosing.

Colchicine has been reported to have a half-life of 4.4 to 16 h with therapeutic dosing and can reach 11–32 h in overdose. Colchicine has been found in white blood cells and in urine 9 days after a single intravenous bolus [7, 29, 30]. Because colchicine is metabolized through cytochrome P-450 CYP3A4, its breakdown may be inhibited or induced. Inhibitors of CYP3A4, such as clarithromycin, cimetidine, ketoconazole, erythromycin, diltiazem, ritonavir, verapamil ER, and grapefruit juice, frequently produce increases in serum concentrations of colchicine. Inducers of CYP3A4 include rifampin, St. John’s wort, phenobarbital, and phenytoin, which tend to lower serum colchicine concentrations. Multiple studies have demonstrated that drugs which inhibit P-glycoprotein, such as clarithromycin and cyclosporine, increase the risk of toxicity by increasing colchicine concentrations [31]. The combination of colchicine and statin medications has become a concern as numerous anecdotal reports have described cases of acute myopathy including rhabdomyolysis [32–35]. In 2010, the AGREE (The Acute Gout Flare Receiving Colchicine Evaluation) study concluded “low-dose colchicine yielded both maximum plasma concentration and early gout flare efficacy comparable with that of high-dose colchicine, with a safety profile indistinguishable from that of placebo.” This conclusion has led to recommendations for using low-dose colchicine for the treatment of gout. The use of low-dose colchicine decreases gastrointestinal side effects and should also reduce potential drug–drug interactions (Table 2) [36].

Pathophysiology

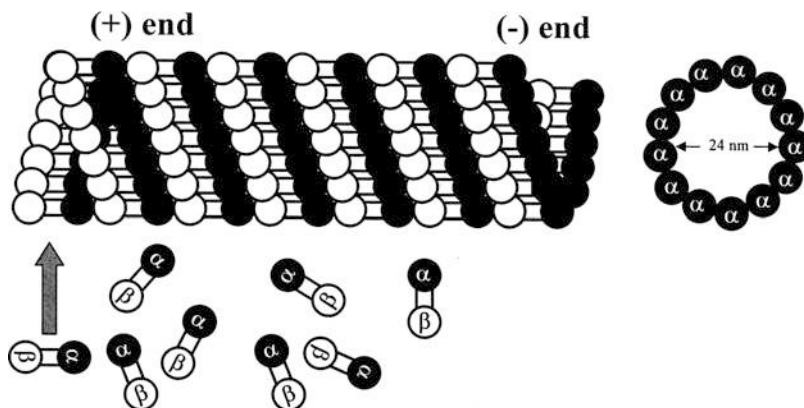
Microtubules are formed by polymerization of protein subunits, G actin and tubulin. Tubulin is present in α , β , and γ forms; α and β tubulin combine as dimers that serve as the building blocks of microtubules, and γ tubulin seems to play a role in the organization of these dimers during the assembly of a tubulin sheet. The sheet connects end to end to form the cylindrical origin

Table 2 Drug interactions [37, 38]

3A4 inhibitors	P-glycoprotein, substrates, and modulators
Macrolides: clarithromycin, erythromycin, telithromycin	Macrolides: erythromycin, clarithromycin
Antibiotics: ciprofloxacin, isoniazid	Cyclosporine
Cimetidine	Tacrolimus
Antifungals: fluconazole, itraconazole, ketoconazole	Verapamil
Calcium channel blockers: diltiazem, verapamil, nifedipine, mibefradil	Statins
Ritonavir, indinavir, nelfinavir, saquinavir	Fexofenadine
Grapefruit juice	Fenofibrate
Antidepressants: fluoxetine, sertraline, nefazodone	Antineoplastics
Protease inhibitors	TCAs
Amiodarone	Digoxin
Cyclosporine	HIV-1 inhibitors
	Glucocorticosteroids
	Ketoconazole

of the microtubule [39]. The microtubule is composed of repeating α and β tubulin subunits in a helical array measuring 24 nm in diameter (Fig. 2) [40]. The tubulin dimer has oppositely charged ends. Because the dimers are aligned repetitively, the microtubule they form has a positive end and a negative end. This alignment confers polarity to microtubules, which is crucial to their function. They are connected in elaborate networks depending on the function they serve within the cell. Microtubules form a diverse array of permanent (stable) and transient (unstable) structures. Stable microtubules are found when long-lived microtubules are needed, such as the axoneme in the flagellum of sperm and the marginal band of microtubules in most red blood cells and platelets or nerve cells. Unstable microtubules are found when cell structures composed of microtubules need to disassemble and assemble quickly. During mitosis, the cytosolic microtubule network that occurs in interphase disappears, and the tubulin from it is used to form the spindle-shaped apparatus that partitions chromosomes equally into daughter cells. Neurons must maintain long axons and do this with the aid of microtubules that continue to assemble (polymerize), and add to the chain. Disassembly of these stable structures has catastrophic effects, such as nonmobile sperm,

Fig. 2 Microtubule assembly occurs at the positive end, whereas disassembly occurs at the negative end. Antitubulin compounds prevent the addition of tubulin at the positive end and stop assembly



nonpliable red blood cells, and retracting axons [39].

Vinca alkaloids, colchicines, and podophyllin all inhibit the construction of microtubules that compose spindles in metaphase. This inhibition interrupts migration of the chromosomes toward the poles during mitosis but does not affect chromosome condensation. Because of this ability, colchicine is used in research to produce metaphase chromosomes for cytogenetic study. Each dimer of tubulin has a single high-affinity binding site for colchicine. When one or two vinca alkaloid-bound, podophyllin-bound, or colchicine-bound tubulin dimers attach to the end of the developing microtubule, additional assembly stops. Although these compounds inhibit spindle formation, they do not cause their disassembly at lower doses. When assembly is halted at the positive end of the microtubule, naturally occurring disassembly at the negative end continues. At high doses, however, some of these compounds also may enhance disassembly [41].

Microtubule formation is regulated by the number of tubulin dimers. As the number of “free” dimers within the cell increases, they bind to ribosomes and shut down the production of tubulin mRNA. The antitubulin compounds, via their inhibition of tubulin dimer polymerization, increase the number available to inhibit mRNA production. They do not seem to affect the more permanent microtubules because at therapeutic doses their impact is primarily on the *assembly* of the microtubule.

Vincristine and vinblastine also inhibit the formation of mitotic spindles, interrupting cell division. They appear to crystallize free tubulin dimers. As a result of this action, they preferentially kill rapidly dividing cells, such as tumor cells. This effect also causes cell death in gut and hair cells because of their rapid division. Although the vinca alkaloids bind to tubulin, preventing polymerization in a fashion similar to that of colchicine and podophyllotoxin, they seem to have a different binding site [40].

The mechanisms of action of colchicine have been studied extensively but remain unclear. Colchicine's action seems to depend on its rings, which are believed to bind microtubules, inhibiting the movement of intracellular granules. This inhibition disturbs the excretion of various components to the cell exterior. Colchicine inhibits multiple aspects of neutrophil activity, including adhesiveness, ameboid activity, mobilization, and degranulation of lysosomes, but the most studied is the inhibition chemotaxis [28]. Colchicine is thought to work primarily through this inhibited chemotactic mechanism in the treatment of gout (Table 3) [42, 43].

Clinical Presentation

Cases of overdose of colchicine are not common but are associated with significant morbidity and mortality. Mortality overall is approximately 10% but approaches 100% for cases in which the ingestion is 0.8 mg/kg or greater [2]. A review

Table 3 Stages of colchicine toxicity

Stage	Onset (postingestion)	Clinical findings
1. Gastrointestinal stage	0–24 h	Nausea, vomiting, diarrhea Abdominal pain Dehydration leukocytosis
2. Multi-organ failure stage	1–7 days	ARDS Cardiac arrhythmias, CHF Cardiac arrest Encephalopathy Cerebral edema Seizures Renal failure Hepatic failure DIC Bone marrow suppression Pancytopenia Hemolysis Metabolic derangements: metabolic acidosis Hypokalemia, hyponatremia, hypocalcemia Hypoglycemia (or hyperglycemia) Hypophosphatemia Myopathy Neuropathy Secondary sepsis
3. Recovery stage	7–21 days	Alopecia Recovery of organ function Rebound leukocytosis

Modified from [27].

by Baum and Meyerowitz found that although about 90% of persons treated with colchicine for gout are men, the intentional use of this drug in overdose occurs more often in women [44].

Acute ingestion of colchicine is heralded by gastrointestinal symptoms for the first 24 h. Profound nausea, vomiting, and diarrhea are common [29]. Abdominal cramping and melanotic stools are reported in several cases [3, 45, 46]. These symptoms can cause circulatory collapse due to fluid losses and electrolyte abnormalities. Gastrointestinal symptoms are used as an end point of

therapy in the treatment of gout. Typically, these symptoms ensue within minutes of ingestion. The cause is believed to be a direct toxic effect of colchicine on the gut epithelial cells [1]. Emesis may be centrally mediated as well, however, as suggested by an animal study by Ferguson [47] in which gastrectomized animals vomited anyway.

Beginning at 24–36 h, the second stage consists of multiple organ failure. Hematopoietic changes begin with noticeable peripheral leukocytosis [1, 16, 30], which reverses quickly and is followed by pancytopenia. Hemorrhage may develop secondary to hepatic dysfunction and thrombocytopenia. Hepatotoxicity and adult respiratory distress syndrome are described in multiple cases. Death during this stage is often secondary to hemodynamic collapse and arrhythmias. Disseminated intravascular coagulation is frequently reported [3, 29, 30, 46, 48]. Systemic abnormalities may include pancytopenia, coagulopathy, hepatic transaminase elevation, acidemia, renal insufficiency, and electrolyte abnormalities, such as hypophosphatemia, hypomagnesemia, hypocalcemia, and hypokalemia. Serum creatine phosphokinase or urine myoglobin concentrations initially should be monitored serially. Septic workup, including blood cultures, is indicated for unexplained fever. Chest radiographs may show interstitial lung changes. Colchicine plasma concentration may confirm the presence of the drug but in many cases does not correlate with the patient's condition [16]. Without preexisting colchicine levels, interpretation of these values is limited. Hepatic and renal dysfunction may prolong drug metabolism and elimination [30].

Bradycardia and irregular rhythms have been seen with intravenous colchicine administration. Hemodynamic profiles of cardiac failure in acute ingestions have been described in several case reports [2]. Cardiac profiles obtained by Sauder and coworkers [49] in a study of eight patients revealed that four patients had declining cardiac index and rising systemic vascular resistance; these patients subsequently died. Asystole has been reported within 24 h of ingestion. In one case, the ingestion of 0.4 mg/kg resulted in

Table 4 Clinical features of antitubulin agent overdose

	Colchicine	Vincristine	Vinblastine	Podophyllin	Etoposide/teniposide
Peripheral neuropathy	Reported	Common	Rare	Common	With vincristine
Hypotension	Reported	Reported	Rare	Reported	With IV infusion
Nausea, vomiting	Common	Common	Common	Common	Common
Fever	Reported	Common	Reported	Common	NR
Leukocytosis	Common	Common	Rare	Reported	NR
Marrow suppression	Common	Reported	Common	Common	Common
Renal failure	Reported	Rare	Rare	In fatal cases	Rare
Liver function abnormalities	Common	Rare	Reported	Common	Reported
Alopecia	Common	Reported	Reported	NR	Reported
Seizures	Reported	Reported	Rare	Rare	With CNS tumors
Acidosis	Reported	Rare	Rare	Reported	NR

CNS central nervous system, IV intravenous, NR not reported

death. Eight of 12 deaths due to colchicine, according to poison center statistics from 1985 to 1997, indicated the cause of death to be cardiac [50].

Oliguric renal failure is a common problem in severe colchicine poisoning. One likely cause of renal dysfunction is the profound hypovolemia from sensible gastrointestinal fluid losses and accumulation of fluids that results from paralytic ileus and marked gastrointestinal tract edema [1, 3]. Volume depletion, combined with hypoxia and myoglobinuria secondary to colchicine-induced rhabdomyolysis, has resulted in azotemia, proteinuria, and hematuria [1, 29, 46].

Reported electrolyte abnormalities include hypokalemia, hyponatremia, hypocalcemia, and hypophosphatemia [30, 46, 49]. Hypocalcemia may be due to a direct effect of colchicine on bone resorption. Animal studies have shown that colchicine inhibits the rise of serum calcium after injection of parathyroid hormone [51].

Neurologic complications reflect central nervous system (CNS) and peripheral nervous system involvement. Mental status changes, including sedation, delirium, and coma, are the most common CNS manifestations. However, the incidence is very rare as colchicine does not cross the blood–brain barrier easily due to P-glycoprotein. Seizures also have been reported. Peripheral nervous system involvement includes myoneuropathy and axonopathy as consequences of chronic and acute overdose [52]. Ascending paralysis and loss of deep tendon reflexes

typically occur [53]. Myelin degeneration found on postmortem pathologic examination was thought to be the underlying peripheral manifestation in colchicine poisoning [1, 3].

Metabolic derangements also are well described in cases of colchicine intoxication. Lactic acidosis secondary to shock and tissue hypoxia is associated with colchicine toxicity; however, a more disruptive effect on cell metabolism also may contribute to the acid–base disturbance seen in many cases [30]. Rhabdomyolysis occurs fairly commonly in colchicine poisoning, manifested by myalgia, weakness, and marked elevation in serum creatine phosphokinase concentrations [27].

Alopecia marks the third stage of toxicity, which may be seen as early as day 6 and as late as day 14. Alopecia is due to the inhibition of mitotic activity in the hair follicles. Most commonly, alopecia begins on the scalp, then involves the axillae, trunk, extremities, and genital area. Regrowth generally occurs after several months, but failure of regrowth has been reported [54–56]. Rebound leukocytosis also occurs in phase III (Table 4).

Diagnosis

The diagnosis of colchicine toxicity is straightforward if a history of exposure is obtained. However, the signs and symptoms of colchicine toxicity could be easily mistaken for other

conditions without a known exposure. These conditions might include enterocolitis, sepsis, toxicity due to heavy metals (iron, arsenic, thallium, mercury), or chemotherapeutic agents. The typical toxidrome seen with colchicine poisoning would include gastroenteritis, hypotension, lactic acidosis, and prerenal azotemia [27].

Treatment

Intensive monitoring of vital physiologic parameters is imperative in a patient with colchicine intoxication. After initial resuscitative measures, attempts may be made to delay absorption. Activated charcoal (1 g/kg) can be administered (evidence level III). However, it is unknown if doing so alters the clinical course of colchicine overdoses. Colchicine undergoes enterohepatic recirculation; however, current evidence does not support the use of multi-dose-activated charcoal in the treatment of its toxicity [23]. Additionally, patients with colchicine toxicity may develop a paralytic ileus, which is a contraindication to this intervention. Hemodialysis has not proved to be beneficial for colchicine poisoning. Any patient with a suspected toxic ingestion of colchicine should be observed for symptoms or signs of toxicity for a minimum of 12 h. If signs of toxicity develop (see section on “[Clinical Presentation](#)”), intensive care unit admission is warranted.

Supportive care is the mainstay of treatment. Intravascular volume and blood product replacement may be necessary, especially if coagulation parameters are abnormal or bleeding is noted. Fluid requirements may be underestimated due to gastrointestinal loss. It is important to maintain renal clearance to enhance colchicine elimination. Ventilatory status should be monitored closely, with intubation and mechanical ventilation provided as indicated. Hemodynamic monitoring also should be performed in a critical care setting initially and on a continuing basis as needed. Vasopressor support and electrolyte replacement may be necessary. Urine output should be followed closely and adjustments made accordingly. As clinical toxicity progresses, patients should be watched for signs of infection, as they

become neutropenic and susceptible to opportunistic pathogens. Seizures should be treated with benzodiazepines or barbiturates (Grade III recommendation), and the possibility of underlying acidosis, hypoxia, or electrolyte abnormalities should be considered and corrected aggressively (Grade III recommendation) [3].

Injections of granulocyte colony-stimulating factor (G-CSF) have been used in several cases to treat bone marrow suppression (Grade III recommendation). Dramatic increases have been reported in some but not all cases [29, 57, 58].

The development of colchicine-specific Fab fragment antibodies is a promising therapy but remains unavailable commercially. These antibodies bind to colchicine and restore tubulin activity in vitro [59]. Studies performed in mice, using thermoregulation as an end point, showed a significant improvement in the group that received colchicine-specific IgG [60]. Anticolchicine antibodies were used successfully in a 25-year-old woman who presented 24 h after ingesting 60 mg (0.96 mg/kg) of colchicine, phenobarbital, and opium extract. She was hemodynamically unstable and required vasopressor support. Colchicine-specific Fab fragments derived from goats were administered intravenously 40 h after the ingestion. The patient's blood pressure began to increase 30 min after Fab administration. During the 6-h infusion of the maintenance dose of Fab fragments, fluid replacement continued, and urine output improved [61].

Some authors have advocated for considering early initiation of either whole blood or plasma exchange in patients presenting with lethal-dose colchicine intoxication. However, more research needs to be done investigating these therapies [62].

Indications for ICU Admission in Colchicine

Any patient with clinical signs of poisoning or confirmed ingested toxic dose.

Special Populations

Colchicine must be used cautiously in elderly patients owing to their increased risk of underlying

hepatic or renal dysfunction [26]. Patients with impaired hepatic or renal function have reduced colchicine clearance. Pediatric patients may be administered colchicine during therapy for conditions such as familial Mediterranean fever [8, 63], acne vulgaris [64], renal amyloidosis [65], or pericarditis [66], to mention only a partial list. There are reports of colchicine toxicity involving children, the first case appearing in the English literature in 2000. Unfortunately, fatal poisoning has occurred in the pediatric population [62, 67–69].

Pregnancy

Colchicine is classified as FDA pregnancy category C, meaning that the benefits may exceed the risks. However, well-controlled studies with colchicine in pregnant women have not been conducted. Colchicine has been shown to cross the placenta.

Key Points in Colchicine Overdose

- Narrow therapeutic index.
- Be aware of interactions between colchicine and CYP3A4 and P-glycoprotein inhibitors.
- Toxicological emergency requiring admission for any known or suspected overdose.
- Toxicodrome includes gastroenteritis, hypotension, lactic acidosis, and prerenal azotemia.
- Cornerstone of treatment is supportive care.

Vinca Alkaloids

The vinca alkaloids are derived from the Madagascar periwinkle (*Catharanthus roseus*), a perennial evergreen herb found in most warm regions of the world. Native to Madagascar, it has been naturalized in most tropical countries including the southern part of the United States. Interest in *C. roseus* among Western researchers began in 1949, when they studied its use in a tea made by Jamaicans for the treatment of diabetes mellitus. Although its use as a hypoglycemic agent did not evolve as a result of this investigation, bone marrow suppression was observed. Many alkaloids eventually were extracted from the plant, including vincristine, vinblastine, vindesine, and vinorelbine. Semisynthetic vinca alkaloids are also in use or under development. Although structurally similar (Fig. 3), these compounds vary in their clinical effects and application in the treatment of neoplastic diseases. The mechanism of action of these compounds is similar to that of colchicine and podophyllin, although with different binding sites on the tubulin dimer. Vincristine is used in combination therapy to treat solid tumors, lymphoma, and leukemia. Vinblastine is used in combination to treat bladder and breast cancers as well as Hodgkin's disease. Vinorelbine has been used for treatment of small cell lung cancer. Recommended doses for vincristine are shown below:

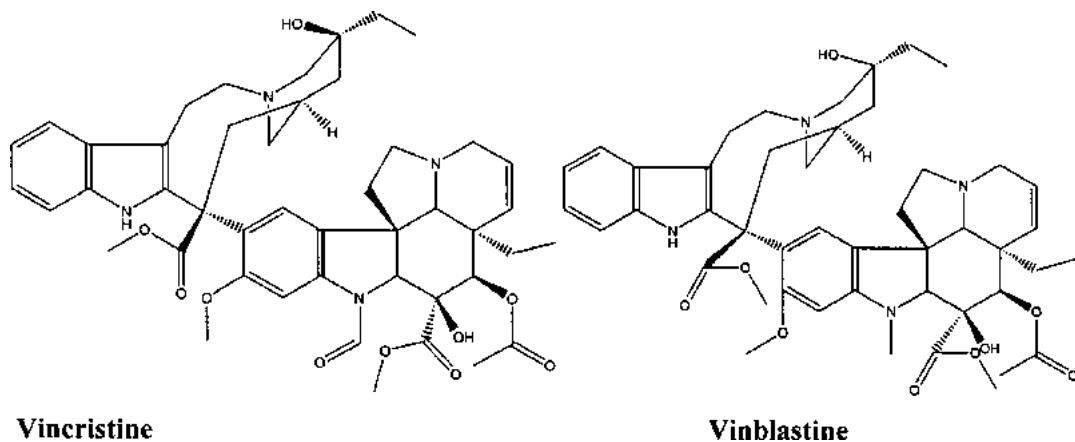


Fig. 3 Chemical structures of vincristine and vinblastine

Vincristine recommended dose for pediatric patients: 1.5–2 mg/m².
Vincristine recommended dose for adults: 1.4 mg/m².
A 50% reduction in the dose is recommended for patients with direct serum bilirubin concentrations exceeding 3 mg/dL [70].

Pharmacokinetics

The vinca alkaloids commonly are injected intravenously and seem to follow a three-compartment model (see Fig. 3). When ingested, vinca alkaloids’ absorption is unpredictable, although vinorelbine is frequently administered orally. When administered intravenously, vincristine rapidly distributes into tissue of the ileum, skeletal muscle, and kidney. It penetrates the blood–brain barrier poorly. Metabolism of these compounds is primarily hepatic. They are excreted in the bile, and less than 1% of vincristine and vinblastine are excreted in the urine. Renal elimination accounts for 18% of vinorelbine excretion.

Pharmacokinetics of Vinca Alkaloids

Compound	Renal elimination (%)	Elimination half-life (hr)
Vincristine ^a	<1	24
Vinblastine	<1	24
Vinorelbine	>18	27.7–43.6

^aClearance after IV administration: [71]

Adults: 189 mL/min/m²

Children: 482 mL/min/m²

Vincristine, and probably all the vinca alkaloids, inhibit the CYP3A subfamily. Troleandomycin, ketoconazole, nifedipine, erythromycin, cyclosporine, and vindesine all seem to increase serum concentrations of the vinca alkaloids. Calcium channel blockers, such as verapamil, seem to decrease protein binding of the vinca alkaloids, increasing the risk of neurotoxicity [72].

Pathophysiology

The nervous system is the primary target organ of vincristine toxicity. Vincristine disrupts the

normal process of microtubule formation, interfering with axoplasmic transport, which accounts for the prevalence of neural injury associated with its administration [73, 74]. At therapeutic doses of vincristine of 1.5 mg/m² (0.06 mg/kg), the onset of peripheral neuropathies may begin within 2 weeks and occurs with a nearly 100% incidence [75].

Vinblastine and vinorelbine seem to depolymerize microtubules at the negative terminus while stabilizing the positive terminus [41]. They cause less inhibition of microtubular polymerization and are less neurotoxic than vincristine. Their primary toxicity is bone marrow, which is often the dose-limiting factor during therapy with either drug.

Clinical Presentation

Acute Toxicity

Vincristine. Paresthesias usually begin in the hands, followed by sensory loss in the feet. Loss of ankle-jerk reflex occurs soon thereafter [76]. Although the sensory loss may progress, it seldom results in more proximal stocking-glove distribution deficits. Motor symptoms follow, with weakness of the extensors of the hands and feet being most pronounced. Nerve conduction studies may show slowing of nerve conduction velocity with decreased amplitude. Electromyography may rarely show signs of denervation in distal muscle. Morphological changes include demyelination with “die-back” pattern of axonal loss and dorsal root ganglion damage [77]. Cranial neuropathies are rare; however, ototoxicity with sudden transient hearing loss has been reported [78]. Sensory and motor symptoms usually abate within a few weeks of discontinuation of therapy, although mild distal sensory loss and absence of ankle-jerk reflexes may persist.

Although CNS penetration at therapeutic doses is relatively low, encephalopathy and seizures have been reported [79, 80]. In rare cases, they are the presenting sign of intravenous overdose and frequently occur a few days to a week after exposure. Initial signs and symptoms of overdose may include bone or muscle pain, abdominal pain, bleeding, or marrow depression [81–83]. Other

adverse effects of vincristine use include autonomic dysfunction, mucositis, paralytic ileus, bladder atony, fever, bone marrow suppression, alopecia, and hypertension [75, 83]. Trinkle and Wu [84] reviewed 18 cases of intravenous vincristine overdose in children (average age 10 years). There were four fatalities with a dose range of 0.2–0.6 mg/kg. The major lethal risk factors were hemorrhage due to thrombocytopenia and neutropenia-related infection. Paresthesias and loss of deep tendon reflexes occurred as early as 24 h. Nausea, vomiting, diarrhea, and abdominal pain usually occurred within 48 h. Paralytic ileus occurred in 66% of patients within a mean of 5 days. Thrombocytopenia and leukocytopenia occurred in most cases [84]. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been a relatively frequent occurrence after vincristine overdose [81, 83, 85].

Accidental intrathecal injection accounts for a large portion of the fatalities, and survival from such exposures is rare regardless of therapy [86]. (See “[Intrathecal Exposure](#)” below.) These therapeutic mishaps usually involve vincristine administration by personnel unfamiliar with the drug or confusion with other antineoplastic drugs that may be administered via that route. Dermal extravasation of vinca alkaloids has been associated with tissue loss [87]. (See “[Extravasation](#)” below.)

Vinblastine and Vinorelbine. These vinca alkaloids are less potent inhibitors of microtubular polymerization and are less neurotoxic than vincristine. Their primary toxicity is bone marrow suppression, which often is the dose-limiting factor during therapy with either drug and is the most common toxic effect of these drugs (see Table 1). Granulocytopenia occurs frequently. There are relatively few reports of overdose [88–91]. After overdose, onset of fever and diarrhea has been reported within a few hours. Pulmonary edema developed in one reported case at day 4 [91]. Vinorelbine also has been associated with bronchospasm and respiratory failure, but concurrent disease may have played a significant role [92].

Chronic Adverse Effects

Myocardial ischemia has been reported after therapeutic doses of the vinca alkaloids [93–96];

however, this patient population tends to be at greater age-related cardiovascular risk. Delayed (24 h) onset of epithelial keratopathy was reported after ocular exposure to vinblastine solution; it resolved over 2 weeks without treatment. Ototoxicity also has been reported (with vincristine and vinblastine). Tinnitus occurred in a 29-year-old man within hours of treatment with vinblastine, doxorubicin, bleomycin, and dacarbazine and lasted 7–10 days after each of multiple treatments; mild sensorineural hearing loss persisted in the high-decibel range [97]. Pancreatitis has been reported after therapeutic doses of vinorelbine [98, 99]. As these cases show, predicting the toxicity of the vinca alkaloids frequently is confounded by coexistent disease and the presence of other chemotherapeutic agents. Similar to vincristine, vinblastine and vinorelbine also have been associated with SIADH [100, 101]. Hepatotoxicity including veno-occlusive disease has been reported particularly in pediatric patients during combination therapy with vincristine (see section “[Special Populations](#)”).

Treatment

Intravenous Exposure

Supportive measures are the mainstay of care. Peripheral neuropathies usually resolve or improve on withdrawal of the drug. Seizures usually respond to benzodiazepines or barbiturates or both (Grade III recommendation). Phenytoin would not be expected to be efficacious (see ► [Chap. 20, “Toxicant-Induced Seizures”](#)). Additionally, a theoretical concern with the use of phenytoin is that it seems to potentiate the effects of vincristine and vinblastine by interfering with tubulin polymerization [102]. SIADH is managed most appropriately by fluid restriction. Vincristine has a large volume of distribution due to tissue uptake and is highly protein bound. Hemodialysis is of little benefit with regard to enhancement of drug clearance. Plasmapheresis has been performed with a favorable outcome [103], but data supporting its use are inadequate. Folinic acid has been used in humans [104] and studied in animals [105], but its efficacy is controversial. If

used, a suggested dosing schedule is “100 mg IV every 3 h for 24 h and then every 6 h for at least 48 h” [70]. Finally, glutamate also has been studied as a preventive intervention against neurotoxicity. In patients receiving therapeutic doses, neurotoxicity seemed to be reduced [106]. This particular intervention, too, is based on limited data.

Indications for ICU Admission in Vinca Alkaloid Overdose

1. The maximum tolerated doses of these drugs are not established. Patients who have received excessive amounts should be admitted for observation on a cardiac monitor.
2. The length of observation after intravenous overdose with one of the vinca alkaloids should be 3–4 days because the onset of symptoms may involve that degree of delay. This is dose dependent, with high-dose exposures reportedly causing onset of symptoms within only a few hours [81, 83].

Intrathecal Exposure

With few exceptions [107, 108], the accidental intrathecal or intraventricular injection of vincristine has resulted in death [86, 109, 110]. Autopsy results have shown evidence of an ascending chemical leptomeningitis; ventriculitis; and necrosis of the spinal cord, brainstem, and cerebellum [111, 112]. Folinic acid [110, 111, 113, 114] and glutamic acid [114, 115] have been administered in many of these cases despite the relative paucity of supporting data and in response to the devastating and typically lethal nature of this injury. CNS washout involves removal of cerebrospinal fluid and replacement by Ringer’s lactate. Ferayan et al. [116] reported significant motor and sensory impairment in a 7-year-old patient who ultimately survived. They employed a technique first described by Dyke [115]. During a routine admission for chemotherapy, 0.5 mg of vincristine accidentally was injected intrathecally. The error was recognized before the injection was complete, and 75 mL of cerebrospinal fluid was

withdrawn immediately thereafter. That volume was replaced with Ringer’s lactate via an additional lumbar puncture. In less than 2 h, a catheter was placed in the right lateral ventricle by way of a burr hole; 1 L of Ringer’s lactate was infused through the ventricular catheter at a rate of 100 mL/h. Afterward, 15 mL of fresh frozen plasma was mixed with each liter of Ringer’s lactate, and the rate was reduced to 55 mL/h. That infusion was continued for 24 h with the effluent passing through the lumbar catheter. Glutamic acid (250 mg every 8 h) was administered via nasogastric tube, and then continued orally for 1 month. The patient became symptomatic 7 days postexposure with urinary retention and sensorimotor impairment of the lower extremities. There was significant residual impairment at follow-up 34 months after exposure [116]. Aggressive replacement and lavage washout is not always successful [86, 110], but at present it seems to be the only viable therapy (Grade III recommendation).

Extravasation

Extravasation typically causes pain, swelling, and erythema within minutes. While blister formation may occur over the subsequent days, skin ulceration usually does not occur [117]. Subcutaneous injection of 250 U of hyaluronidase in 6 mL of normal saline circumferentially at the site has been recommended; this should be followed by the application of heat for 1 h in the event of extravasation of vincristine or vinblastine. This procedure should be repeated four times daily for 3–5 days. Boman et al. (1996) demonstrated significant reduction of dermal toxicity when vincristine was administered in liposomes [118].

Special Populations

Children are the most common victims of accidental overdose or intrathecal injection. This is usually due to lack of familiarity with the drug or confusing it with another agent. It is imperative that stringent protocols for identification and administration of these compounds be

followed because toxicological treatment, particularly after intrathecal administration, is of limited efficacy.

- Hepatic veno-occlusive disease has been reported in several pediatric and some adult patients [119]. Bisogno et al. studied 41 patients with veno-occlusive disease and found a higher percentage of patients in children less than 1 year of age. Risk factors appear to be young age and concomitant radiotherapy [120].
- Renal Failure: Vinblastine 14%, vincristine 12%, and vinorelbine 18% are eliminated in the urine. This is primarily the parent drug and a smaller amount of the metabolite.
- Vincristine can induce severe peripheral neuropathy in patients with Charcot–Marie–Tooth syndrome. Vindesine has been successfully used as a substitute [121].
- Vinblastine, vincristine, and vinorelbine are rated FDA Category D (risks may exceed benefit) for pregnancy and breast-feeding. Human data are limited but animal studies suggest high risk [122–124].
- Patients taking drugs that inhibit CYP3A sub-families such as itraconazole and ketoconazole are at increased risk of developing toxic concentrations (Grade III recommendation) (see Table 2) [113, 114, 125].
- Occupational Exposures: Some studies have raised concerns regarding potential occupational exposures to vinca alkaloid in veterinary and human health-care workers. However, serious adverse health effects outside of allergic reactions have yet to be demonstrated [126–129].

Key Points in Vinca Alkaloid Overdose

1. Fatal exposures are almost always the result of iatrogenic administration.
2. People inexperienced with the use of these compounds should work under close direct supervision of medical professionals with substantial training and experience in the use of these compounds.
3. Therapeutic errors have been avoided by the institution of strict protocols for identification and administration of these drugs.

4. Administration via mini-bags may reduce intrathecal injection [130]

Podophyllin and Podophyllin Derivatives

Podophyllotoxin (Fig. 4) is found in the rhizome and roots of *Podophyllum peltatum*, also known as *mandrake* or *May apple*. Native Americans used podophyllotoxin as an emetic, and the Chinese used it (*gui jiu*) as an abortifacient, as treatment for snakebites, and as an aid to purging intestinal parasites [131–133]. Podophyllin was included in the United States Pharmacopeia in 1820 [134]. Purification and isolation of podophyllotoxin was first accomplished in 1880 [132, 133]. Podophyllotoxin resin, or podophyllin, was used widely in the United States as a cathartic and an ingredient in proprietary medicines (e.g., Carter’s Little Liver Pills) and topically in a 20–25% solution for condylomata until such uses were associated with reports of serious toxicity [135–144].

Herbal remedies erroneously may contain podophyllin because *mandrake* also is used to refer to *Mandragora officinarum*, which has anticholinergic properties [145]. Poisoning also has been reported with herbal remedies obtained in countries outside the United States [146–149].

In 1942, podophyllin was reported to treat venereal warts successfully, and in 1947 podophyllin-induced mitotic arrest was shown, leading to the investigation of its use for cancer treatment [132, 134]. In response to the high toxicity and low water solubility of purified podophyllin, chemical modification of the compound was carried out, and many of the resulting compounds were studied. In the 1960s, synthesis and biologic testing of the podophyllin derivatives teniposide and etoposide were initiated. Currently, prescription ointment containing 0.5% podophyllin (Podofilox[®], Condyllox[®]) (US brand names are given in examples. These may vary depending upon the country.) and physician-applied 25% podophyllin solution (Podocon –25[®]) are used for the treatment of anogenital warts [150, 151]. Podophyllin also is used topically to treat oral hairy leukoplakia [152]. Etoposide (VePesid,

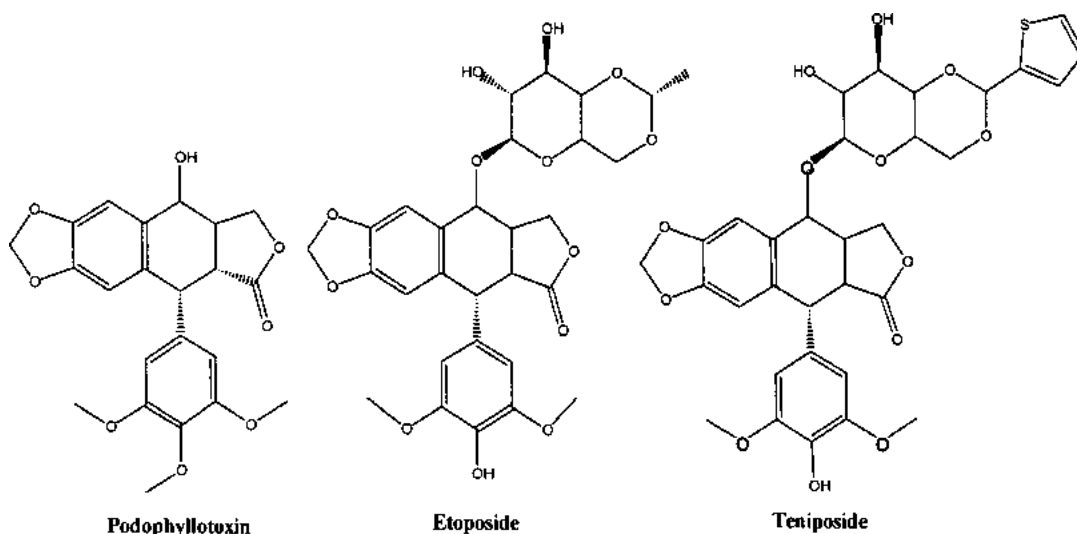


Fig. 4 Podophyllin and derivatives

Etopophos) and teniposide (Vumon) are used in chemotherapy regimens for cancers, including testicular cancer, small cell lung cancer, lymphoma, and acute lymphoblastic leukemia [40, 132, 134, 153–155].

Pharmacokinetics of Podophyllin and Podophyllin Derivatives

Podophyllin [143, 156, 157] Available in topical preparation from 0.5% to 25% in alcohol or benzoin tincture

Highly lipid soluble

Well absorbed across friable tissue

Dermal application of 0.1–1.5 mL of 0.5% topical preparation led to peak serum concentrations of 1–17 ng/mL 1–2 h after application with an elimination half-life of 1–4.5 h

Oral and intravenous pharmacokinetic data unavailable

Etoposide [150, 155, 158] Oral formulation with polyethylene glycol, citrate, and glycerin

Intravenous formulation with polyethylene glycol, polysorbate 80, and 30% ethanol

Poor water solubility

Renal elimination (significant in children, 55% recovery in urine at 24 h)

Oral bioavailability of 50%

No significant first-pass effect

97% protein bound

Volume of distribution highly variable between 7 and 17 L/m²

Terminal half-life 3–11 h after intravenous infusion

Teniposide

Intravenous formulation with ethanol, which is reconstituted before infusion

Greater than 99% protein bound

Volume of distribution highly variable between 3 and 44 L/m²

Half-life variable between 6 and 48 h, depending on the model

Biliary excretion 10% of elimination

Some central nervous system penetration

Pathophysiology

The cell cycle consists of four phases: *G*₁ (growth), *S* (DNA duplication), *G*₂ (preparation for cell division), and *M* (mitosis – cell division). Interphase consists of all phases except mitosis [159]. Although the spindle poisons, such as colchicine, podophyllin, and the vinca alkaloids, act in mitosis (specifically, causing metaphase arrest),

podophyllin derivatives (etoposide and teniposide) act in interphase and prevent mitosis.

Podophyllin, similar to colchicine, binds reversibly to tubulin at the colchicine-binding site, resulting in mitotic arrest [40, 131]. Microscopically, this activity results in metaphase arrest with clumped chromosomes because the mitotic spindle is unable to form without microtubules [132]. Disruption of microtubules also causes decreased cellular transport. Podophyllotoxin also inhibits the incorporation of labeled thymidine and uridine into cells by inhibiting nucleoside transport [160]. Neurotoxicity is thought to be related to microtubule binding and inhibition of axoplasmic flow [161].

Podophyllotoxin derivatives have a mechanism of action distinct from that of the parent compound. Etoposide does not inhibit microtubule assembly compared with podophyllin [160, 161]. Cells treated with etoposide, teniposide, and similar derivatives were found to have a low mitotic index, indicating that cells were inhibited from entering mitosis [162]. Time analyses indicated that the cells likely arrest in late S or early G₂ phase [162, 163]. Later analyses showed that these derivatives may bind to tubulin, but this effect is seen at much higher and clinically impractical doses [132].

Radiolabeled nucleoside (thymidine) incorporation into DNA is inhibited with etoposide and teniposide [162, 164]. This mechanism of action is shared with podophyllin. Inhibition of cell proliferation is not linked to this mechanism, however [162, 165].

In 1974, DNA fragmentation by etoposide and teniposide was reported and represented a breakthrough in the understanding of the mechanism of action of podophyllin derivatives [160]. Podophyllin itself has no effect on DNA. Structure–activity studies indicated that derivatives with a hydroxyl group at the C-4' position are required for this activity [160, 166]. DNA breakage was found to correlate well with the cytotoxic effects of the drugs [167]. Subsequently, podophyllin derivative–induced DNA fragmentation has been correlated with inhibition of topoisomerase type II, which is essential for uncoiling of DNA before replication [168]. Topoisomerase

II inhibition is now believed to represent the primary mechanism of action of these drugs, and they are classified today as topoisomerase interactive agents along with anthracyclines, such as doxorubicin [132, 134, 155]. Current research is ongoing regarding the antitumor potential of novel podophyllin derivatives, some of which have reached clinical trials [169–172].

Clinical Presentation

During therapeutic administration of etoposide and teniposide, the most significant dose-limiting effect is bone marrow suppression (seen in 90% of patients), with granulocyte nadirs occurring in 7–14 days and platelet nadirs occurring in 9–16 days after administration. Marrow recovery usually occurs within 20 days [134, 153, 158, 173]. Nausea, vomiting, anorexia, and diarrhea are reported but are milder when caused by other chemotherapeutic agents [134]. At high doses, mucositis may be dose limiting. Anaphylaxis may occur. CNS depression and hypotension have been reported during intravenous infusion (see Table 1). Transient elevations in liver function tests have been reported. In children with acute lymphocytic leukemia, treatment has been associated with the development of secondary leukemias [174, 175]. Hemolysis and renal failure have been reported in conjunction with teniposide-related antibody [176]. CNS depression, hypotension, and metabolic acidosis have been reported in children treated with teniposide; however, they also had clinically significant ethanol concentrations due to the high ethanol concentration in the infusion [177]. Neurologic manifestations, such as peripheral neuropathy, are less common after administration of the topoisomerase II inhibitors than with the spindle poisons, but they have been reported as well, often in high-dose use and in conjunction with drugs such as vincristine [178, 179]. Neurologic signs and symptoms, such as somnolence and seizures, have been reported after high-dose etoposide therapy for malignant glioma [180]. One case report of inadvertent supratherapeutic use of oral etoposide for 25 days detailed a reduction in T

lymphocytes and blastic transformation that persisted at 57 months along with relapse-free remission [181]. Etoposide treatment induces other malignancies such as acute myelocytic leukemia and myelodysplastic syndrome [182].

Podophyllin is far more toxic than its derivatives and has clinical effects similar to those of colchicine. Fatality has been reported after ingestion of 350 mg [183], and survival has been reported after ingestion of 2.8 g [98]. Toxicity has occurred from ingestion [136, 140, 144, 149, 153, 183–187], cutaneous absorption [132, 141, 143, 161, 188, 189], subcutaneous injection [190], and intramuscular injection [191]. Cases of toxicity from cutaneous absorption typically involved prolonged contact, large surface areas, or friable mucosa. Death has been reported after cutaneous application [185, 192].

The hallmarks of toxicity include nausea, vomiting, altered mental status progressing to coma, rapidly progressive peripheral neuropathy with paresis and areflexia, and delayed myelosuppression. These effects have been reported to be delayed 10 h after ingestion [136] and 20 h after topical application [188]. Review of the case reports indicates, however, that the patients initially developed gastrointestinal symptoms (one was given Syrup of Ipecac) and alteration in mental status (one also was ethanol intoxicated), followed by delayed and profound CNS depression and coma. Several reports of toxicity after cutaneous exposure detailed vomiting 12–13 h post application followed by a coma within 30 h of application [141, 189]. Other reports included early gastrointestinal symptoms followed by delayed (24 h) coma. Some patients may present primarily with peripheral neurologic symptoms, such as neuropathy and paresthesia [137, 146, 147, 191, 193]. Patients may recover fully from coma, which may last 10 days [135, 138, 141, 143, 188]. Electroencephalogram may show diffuse slowing, with cerebrospinal fluid findings typically normal but, at times, showing elevated protein [138, 194]. Fever, seizure activity, and visual/auditory hallucinations also have been reported.

Patients often present with tachycardia and tachypnea. Hypotension has been reported. In fatal cases, renal failure and circulatory collapse

may occur [144, 187, 189, 192]. Status epilepticus occurred shortly after ingestion in a pediatric case [186]. Noncardiogenic pulmonary edema and idioventricular bradycardia have been reported in a fatal case [192]. Necrotizing myopathy has been reported in a patient who died 9 weeks after podophyllin ingestion owing to sepsis [187].

Survivors may have neurologic sequelae, such as persistent peripheral neuropathy lasting months to several years, that may manifest after the initial encephalopathy has resolved [184, 195]. Some patients have developed persistent lower extremity paralysis and encephalopathy and radiologic findings of cerebral atrophy [149, 186, 196]. Dorsal radiculopathy, manifesting as profound loss of position sense, is reported [184]. Podophyllin has been proposed as an experimental model for deafferentation [146]. Absence of alopecia is notable in that it clinically differentiates podophyllin from acute colchicine or vinca alkaloid toxicity.

Diagnosis

Initially, leukocytosis may be seen ($55,000/\text{mm}^3$) [143]. Granulocytopenia and thrombocytopenia are delayed by 5 days and typically resolve over 2–3 weeks. Peripheral leukocytes may show enlarged nuclei with dense chromatin granules and cytoplasmic and nuclear vacuolization [136]. Bone marrow examination may reveal evidence of mitotic arrest [142, 143, 188] and vacuolization of erythroblasts and plasma cells [157]. Lactic acidosis has been described in a fatal case in a patient who had concomitant alcoholic cirrhosis [136]. Hypocalcemia has been reported [140], along with elevated serum hepatic transaminase and uric acid concentrations.

Autopsy findings include mitotic arrest in granulocytes and intestinal mucosal cells; diffuse petechial hemorrhages; pulmonary, renal, and hepatic congestion; and cerebral edema [136, 144, 189]. The bone marrow is hypocellular with cytoplasmic vacuolization of myeloid precursors [197].

Abnormalities on computed tomography or magnetic resonance imaging show cerebral atrophy in some survivors [149, 196]. Some patients have developed persistent lower extremity

paralysis; nerve biopsy specimens may reveal axonal degeneration and loss of large myelinated fibers, with gradual regeneration as recovery occurs [110, 112, 149].

Because of its prominent early gastrointestinal effects, toxicity with podophyllin and derivatives may be confused with gastrointestinal disorders. In addition, podophyllin use may not be reported to the treating physician if it is applied as an ointment or applied by the patient's physician in the office. The common presentation of fever, lethargy, and leukocytosis mimics CNS infection. The presentation of hypotension, altered mental status, and fever mimics septic shock. Podophyllin toxicity may present with ascending paralysis and loss of reflexes similar to Guillain-Barré syndrome. Delayed bone marrow suppression leads to thrombocytopenia, granulocytopenia, and anemia, which may cause the treating physician to suspect other causes of bone marrow suppression, such as infection or malignancy.

Treatment

Gastrointestinal decontamination with activated charcoal may be beneficial after an acute suicidal podophyllin ingestion if given within the first hour postingestion. However, it is not known if this intervention alters the clinical course or outcome. Decontamination of skin should be performed if topical preparation has been applied. The mainstay of treatment is supportive care, including prevention of infection and screening for delayed bone marrow suppression. Blood products should be used if needed. Hemoperfusion has been used for podophyllin toxicity with variable results [136, 142, 143, 149, 185, 188, 192]. Because of the high lipid solubility, volume of distribution, and degree of protein binding (97–99%) of podophyllin and its derivatives, hemodialysis is not likely to be useful.

Indications for ICU Admission in Podophyllin or Podophyllin Derivatives Poisoning

1. Because of delayed and profound central nervous system effects, observation in an

ICU setting for at least 24 h should be considered for any patient with a significant exposure to podophyllin or podophyllin derivatives, particularly patients with evidence of altered mental status and rapidly progressive neuropathy.

2. Hemodynamic instability, seizures, or respiratory distress.

Although G-CSF has been used with some success to treat colchicine-induced neutropenia, its use has not been reported in podophyllin poisoning. G-CSF has been used in combination chemotherapy, including etoposide, for the prevention and treatment of hematopoietic toxicity and to facilitate more intensive chemotherapy regimens [198–203]. There is no specific antidotal therapy for podophyllin toxicity or that of its derivatives, etoposide and teniposide.

Key Points in Podophyllin Toxicity

1. Podophyllin poisoning is typically reported after ingestion or large surface dermal application to friable mucosa.
2. Severe symptoms can be delayed up to 20 h, particularly after dermal application.
3. Treatment is primarily supportive.

Special Populations

Pregnant Patients

These drugs are not intended for use in pregnancy. Podophyllin has been used to induce abortion. Reports link podophyllin to intrauterine fetal demise and birth defects [137, 204, 205].

Oncology Patients

In addition to increased risks of infection associated with immunosuppression and bone marrow suppression, after single-agent administration, concomitant cytotoxic medication use may lead to a synergistic increase in neurologic and hematologic toxicity.

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Part XIII

Drugs of Abuse

Nicholas J. Connors and Robert S. Hoffman

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This chapter is a revision of the chapter by Patrick E. McKinney and Robert D. Palmer in the first edition of this book.

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This chapter addresses drugs that have the basic phenethylamine structure with various substitutions (Fig. 1). Amphetamine and methamphetamine, substituted amphetamines (3,4-methylenedioxymethamphetamine [MDMA; “Ecstasy”] and related compounds), related anorexigens, and new psychoactive substances (novel drugs of abuse) are discussed.

Plant-derived stimulants structurally related to amphetamine have been used by local populations for thousands of years. Ephedrine from *Ephedra* (*ma huang*) has been used in China for more than 5000 years, and cathine and cathinone from *Catha edulis* have been used in East Africa for more than 600 years. Both of these plants, and their isolated active ingredients, continue to be used today as medications, drugs of abuse, and in social rituals.

Although amphetamine was first synthesized more than 100 years ago, the first investigations of its pharmacologic properties and potential clinical use began in the 1920s. In 1932, Smith, Kline, and French introduced an over-the-counter nasal inhaler containing *d/l*-amphetamine under the trade name Benzedrine[®] marketed for congestion. This preparation was easily abused for the central nervous system (CNS) stimulant properties. Each Benzedrine[®] inhaler contained a folded paper impregnated with 250 mg of amphetamine base along with other aromatic compounds. This paper was removed and portions of it were swallowed or soaked in beverages, then ingested [1]. Benzedrine[®] abuse by American students, musicians, truck drivers, and prisoners became problematic, and the clinical and social difficulties now classically associated with amphetamines were detailed in reports published in the 1930s and 1940s. In 1949, the Benzedrine[®] inhaler was renamed Benzedrex[®] and reformulated to contain propylhexedrine, a potent vasoconstrictor with approximately 8% of the CNS stimulant activity of amphetamine. Abuse of propylhexedrine was soon reported, however, and continues to occur sporadically [2].

Early claims of amphetamine’s efficacy against fatigue and tiredness were reported in the lay press and the medical literature, and by the 1940s, amphetamines were widely prescribed for various indications, including barbiturate overdose, shock, coma, smooth muscle spasm of the

genitourinary or gastrointestinal tract, chronic encephalitis, postural hypotension, and “problem children and enuresis”[1–3]. During World War II, amphetamine use was widespread among the combatants and domestic workforces in the USA [4]. Legitimate prescribing of amphetamine in the 1960s and 1970s reflected its use as an anorexiatic, but vast amounts were diverted for illicit use. In 1969, the legal production of amphetamine was between 80,000 and 100,000 kg, enough for fifty 10-mg tablets per each person in America [4]. Federal regulation of prescribing patterns and restrictions on approved indications for amphetamines led to a decrease in the quantity manufactured by pharmaceutical companies. As legitimate manufacture declined, illicit amphetamine and methamphetamine production took its place. Clandestine synthesis and manufacture is now a major problem throughout many parts of the world.

The true prevalence of amphetamine and related drug use and resultant medical complications are difficult to gauge, but it is clear that use is widespread. Data from the 2013 US National Household Survey of Drug Abuse demonstrate that 595,000 people used within the past month [5]. The 2014 Annual Report of the American Association of Poison Control Center’s (AAPCC) National Poison Data System reveals 22,753 cases of exposure to amphetamines and related compounds, hallucinogenic amphetamines, or methamphetamines.

In that report, 10 deaths were attributed to toxicity from amphetamines and related compounds, 48 were attributed to toxicity from methamphetamine, and 12 were associated with hallucinogenic amphetamines [6]. Figures from the US Drug Abuse Warning Network Emergency Department (ED) data indicate that methamphetamine-related ED visits are surging again, with 102,961 visits reported in 2011, after decreasing from 132,576 visits in 2004 to 64,119 in 2009 [7]. While methamphetamine use, abuse, and toxicity was primarily a concern in the western USA, use is now nationwide. Amphetamine and amphetamine derivative use and toxicity are a worldwide phenomenon [8]. Global Methamphetamine seizures increased 158% between 2008 and 2013 [9].

Seizures of “amphetamine-type stimulants” peaked in 2011 and have remained high. These

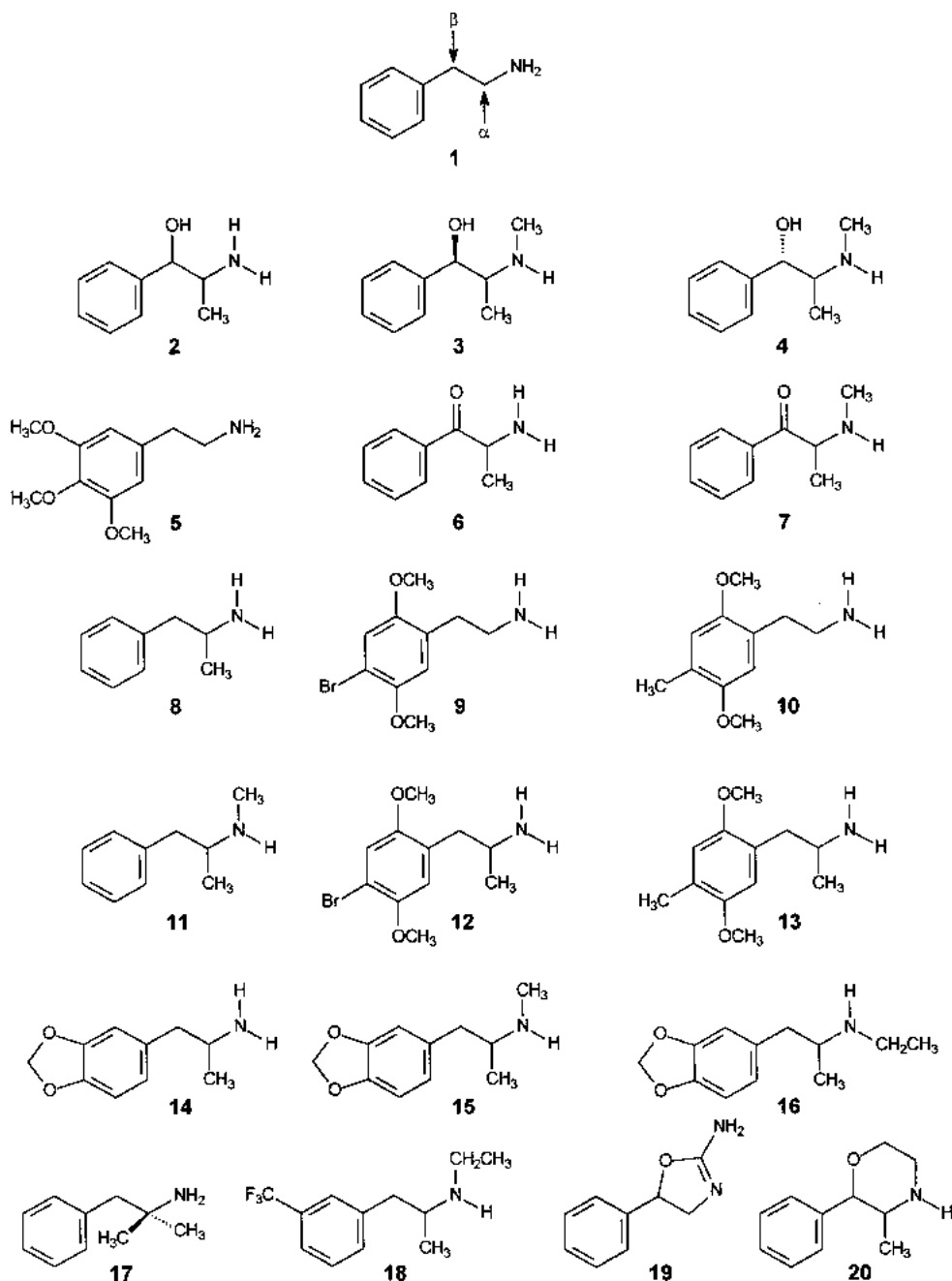


Fig. 1 Chemical structures of phenethylamines: 1, phenethylamine; 2, phenylpropanolamine; 3, ephedrine; 4, pseudoephedrine; 5, mescaline; 6, cathinone; 7, methcathinone; 8, amphetamine; 9, 4-bromo-2,5-dimethoxyphenethylamine; 10, 4-methyl-2,5-dimethoxyphenethylamine (2-CD); 11, methamphetamine; 12, 2,5-dimethoxy-4-bromophenylisopropylamine (DOB); 13, 2,5-dimethoxy-4-methylphenylisopropylamine (DOM); 14, 3,4-methylenedioxyamphetamine (MDA); 15, 3,4-methylenedioxymethamphetamine (MDMA); 16, 3,4-methylenedioxyethamphetamine; 17, phentermine; 18, fenfluramine; 19, aminorex; 20, phenmetrazine

increases are largely driven by increased global methamphetamine use. Sale in Asia and South-East Asia has increased with trafficking through distribution centers in West Africa and transport through Southern Africa and Europe, suggesting worldwide networks. Use has also increased throughout North America and Europe. In 2011, 9,500 seizures of methamphetamine were reported by 22 European countries, led by Turkey, Norway, Lithuania, Sweden, and Latvia. Of note, seizures in the Czech Republic and Germany increased significantly since 2008 [10]. Worldwide “Ecstasy” use is much lower and appears to be decreasing in North America, Europe, and Australia, though use increased in Oceania, and East and South-East Asia between 2008 and 2014 [9].

Available forms of amphetamines include pharmaceutical preparations and clandestinely synthesized formulations. Pharmaceutical preparations include amphetamine, methamphetamine, methylphenidate, and lisdexamfetamine (see also Fig. 1). These preparations generally are approved only for short-term weight loss, narcolepsy, and attention-deficit disorder; however, they are used clinically for a variety of conditions, including depression, Tourette syndrome, closed head injury, pain, stroke, and depression. Additionally, they are used for psychiatric conditions, including mania, schizophrenia, and obsessive-compulsive disorder. Available forms include tablets, capsules, sustained-release forms, and elixirs. Concentration of active ingredients varies, and impurities, adulterants, and by-products of synthesis may contribute to toxicity. Amphetamine and methamphetamine are often called “speed” and “crank” (Table 1) and may be snorted, injected, or ingested. A crystalline form of methamphetamine, known as “ice,” is purified by recrystallization. This form has a relatively low melting point, allowing it to be volatilized and inhaled. Crystal methamphetamine abuse first was reported in Asia in the early 1980s [11]. Concerns that this might produce epidemic problems of a magnitude similar to that of problems that occurred with cocaine have been largely unfounded.

The term “*designer drug*” originated in the United States in the early 1980s to describe compounds manufactured by street chemists that resemble various legal and illicit parent chemicals

Table 1 Common street names of amphetamine derivatives

Amphetamine
amp, browns, hearts, fives, tens, white cross, beans, bam, black beauties, speed, bennies, cranks, crystal, dexies, greenies, lidpoppers, pep pills, pink and green amps, sparkle plenty’s, uppers, whites
Methamphetamine
bambita, crystal, meth, speed, crank, ice, glass, shabu, peanut butter crank
3,4-Methylenedioxyamphetamine
XTC, Ecstasy, Adam, X, E, Molly, clarity, essence
4-Bromo-2,5-dimethoxyphenethylamine
CBr, bromomescaline, nexus, Venus, N, Eve, synergy, 2C-B
3,4-Methylenedioxyamphetamine
love drug

Note: Street names are region specific and often overlap. The actual content of illicit drugs may be a function of drug substitutions, by-products of synthesis, and adulterating agents

with minor structural modifications [12]. Current terminology labels these chemicals “synthetics” or “hallucinogenic amphetamines.” Contrary to popular belief, most hallucinogenic amphetamines are not novel compounds developed by street chemists; rather, they are compounds that were studied in the past by researchers and pharmaceutical companies. The description of the synthetic process and pharmacologic activity of these compounds (numbering in the hundreds) is easily accessible in the scientific literature and the popular press [13]. Many of these substances were never formally tested for safety, efficacy, or adverse effects and their pharmacokinetics and pharmacodynamics may be poorly characterized, if studied at all. The manufacture of these substances often occurs in conditions that are unsanitary, chemical reactions may be performed poorly, and inappropriate substitutions for unavailable reagents may occur.

3,4-Methylenedioxyamphetamine is the prototypical hallucinogenic amphetamine. It was originally patented by Merck in 1914 and studies were performed evaluating its use in psychotherapy, though it did not prove safe and effective. 3,4-Methylenedioxyamphetamine is a stimulant and entactogen, inducing euphoria and increased sensory awareness [14]. In the 1980s,

it was marketed as “Ecstasy” and “E,” and illicit use increased significantly [15]. The popular press noted the worldwide phenomenon of MDMA use, especially at “rave parties,” large dance gatherings with electronic music [16]. 3,4-Methylenedioxy-methamphetamine and related compounds are usually taken orally and are available as tablets, capsules, crystals, or powder; in recent years use of crystalline and powder MDMA by nasal insufflation (“snorting”) is increasing. Significant variability in MDMA content in tablets is reported, ranging from 1 to 225 mg per tablet [14]. Contamination is high, with only 79% of tablets found in one study to contain pure MDMA, while the remainder included chemicals such as paramethoxyamphetamine (PMA), ketamine, lidocaine, ephedrine, caffeine, and others [14]. Use of “Molly,” short for “molecule,” began in the 2000s. Molly was initially sold as a powder, though tablets are also common. It is marketed to users as pure MDMA and potentially used due to the perception of greater safety as the adverse effects of Ecstasy are attributed to contaminants. Confusion arises as Molly has also come to refer to several other synthetic drugs.

The emergence of new psychoactive substances (often referred to as “bath salts” in the USA and “legal highs” in Europe) including synthetic cathinones and other hallucinogenic amphetamines occurred in the late 2000s. Along with synthetic cannabinoid receptor agonists, the use of synthetic cathinones increased significantly and received significant media attention. Calls to US poison centers about “bath salts” started in 2009. Mephedrone, methylenedioxypyrovalerone, methylone, and various product names were first mentioned in the AAPCC’s annual report in 2010 as an emerging public health threat when there were 5,624 exposures [17]. The trend increased with 24 reported deaths in 2011 [18]. Given the numerous chemicals and product names (with unknown chemical composition), it is difficult to accurately track exposures. The annual reports of the AAPCC start to group all synthetic stimulants together and refer to them as hallucinogenic amphetamines, with 12 attributed deaths in 2014 [6]. Interestingly, the use of synthetic cathinones seemed to decrease over the

subsequent years in the USA, in conjunction with media reports of psychosis and violent behavior. The most recent annual report attempts to name the presumed agent in fatality reports noting two deaths due to 2,5-dimethoxy-4-ethylphenethylamine and two to uncategorized amphetamine (hallucinogenic) [19]. This trend is in stark contrast to the experience in Europe where seizures of synthetic cathinones reported to the EU Early Warning System have increased to greater than 10,000 between 2011 and 2013. Additionally, from 2008 through 2014 there have been growing numbers of new synthetic cathinones identified each year [20]. England and Wales report nine deaths due to these agents in 2007, but 60 in 2013 [9]. Analysis and characterization of these chemicals is enhanced by programs such as Sweden’s STRIDA project, which has reported sympathomimetic toxicity and death due to confirmed cases of 3-methylmethcathinone [21]. In Australia, the number of seizures of these chemicals peaked at 132 in 2011–2012, but have been on the increase again with 92 reported in 2013–2014 [22].

Chemicals such as PMA and paramethoxy-methamphetamine (PMMA) gained attention as contaminants of Ecstasy that are often associated with fatalities. Originally described in Australia in the 1980s, PMA causes fatal hyperthermia, dysrhythmias, and intracranial hemorrhage [23]. PMMA causes similar signs and is also associated with fatalities earning it the street names “Death” and “Dr. Death” for both [24].

Illicit drug development has continued with the emergence of the “2C” class of chemicals known for very high potency. Originally developed by Dr. Alexander Shulgin and described in his book, *PIHKAL (Phenylethylamines I Have Known and Loved)*, the 2Cs are phenethylamines with methoxy groups at the 2 and 5 positions on the phenyl ring and a halogen or lipophilic group at the 4 position. The 2Cs are highly serotonergic due to the presence of the methoxy groups, but can be used as the basis to synthesize a strong stimulant with the addition of a 2-methoxybenzyl group to the nitrogen of the phenethylamine’s amino group. These are now marketed as research chemicals or “herbal LSD” and sold via the

Internet. They are distributed on blotter papers due to the microgram doses that are required for clinical effect and cause seizures, hallucinations, muscle rigidity, and rhabdomyolysis [25].

Local, state, and federal legislatures struggle to control synthetic drugs. Each molecular modification made to a banned substance results in a slightly different chemical, which may not be scheduled by authorities, allowing producers and abusers to avoid criminal prosecution. The US Controlled Substances Analogue Enforcement Act of 1986 largely attempted to close this loophole, but controversy in court regarding what precisely is meant by “analog” has hindered prosecution. In the lawsuit captioned *United States v. Damon S. Forbes*, a federal district court in Colorado dismissed the prosecution’s case because the law is too vague [26]. More recently, in *McFadden v. United States*, the US Supreme Court upheld a lower court’s conviction of a distributor of bath salts after he marketed them with wording borrowed from the analog act, including “not for human consumption” and noting that the product did not contain any controlled substances or analogs, though he did compare them to cocaine and methamphetamine [27]. The legal status of these chemicals varies significantly between nations. While several countries have utilized existing consumer or medication safety legislation to curtail distribution of new chemicals, Ireland, Austria, Portugal, and Romania have passed laws specifically aimed at preventing the distribution of at new agents and in Sweden police were granted the authority to confiscate and destroy harmful substances [28]. The synthesis of many of these compounds is relatively uncomplicated and inexpensive, however, and the lure of potentially large profits and the continued popularity of many of these substances make the hallucinogenic amphetamine phenomenon unlikely to be short-lived.

Chemistry and Pharmacology of Amphetamines and Derivatives

The word *amphetamine* is an abbreviation for *alpha-methylphenethylamine* [29]. The class of CNS stimulant drugs to which amphetamine

belongs is called the phenethylamines. The basic structure of this group of drugs is an aromatic ring (*phen* for phenyl) attached to a two-carbon chain (*ethyl*) bearing a basic nitrogen at the distal end of the carbon chain (*amine*) (see Fig. 1). Although primarily regarded as CNS stimulants, substitution of the fundamental phenethylamine nucleus can result in effects including sedation, stimulation, and hallucinations [29]. The large number of phenethylamine derivatives that have been synthesized allows detailed study of the structure-activity relationships of this series of compounds [29, 30]. Based on these structure-activity relationship investigations, some general inferences can be made about the pharmacologic effects of a given phenethylamine derivative based on its chemical structure as this has significant effects on which neurotransmitter is principally affected. There are essentially four sites on the phenethylamine on which substitution would affect the overall pharmacology of the compound: the amino group, the α and β carbons of the ethyl chain, and the aromatic ring.

Substitution of the amino nitrogen with a single methyl group increases central activity, as is seen when comparing methamphetamine with amphetamine [31]. Conversely, amphetamine causes more pronounced peripheral actions than methamphetamine. Mono-*N*-substituents larger than methyl groups cause a decrease in excitatory properties with retention of anorexiant effects. This observation has been exploited in the development of antiobesity agents that have reduced the potential for abuse relative to the amphetamines [31, 32]. Di-substitution of the nitrogen to form a tertiary amine significantly reduces activity, frequently to the point of abolition [31].

Substitution of the α carbon (to the nitrogen) with lower alkyl groups causes the CNS stimulant and anorexiant effects. The lack of significant CNS effects in compounds without substitutions at the α -position (e.g., β -phenethylamine) apparently is due to their facile degradation by monoamine oxidase (MAO) into compounds that do not penetrate the CNS. Compounds with an alkyl α -substituent (e.g., amphetamine) are poor substrates for MAO, have good oral bioavailability, and readily penetrate the CNS [32]. The branching at the α -carbon induces a chiral center. With respect to the absolute

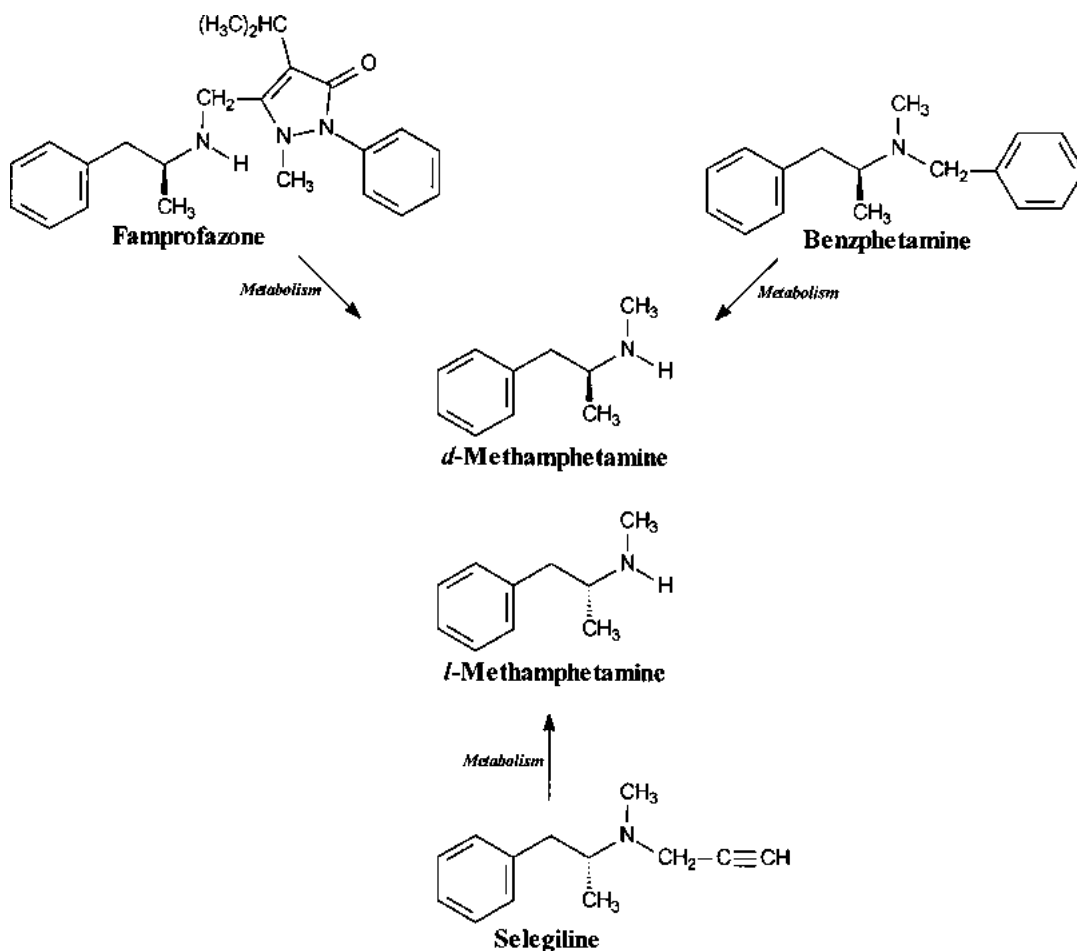


Fig. 2 Metabolic transformations of prescription medications to both isomers of methamphetamine

configuration of amphetamine, two isomers exist (*dextro* [*d*] and *levo* [*l*]). The pharmacologic profiles of these two compounds are distinct. The alerting activity of the *levo* (R)-isomer is only about one tenth that of the *dextro* (S)-isomer and about half the strength as a psychotomimetic [33]. This stereospecificity also is apparent with methamphetamine [31]. The *l*-isomer of methamphetamine (present in Vicks[®] Inhalers as *l*-desoxyephedrine) has greater peripheral sympathomimetic and less CNS stimulant activity than the *d*-isomer. The *l*-isomer is also formed as a metabolite of the anti-Parkinson's drug selegiline (Fig. 2) [34]. The greater CNS stimulation induced by *d*-methamphetamine makes it the preferred agent not only as an illicit stimulant but also as a therapeutically useful antiobesity agent. The *d*-isomer of

methamphetamine is a metabolite of the antiobesity agent benzphetamine [35]. The European over-the-counter analgesic/antipyretic famprofazone is metabolized to the *d*-isomer and *l*-isomer of methamphetamine, although the *l*-isomer predominates (see Fig. 2) [36].

Several compounds oxidized at the β -carbon (e.g., cathinone, ephedrine, and pseudoephedrine) retain CNS activity. Hydroxylation at this position lowers potency. Substitution with a keto, phenyl, or hydroxyl group at the β -carbon results in about 50%, 18%, and 4%, respectively, the stimulant activity of phenylisopropylamine. This decreased potency is due largely to the diminished ability of the hydroxylated compound to cross the blood-brain barrier [31]. Phenylpropanolamine has only about 1% of the ability to cross the

blood–brain barrier as its nonhydroxylated congener, amphetamine [33].

Substitution of the phenyl ring, particularly with alkoxy moieties, diminishes central sympathetic activity and increases hallucinogenic effects [32]. Exceptions to these generalizations are common, e.g., PMA and PMMA both retain sympathomimetic properties. Significant serotonergic effects are also produced by these same substitutions and clinical effects ranging from altered perceptions to hallucinations are noted. Hydroxylation of the aromatic ring also leads to diminished central activity presumably due to decreased blood–brain barrier penetration. Halogenation of the phenyl ring reduces sympathomimetic effects, but serotonergic effects can be enhanced [32]. These structural variations are shown in Fig. 1.

Pharmacokinetics of Amphetamine and Methamphetamine

Amphetamine

Volume of distribution: 3.2–6.1 L/kg

Half-life: 3.5–34 h

Protein binding: 16%

pK_a: 9.9

Active metabolite: norephedrine

Methamphetamine

Volume of distribution: 3–7 L/kg

Half-life: 6–15 h

Protein binding: 10–20%

pK_a: 9.9

Active metabolites: amphetamine, norephedrine

3,4-Methylenedioxymethamphetamine

Half-life: 7.6–8.7 h

Active metabolite: 3,4-methylenedioxymphetamine

*Half-life longer with alkaline urine.

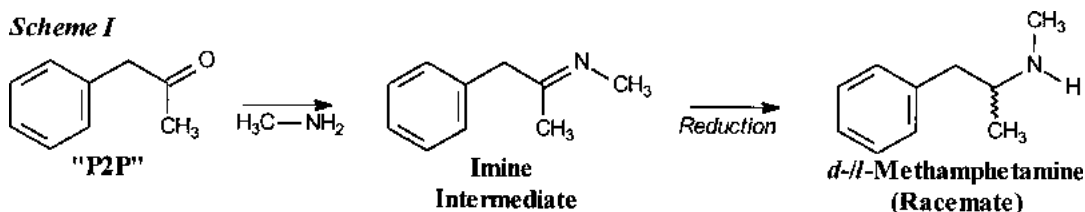
time. Motorcycle gangs were the primary manufacturers and sellers of methamphetamine throughout California in the 1970s. Over time, drug trafficking organizations operating between the United States and Mexico began to produce, distribute, and sell substantial quantities of methamphetamine throughout the United States [37]. Worldwide, Asia has seen significant growth in methamphetamine manufacture. Reports suggest major production of tablets occurs in Myanmar that are then smuggled into China and Thailand [9]. Although a wide variety of synthetic approaches are possible for the preparation of methamphetamine, only a handful are used with any regularity for illicit production of the drug. Other derivatives, such as MDMA, 3,4-methylenedioxymphetamine, and 2,5-dimethoxy-4-bromoamphetamine, tend to be more difficult to prepare and are produced less commonly. Methamphetamine street chemists or “cooks” learn synthetic procedures by word-of-mouth, apprenticeship with another cook, in jail, books, the Internet, and, occasionally, the primary chemical literature. Poor training, technique, and facilities, combined with generalized chemical ignorance and misinformation, can lead to relatively poor yields of methamphetamine, heavily contaminated product, and production of potentially toxic synthetic by-products.

Historically, illicit preparation of methamphetamine centered on derivatization of phenyl-2-propanone (P2P); typically, this involved condensation of the P2P with methyl amine to form the imine (Schiff base) followed by reduction to form the amine (methamphetamine) (scheme I in Fig. 3). The P2P method is not a stereospecific synthesis (i.e., it produces a 50:50 *d:l* mixture). Although popular for many years, use of methods involving P2P has declined substantially since the 1990s. The impetus for this decline is multifactorial. In the United States, P2P is now a Drug Enforcement Administration schedule II compound (restricted), and the detection of a “P2P lab” is easy because P2P has a pungent odor, likened to cat urine. The process is also time consuming and requires special materials [37]. Finally, the process evolved when ephedrine and pseudoephedrine, starting materials for

Illicit Synthesis of Methamphetamine

The illicit synthesis of methamphetamine is not difficult and requires little or no formal education in synthetic chemistry. Manufacturing sites evolved from small labs to “superlabs” capable of manufacturing pounds of methamphetamine at a

Scheme I



Scheme II

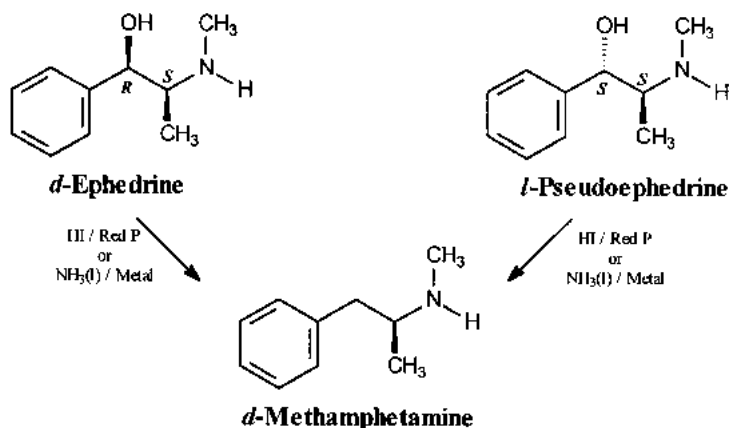


Fig. 3 Methods of illicit preparation of methamphetamine

alternative reductive dehydroxylation methods, were readily available.

The reductive removal of the benzylic (β) hydroxy group of ephedrine or pseudoephedrine has become the preferred illicit synthetic approach to methamphetamine. One of the most common methods of reductive methamphetamine production from ephedrine or pseudoephedrine employs red phosphorus and hydriodic acid (scheme II in Fig. 3). In efforts to avoid detection, cooks often obtain the necessary chemicals from veiled sources. Red phosphorus is extracted from matchbook strikers or road flares, and hydriodic acid is produced in situ by mixing mineral acids with iodine crystals used for water purification.

Another common method employed by clandestine chemists for reductive dehydroxylation of ephedrine or pseudoephedrine involves the use of an alkali metal, such as lithium or sodium, in the presence of liquid ammonia (scheme II in Fig. 3).

This method of illicit methamphetamine production often is referred to as the "Nazi" method, though it is technically known as the "Birch reduction." The metals typically are obtained from batteries, and the ammonia is obtained from agrochemical sources. Reduction of either *l*-ephedrine or *d*-pseudoephedrine via the red phosphorus/hydriodic acid or the "Nazi" method yields only *d*-methamphetamine, another reason cooks tend to favor these methods and starting materials.

Likely due to simple processes and easily available precursors, small labs began to produce significant amounts of methamphetamine causing problems in the communities where they were located. Clandestine methamphetamine laboratories may be the source of toxic exposures to the general public, fire fighters, and other first responders [38]. Mineral acids cause serious burns, and metal/ammonia reduction has

associated inhalational and dermal burn hazards due to residual ammonia or metal hydroxide left after production. Red phosphorus does not share the propensity to induce catastrophic liver damage possessed by yellow phosphorus (This is discussed in detail in ► Chap. 84, “Phosphorous”). Residual unreacted sodium or lithium metals or hydride-reducing agents present an explosive or corrosive hazard if they come in contact with atmospheric moisture or decontamination water. Additional concerns associated with clandestine methamphetamine synthesis are exposure to a variety of organic solvents, such as diethyl ether, acetone, and dichloromethane, and burns and blast injuries from chemical explosions.

Many synthetic by-products are formed because of impure starting materials, primitive facilities, and chemical ignorance [39, 40]. These by-products can be structurally diverse and may be present in highly variable amounts in a given mixture of methamphetamine. They may also contribute to the toxicity of a given batch of illicit methamphetamine, but few studies have examined this possibility. A notable example is the lead poisoning of IV methamphetamine users in Oregon in 1988 when there were 37 suspected and 14 confirmed cases [41].

By 2004 several US states had enacted laws to reduce the availability of pseudoephedrine with federal law passed in 2005. A short period of decreased methamphetamine exposure was noted, but production shifted outside of the United States, where it remains, managed mainly by Mexican trafficking organizations. More recently, there has been a resurgence of smaller labs domestically producing very small batches of methamphetamine using equipment like a 2 l bottle in a process known as “shake and bake,” which is generally the Nazi method on a very small and mobile scale [37].

Pathophysiology of Phenylethylamine Effects

Although the data are complex and sometimes conflicting, most suggest that amphetamines cause clinical effects indirectly, by increasing the

synaptic concentration of biogenic amines (dopamine, norepinephrine, serotonin) through increased release from presynaptic nerve terminals and decreased reuptake from the synapse [42]. The degree to which any of these neurotransmitters is affected depends on the structure of the particular amphetamine derivative. Some evidence indicates that amphetamine may act directly on catecholamine receptors, but this is believed to be a minor mechanism [43]. The effects of amphetamine on neurotransmitter systems are studied most extensively on dopaminergic neurons, which provide a model to explain amphetamine-induced biogenic amine effect. Normally the dopamine reuptake transporter system removes dopamine from the synapse. In the presence of amphetamines, the direction of this transport is reversed, resulting in movement of catecholamines out of the neuron [44]. The reuptake transporter system is sodium dependent, although evidence exists for sodium-independent transporters as well [45]. Amphetamines also cause release of intracellular dopamine in a manner that is independent of depolarization and calcium flux. Additionally, amphetamines enter the neuron by passive diffusion or exchange diffusion through the reuptake transporter, where amphetamine enters the cell concurrent with transport of dopamine out of the cell [46]. Amphetamine may also enhance internalization or phosphorylation of the dopamine transporter, inhibiting dopamine reuptake from the synapse [44]. Amphetamine decreases vesicular uptake of dopamine, increasing the cytoplasmic dopamine concentration. This decrease may be due to effects of amphetamine on vesicular monoamine transporter-2 or diffusion of amphetamine into the vesicles to change the pH preventing vesicular dopamine uptake [44]. The increased intracellular dopamine contributes to the pool available for release [47]. At high concentrations, amphetamines also have a weak inhibitory effect on MAO type A; however, this effect is unlikely at concentrations achieved by commonly used doses [48, 49].

At low doses, amphetamine increases central release of norepinephrine, which seems to induce appetite suppression and, in animal models, some forms of increased locomotor behavior.

Amphetamines reduce appetite and food intake in humans and many animal models [42, 50]. Higher doses are associated with an increased release of dopamine, which contributes to the anorexiant effect and results in stereotypical behaviors and other forms of increased locomotor activity in animal models [42, 51]. High doses of amphetamines or lower doses of serotonin-selective forms, such as MDMA, increase release of serotonin that may alter perceptions and, together with dopamine increase, may cause psychosis.

Amphetamine-induced psychosis and stereotypical behaviors are used as a model for schizophrenia in animals, and there are many similarities between these conditions in humans. Both conditions are thought to result from dopaminergic overactivity, and both respond to typical antidopaminergic antipsychotics. In animal models, increased amphetamine-induced dopaminergic activity in the nucleus accumbens results in an increase in general locomotor activity, whereas a dopamine increase in the striatum results in species-specific stereotypical behaviors, such as rearing, licking, and gnawing. These behaviors are dose dependent, with higher doses required to induce the more characteristic individual stereotypical behaviors [42]. These stereotypical behaviors are represented in humans as compulsive performance of repetitive tasks, such as assembling or disassembling mechanical objects, pacing, or foot tapping.

The hallucinogenic amphetamines, notably MDMA, and some pharmaceutically developed preparations, such as fenfluramine, have prominent serotonergic actions that account for some of their short- and long-term effects. Much of the research regarding these compounds focuses on MDMA. Because of MDMA's importance as a drug of abuse, it is discussed in detail. MDMA acts by several mechanisms (similar to the previous discussion of dopamine) to increase the concentration of serotonin in the synapse [52–54]. Animal models demonstrate that MDMA, when given at excessive doses, is associated with serotonergic neuronal injury, a reduction of activity of the serotonin synthetic enzyme tryptophan hydroxylase and decreased density of the serotonin uptake transporter [15]. The loss of

serotonergic axons, as shown by histopathologic studies, occurs in a variety of animal models [55, 56]. Primate studies document serotonin neuronal loss lasting 7 years, suggesting that these changes are permanent [57]. Some human data support these findings. Controlled studies in MDMA users documented decreased concentrations of 5-hydroxyindoleacetic acid in cerebrospinal fluid, altered neuroendocrine responses to serotonin agonists, and decreased serotonin transporter binding as shown by positron emission tomography [58–60]. These studies, when coupled with clinical investigations suggesting that MDMA users have impaired memory and cognitive performance and long-term psychiatric complaints, build a case for serotonergic neuronal toxicity, especially in cases of high doses or prolonged use [60–63]. All of these data are confounded, however, by the fact that the subjects studied also had exposure to multiple other drugs. Similar data suggest that methamphetamine may cause persistent neurochemical deficits in dopaminergic and serotonergic neurons [64].

Clinical Presentation and Life-Threatening Complications

Systemic Effects

Systemic toxicity after use of the amphetamines reflects a hyperadrenergic crisis that may be severe including hyperpyrexia, tachycardia, hypertension, and agitation. Rhabdomyolysis, hepatorenal failure, disseminated intravascular coagulation, dysrhythmias, cardiovascular collapse, and death may result [65, 66]. The relative contributions of norepinephrine and serotonin to the genesis of these clinical findings are unknown, and patients exhibit features of serotonin toxicity and the sympathomimetic toxidrome (see ► [Chaps. 24, “Serotonin Syndrome,”](#) and ► [25, “Sympathomimetic Syndrome”](#)). This clinical picture can occur with the traditional amphetamines and the substituted amphetamines and is reported both at therapeutic doses and in overdose [65–67]. The features of the clinical presentation of phenethylamine toxicity are summarized in Table 2.

Table 2 Clinical manifestations of phenethylamine toxicity

Cardiovascular	Neurological	Pulmonary	Gastrointestinal	Metabolic	Muscular	Skin
Hypertension Sinus tachycardia Ventricular tachydysrhythmias Vasculitis Valvulopathy Cardiomyopathy Myocardial ischemia/ Infarction Hypotension	Euphoria Agitation/ violent behavior Paranoia Hallucinations Seizures Coma Intracranial bleed/ infarction Venous sinus thrombosis Hyperreflexia Mydriasis Chorea	Pulmonary edema, and ARDS Pulmonary hypertension	Nausea Vomiting Hepatitis Diarrhea Gut ischemia	Acidosis Hyperpyrexia Hyponatremia: SIADH or dilutional	Bruxism Trismus Rhabdomyolysis	Flushing Diaphoresis Excoriations

SIADH syndrome of inappropriate antidiuretic hormone, *ARDS* Acute respiratory distress syndrome

Severe hyperthermia is associated with a poor clinical outcome. The precise mechanism of amphetamine-mediated temperature elevation is unknown. In animal models, hyperthermia was not attenuated by decapitation, but it was improved with curare, suggesting that temperature elevation was secondary to muscular heat generation [68, 69]. Other animal models suggest, however, that hyperthermia is centrally mediated and appears to be blunted by treatment with serotonin and dopamine antagonists [70]. Clinical reports describe cases of hyperthermia with and without excess agitation or muscular activity [71].

Central Nervous System Effects

The CNS is the principal site of action of the amphetamines, and consequently many of the clinical signs and symptoms of toxicity reflect CNS effects. Therapeutic use of amphetamines is usually accompanied by feelings of energy and well-being. Anorexia is a common and often desired effect. As toxicity progresses, agitation and unpredictable behavior become manifest. Animal studies note frequent stereotypical species-specific behaviors [42]. This behavior manifests in the clinical setting as repetitive tic-like movements or continued performance of certain tasks. Aggressive and paranoid behavior is common, and

injuries and death due to violent behavior and excessive risk taking are common [72]. Rodent studies show that aggressive behaviors and mortality are enhanced under crowded conditions [73, 74]. Large doses can result in seizures that may be due to direct drug effect or may be secondary to intracranial hemorrhage [75, 76].

Intracerebral hemorrhage is associated with amphetamine use irrespective of blood pressure [68]. Intraparenchymal and subarachnoid bleeding can occur, and patients with preexisting arteriovenous malformations may be at increased risk. Vasculitis is strongly associated with both oral and intravenous use of amphetamines. This small- and medium-vessel disease produces a beading pattern on radiologic imaging and can occur in the brain and other vascular beds [75, 76]. Ischemic strokes are also described.

Cardiovascular Effects

The acute cardiovascular effects of amphetamines largely reflect sympathomimetic effects. Lower doses are typically associated with sinus tachycardia, palpitations, and mild hypertension. Larger doses may produce supraventricular and ventricular dysrhythmias [77]. Hypertension may be severe and result in end-organ damage. Occasionally, isolated constriction of vascular beds results in

localized organ ischemia [78, 79]. In addition to vasospasm, necrotizing angitis of smaller vessels occurs, creating a beading pattern on radioangiography [75]. Myocardial ischemia, infarction, and global cardiomyopathy are reported, although these complications seem to be less frequent compared with cocaine use [80]. Fenfluramine, dexfenfluramine, and aminorex fumarate, anorexigenic agents that are no longer sold in most countries, were associated with pulmonary hypertension and valvulopathy [81].

Gastrointestinal Effects

Gastrointestinal effects of amphetamines probably reflect the ability of these drugs to compromise vascular supply, either through systemic hypoperfusion or through localized vasospasm. Ischemic gut is reported [79]. Many cases of hepatitis associated with amphetamine use are described, and these cases continue to accumulate with regard to the hallucinogenic amphetamines [82–84]. The mechanism of liver injury is not entirely clear; some cases are associated with hyperthermia, but other cases occur in patients with normal temperatures [83]. Data show hepatocytes exposed to methamphetamine suffer damage due to reactive oxygen species causing glutathione depletion, lipid peroxidation, and mitochondrial toxicity [85]. Currently, no antidotal therapy seems to be successful and supportive care is the mainstay of therapy. The role of liver transplantation in cases of amphetamine-induced liver failure is unclear, and success rates are low [83].

Dermatologic/Muscular Effects

Along with other stimulants, the amphetamines cause rhabdomyolysis [86]. The mechanism of muscle damage is unclear but may include agitation, extreme motor activity, seizures, hyperthermia, coingestion of other toxins (e.g., cocaine, tobacco, ethanol), or a combination of these factors [87]. Patients typically present with an elevation of creatine phosphokinase and have a positive urine dip-stick ortho-toluidine test for hemoglobin

and myoglobin [87]. Chronic amphetamine use is associated with alopecia, although the mechanism is unknown [88]. Self-inflicted excoriations can occur when compulsive or repetitive behaviors cause the patient to scratch repeatedly. Delusions of parasitosis (“crank bugs”) while rare may be accompanied by disfiguring attempts to remove the perceived insects or worms from the skin [89].

Pulmonary Effects

Amphetamines cause both cardiogenic pulmonary edema and the acute respiratory distress syndrome [80]. Pulmonary hypertension was well described with fenfluramine, dexfenfluramine, and aminorex fumarate use, but it is also associated, in a case report, with illicit amphetamines [90]. Asthma may be exacerbated. Any pulmonary complication associated with injection drug use (e.g., infection, granulomas) may also occur. Pneumothorax or pneumomediastinum result from barotrauma associated with inhalational drug use.

Genitourinary Effects

Urinary frequency and acute urinary retention are associated with MDMA [91]. Although renal dysfunction may occur in conjunction with amphetamine toxicity, it is believed to be secondary to rhabdomyolysis, volume depletion, vasculitis, hyperpyrexia, or a combination of secondary factors rather than direct drug toxicity.

Psychiatric Effects

Chronic high-dose use of amphetamines and their derivatives can result in amphetamine-induced psychosis [92]. Typically, users have paranoid ideation with ideas of reference [61, 62]. As the psychosis progresses, hallucinations may develop, and paranoid delusions may provoke sudden violent responses. Symptoms usually abate or disappear with abstinence, but recovery is often delayed and occasionally incomplete [62]. A variety of other psychiatric illnesses,

including depression, anxiety disorders, and panic attacks, are also associated with use of amphetamines [62, 77].

Oral Effects

Long-term use of methamphetamine is associated with characteristic dental pathology commonly known as “meth mouth.” Abusers have extensive dental caries. Potential explanations include poor oral hygiene, increased intake of food and beverages with high sugar content, and bruxism. There are contradictory data to implicate decreased saliva in this phenomenon [93].

Clinical Presentation and Life-Threatening Complications Associated with Various Designer Drugs

Toxicity of the hallucinogenic amphetamines largely reflects the sympathomimetic toxidrome that occurs with overdose of amphetamine and methamphetamine. The ring substitutions confer serotonergic activity that can produce specific clinical findings and toxicity. Data for some of the lesser used phenethylamines are sparse. There are considerable data, however, describing toxicity due to MDMA from case reports and series describing side effects and toxicity in the psychotherapeutic setting, pharmacokinetic and pharmacodynamic studies, or after recreational use. Capsules or tablets of MDMA average about 200 mg each, though they vary widely with a reported range of 66–465 mg [94].

Hayner and McKinney [95] divided adverse reactions to MDMA into three classes: (1) acute reactions with therapeutic doses, (2) overdose reactions, and (3) residual effects. Acute reactions at therapeutic doses commonly include tachycardia, tremor, tight jaw muscles, bruxism, nausea, headache, and sweating. Less commonly, extremity numbness and tingling, hallucinations, ataxia, blurry vision, and nystagmus are reported. Mydriasis, hyperreflexia, and gait instability may also occur. Ventricular dysrhythmias and cerebrovascular accidents are reported after allegedly

“therapeutic ingestions” of amphetamine and MDMA [65]. Users also report a variety of emotional and cognitive effects, including euphoria, increased energy, decreased appetite, positive changes in attitude or feelings, expanded mental perspective, and heightened sensual arousal [96]. Although MDMA often is referred to as the “love drug,” its effect on sexual function is often detrimental [97]. While most of MDMA’s psychological effects are described as positive and relate to the perception of improved insight and interpersonal communication, undesirable symptoms, such as anxiety, nervousness, and depression, can occur. Difficulty with cognition and judgment is noted in volunteers [98].

Toxicity from MDMA is manifested by sympathetic excess similar to amphetamine toxicity, including tachycardia, dysrhythmias, hypertension progressing to hypotension, hyperthermia, muscular rigidity, disseminated intravascular coagulation, rhabdomyolysis, and acute kidney injury [65, 95, 99]. Some patients with MDMA toxicity also have superimposed serotonin toxicity (see ► Chap. 24, “Serotonin Syndrome”) caused by the serotonergic effect of the drug. Because these drugs are metabolized in part by CYP2D6, genetic poor metabolizers or those individuals who take medications that inhibit this enzyme may be at increased risk [100–102]. MDMA toxicity is associated with raves, dance clubs, and electronic music festivals [65, 103, 104]. Vigorous dancing coupled with inadequate fluid intake may predispose MDMA users to hyperthermic crisis and collapse [65]. Recommendations to keep hydrated are occasionally taken to excess, however, and several cases of severe hyponatremia are reported in rave participants. Hyponatremia is attributed to MDMA-induced SIADH and combined with the intake of hypotonic fluids [100, 105–107]. Cases of acute hepatitis are reported after single doses and chronic use of MDMA [65, 82, 84]. Hepatitis usually resolves, but some cases have progressed to fulminant hepatic failure ending in death or requiring liver transplantation [82]. Aplastic anemia is also reported [108, 109]. MDMA modulates immune function in vitro, but the clinical correlates of this finding are uncertain [110].

The third category of reactions described by Hayner and McKinney are attributable to residual effects [95]. Mild residual reactions, such as exhaustion, fatigue, depression, nausea, numbness, and flashbacks, and more significant symptoms, such as anxiety attacks, persistent insomnia, rage reactions, and psychosis, are described. These residual symptoms persist for hours to 2 weeks. Others describe a variety of psychiatric effects, primarily panic disorders, psychosis, flashbacks, and depression that may be delayed in onset and may persist for months [61, 111, 112]. These cases seem to vary with respect to duration of symptoms and response to various psychotherapeutic agents, including haloperidol, amitriptyline, and fluoxetine. MDMA-induced disruption of serotonin homeostasis may be responsible for several psychiatric disorders after use due to the association between disordered serotonin and depression, psychosis, anxiety, panic, and eating disorders and data showing MDMA causes marked reduction of serotonergic neurons in primates [55]. Additionally, there is evidence that MDMA use is associated with subtle cognitive deficits [113].

Diagnosis of Toxicity from Phenethylamines

The diagnosis of phenethylamine use and toxicity should be based primarily on the recognition of the clinical features of sympathetic excess (see ► Chap. 25, “Sympathomimetic Syndrome”), hallucinations, and, in the case of ring-substituted derivatives such as MDMA, serotonin toxicity or serotonin syndrome (see ► Chap. 24, “Serotonin Syndrome”). Other conditions that result in the clinical findings of excess sympathetic tone, fever, or hallucinations should be considered. See Table 3 for a list of differential diagnoses. Some phenethylamines are associated with other toxicities that may not be secondary to this sympathetic excess, such as hepatotoxicity. Clinicians should be aware of these idiosyncratic toxicities as well.

Laboratory tests and radiographic studies serve primarily to identify medical or traumatic causes

Table 3 Differential diagnosis of sympathomimetic intoxication

Toxicologic
Cocaine
PCP/ketamine
Anticholinergics
Salicylates
Lithium
MAO inhibitors
Theophylline/caffeine
Nitrophenols
LSD
Psilocybin
Isoniazid/monomethylhydrazine
Amoxapine
Tricyclic antidepressants
Scorpion envenomation (<i>Centruroides sculpturatus</i>)
Serotonin toxicity/Serotonin syndrome
Neuroleptic malignant syndrome
Ethanol/sedative-hypnotic withdrawal
Nontoxicologic
Sepsis/meningitis/encephalitis
Intracerebral hemorrhage or infarction
Pheochromocytoma
Thyrotoxicosis
Temporal lobe epilepsy
Heat-related illness
Psychosis
Hypoglycemia/hyperglycemia

LSD lysergic acid diethylamide, *MAO* monoamine oxidase, *PCP* phencyclidine

that may account for the clinical condition of the patient or that may be present concurrently with phenethylamine use. During initial stabilization, a rapid blood glucose determination is indicated. In patients with altered mental status, tachycardia, and fever with unclear history, infectious processes should be suspected, and an appropriate search for a source should be conducted, including a chest radiograph, urinalysis, lumbar puncture, and blood cultures, as clinically indicated. This constellation of signs and symptoms may also reflect an intracerebral hemorrhage (unrelated or secondary to stimulant use), and a computed tomography scan of the head may be indicated. The complete blood count may show hemoconcentration from decreased fluid intake or increased insensible fluid losses. The white

blood cell count may be elevated with a leftward shift secondary to demargination from catecholamine excess. Electrolyte analysis may show hyponatremia, hypernatremia, or hyperkalemia. A metabolic acidosis may be present due to lactate-associated metabolic acidosis from hypoperfusion, or seizure activity. Respiratory alkalosis may occur as compensation for metabolic abnormalities, or it may occur primarily, as a result of anxiety or amphetamine stimulation of the respiratory center. In cases of significant toxicity, creatine kinase and troponin-I may be measured to assess rhabdomyolysis and cardiac ischemia. Urinalysis may show a positive dip-stick ortho-toluidine test indicating blood, free hemoglobin, or myoglobin. Liver function tests may be indicated if amphetamine-induced hepatitis is suspected.

If the diagnosis is unclear, measurement of serum salicylate, theophylline, and lithium concentrations is indicated because these substances may show a similar clinical picture in overdose. Thyrotoxicosis may also mimic amphetamine toxicity and can be assessed with a measurement of serum thyroid stimulating hormone and free serum thyroxine concentrations. Amphetamine use may cause elevation of serum thyroxine concentrations, which resolves when drug use is stopped [114]. Withdrawal from ethanol or sedative-hypnotic drugs may present a similar clinical picture that may be deduced from historical details.

Laboratory Analysis for Amphetamine Compounds

While it would be ideal to be able to obtain a quick, inexpensive qualitative determination of drugs of abuse, current methods of screening are not adequately specific to confirm the presence of amphetamine. The sensitivities and specificities of a urine drug screen in the presence of hallucinogenic amphetamines are unknown. The most common analytic technique for qualitative screening for amphetamine-like stimulants is the immunoassay. A variety of immunoassays have been developed to detect phenethylamines, including

radioimmunoassay, kinetic interaction of micro-particles in solution, cloned enzyme donor immunoassay, and enzyme-multiplied immunoassay technique, among others. Although there are differences among these techniques, they all employ an antibody designed to recognize the chemical structure of amphetamine. The specificity of the antibody depends on the uniqueness of the chemical structure of the analyte. In the case of compounds structurally unrelated to phenethylamines, such as cocaine, there are few substances that would interfere with the immunoassay and cause a false-positive result. As demonstrated above, a wide variety of compounds containing the basic phenethylamine nucleus exist, some of which are frequently prepared illicitly and abused (e.g., methamphetamine) and others that are available over the counter and used therapeutically (e.g., pseudoephedrine). The possibility of a false-positive immunoassay result for amphetamine from a structurally related compound is greatly increased. There is not a complete lack of specificity, however. Antibodies are designed specifically for interaction with amphetamine and methamphetamine. Although other compounds interact with the antibodies, it is typically only at drug concentrations greater than the concentration threshold required to give a positive result for amphetamine and methamphetamine. A positive result for an immunoassay is reported when a concentration greater than a predetermined cutoff value is detected. Concentrations less than this cutoff are considered negative because there exists a statistically significant chance that the result is due to an interfering compound. One of the more commonly used immunoassays in the USA is the EMIT-II monoclonal amphetamine/methamphetamine assay (Beckman Coulter®, Brea, California). The US Substance Abuse and Mental Health Services Administration set a cutoff concentration of 1000 ng/mL in urine as a positive *d*-amphetamine and *d*-methamphetamine for federal workers [115]. The EMIT-II package insert reports the concentrations of a series of other phenethylamine compounds that produce a positive result approximately equal to that of the 1000 ng/mL cutoff calibrator (Table 4) [116]. A few nonstimulant compounds do not possess the

Table 4 Approximate concentrations producing a positive result equivalent to the 1,000 ng/mL cutoff calibrator in Beckman Coulter's® Emit II monoclonal amphetamine/methamphetamine assay

Compound	Concentration (ng/mL) testing positive
d-Amphetamine	1,000
d-Methamphetamine	1,000
d,l-Amphetamine	1,961
d,l-Methamphetamine	1,500
MDA	3,794
MDMA	13,037
MDEA	11,192
Bupropion	814,000
Fenfluramine	75,000
Tranylcypromine	85,000
Propranolol	306,000
l-Ephedrine	2,240,000
Tyramine	390,000
Pseudoephedrine	4,340,000
Carbamazepine	250,000
Dextrophan	280,000
Zolpidem	100,000
Pseudoephedrine	670,000

MDA 3,4-methylenedioxyamphetamine, *MDMA* 3,4-methylenedioxymethamphetamine, *MDEA* 3,4-methylenedioxyethylamphetamine

Data from Beckman Coulter® product insert [116]

classic phenethylamine skeleton but may give a false-positive result for a phenethylamine immunoassay screen. The exact reasons for these interactions are not clear. Immunoassay tests exist for MDMA, but their use on a urine drug screen panel is hospital or clinic dependent. MDMA may be detected by methamphetamine immunoassay, but at a significantly higher concentration than is required for the MDMA test. The new psychoactive substances are not detectable on the standard amphetamine, methamphetamine, or MDMA immunoassays, likely due to their major structural differences from these chemicals [117]. Testing for these chemicals is possible with gas chromatography and mass spectrometry, though this requires additional cost and time. Given the lack of specificity, the clinical utility of the urine amphetamine immunoassay is unclear. Patients should be treated for amphetamine toxicity empirically based on their clinical presentations, laboratory results, and low risk for other emergent pathology unrelated to drug toxicity.

Forensic cases involving employment disputes or criminal prosecution may require confirmation of a positive immunoassay result. Confirmation is typically performed using gas chromatography with mass spectrometric detection. This method allows definitive structural identification and quantitation of the analyte and is mandatory in child custody cases and other legal situations where there is no room for false positive immunoassay results. The lack of correlation between blood or urine concentrations of phenethylamine stimulants and clinical response makes such confirmation in clinical cases typically unnecessary.

Clinical and forensic interpretation of concentrations of methamphetamine in blood is an area fraught with difficulty. They are expensive and usually require the capabilities of a commercial laboratory, delaying results for days from when the sample is obtained. There does not seem to be a consistent link between measured concentration and degree of intoxication or impairment. Similarly, deaths have been attributed to methamphetamine intoxication at concentrations well below those found in individuals who have survived without deficit [118]. Any detectable concentration of methamphetamine should be considered potentially toxic and correlated with the clinical circumstances.

Treatment of Patients with Phenethylamine Toxicity

Initial treatment of patients with toxicity from amphetamine derivatives should be directed toward assessment and stabilization of the airway, breathing, circulation, and temperature. Agitation and combativeness may make the initial evaluation and treatment of these patients difficult. Rapid control of the situation is essential because significant hyperthermia or other vital sign or laboratory abnormalities may require emergent therapy. Benzodiazepines (e.g., diazepam or midazolam) and butyrophenones (e.g., haloperidol or droperidol) have been recommended for agitation in these cases [86, 119] (Grade III recommendation). Diazepam decreased amphetamine- and methamphetamine-induced tremor,

piloerection, and seizures in rats but did not prevent death in one pretreatment model. In the same study, haloperidol, and to a lesser degree, propranolol decreased deaths in rats with amphetamine toxicity, but not those with methamphetamine toxicity. Haloperidol had no effect on seizures [120]. The ability of haloperidol to protect against amphetamine-induced mortality and the effect of diazepam on seizure reduction have been substantiated [121, 122]. In a retrospective human study, droperidol and lorazepam both reduced agitation, heart rate, blood pressure, and temperature, but lorazepam required more frequent dosing [123]. In patients with toxicity due to NBOMe or 2C class exposures, benzodiazepines were administered in 40% of cases [124]. Retrospective data reveal pediatric patients with methamphetamine toxicity treated with benzodiazepines and haloperidol recovered without adverse events [125]. There is significant potential for adverse drug effects when using butyrophenones including dose-dependent QT interval prolongation, reduction of seizure threshold, impaired heat dissipation, and dystonias [126–128]. Because of these potential complications, we consider benzodiazepines as the first-line agents for sedation. We recommend treatment with a benzodiazepine with a short time to peak effect, e.g., midazolam or diazepam. (Grade I recommendation based on animal data and III recommendation based on human data) [120, 122, 129]. Diazepam is preferred over midazolam due its longer half-life. (Grade III recommendation) [129] IV administration is ideal to achieve the most predictable pharmacodynamics, though midazolam can be given intramuscularly in cases where sedation is required prior to establishment of an IV. Initial doses of 5 mg diazepam IV or 5–10 mg midazolam IM should be administered with reevaluation in 10 min and further administration of repeat doses to achieve adequate sedation. (Grade III recommendation) [129]. Significant doses may be necessary to control the patient. Physical restraint of the patient may also be necessary until adequate sedation is achieved. Paralysis and endotracheal intubation are options for behavioral control and treatment of toxicity when other measures have failed. Patients with

hypoventilation or those without intact airway protective reflexes should also undergo endotracheal intubation. IV access should be obtained in all cases in which there are significant vital sign abnormalities or mental status changes. Patients should be placed on a cardiac monitor and administered oxygen as needed.

Hyperthermia (temperature > 40.5 °C) must be diagnosed rapidly and treated aggressively. Initial control of agitation must be definitively obtained in these circumstances to prevent further heat generation. A rectal temperature should be obtained to determine the accurate core temperature as an oral value can be falsely low due to tachypnea and poor technique. Vigorous use of benzodiazepines should be given simultaneously with cooling by ice water submersion. (Grade III recommendation) [130]. If this approach is not successful, the patient may require intubation and chemical paralysis to reduce muscular thermogenesis. Hyperthermia from methamphetamine and MDMA has been treated with risperidone in a pretreatment rat model, but it is unclear if any of the animal models mentioned above are applicable to humans [131, 132]. Acetaminophen, aspirin, and cooling blankets have little value in these circumstances. The use of dantrolene (see ► Chap. 142, “Dantrolene”) in toxin-induced hyperthermia has not been studied, but it may be administered if the above-listed measures have failed [133] (Grade III recommendation). In cases of significant temperature elevation, core temperature should be monitored with a continuous esophageal, rectal, or bladder probe, if available.

Gastrointestinal decontamination is not frequently an issue because many patients have used amphetamines by the intravenous or inhalational route. Nasal insufflation is not likely to be accompanied by a significant amount of drug in the gastrointestinal tract. In patients with a significant recent oral ingestion or in body packers/stuffers, gastrointestinal decontamination may be helpful. Gastric lavage is unlikely to be of benefit and should not be used. Activated charcoal delayed the onset to symptoms and reduced mortality when given after methamphetamine in a mouse model [134]. Activated charcoal

administration has not been shown to alter the outcome of these patients and given the risk of imminent seizures and subsequent loss of airway reflexes is not generally recommended. In the rare case of a patient with MDMA toxicity who presents within an hour of ingestion and is intubated for respiratory distress or behavior control, activated charcoal has some theoretical benefit.

Seizures should be treated initially with a benzodiazepine. (Grade I recommendation based on animal data and grade III recommendation based on human data). If seizure activity persists, phenobarbital or propofol should be added (Grade III recommendation), with airway protection as needed. Phenytoin will likely be ineffective in toxin-induced seizures. Continued seizure activity that is unresponsive to benzodiazepines and barbiturates, especially if it is contributing to significant hyperthermia, should be treated with neuromuscular blockade followed by electroencephalographic monitoring and consideration for general anesthesia. If focal neurologic deficits or persistent nonfocal findings such as coma are present, consideration should be given to the possibility of intracranial bleeding or infarction, and a computed tomography scan of the head is indicated.

Indications for ICU Admission in Amphetamine and Amphetamine-Derivative Toxicity

Clinically significant cardiac dysrhythmias

Cardiac ischemia

Severe hypertension ($\geq 200/125$ mmHg)

Coma

Intracranial hemorrhage/infarction

Intractable seizures

Agitation

Hyperthermia (≥ 40.5 °C)

Multisystem organ failure

Amphetamines cause a variety of dysrhythmias. Sinus tachycardia alone without hemodynamic compromise usually does not require specific treatment. Sinus tachycardia can be treated with sedation, volume resuscitation, and temperature control. Typically treatment with benzodiazepines will be most helpful, controlling

psychomotor and cardiac effects. Ventricular tachycardia, ventricular fibrillation, atrioventricular blockade, and QT prolongation are described as consequences of phenylethylamine toxicity [135, 136]. Standard advanced cardiac life support measures should be undertaken including antidysrhythmics, cardioversion, and defibrillation.

Agents with α -adrenergic antagonism, such as phentolamine (5 mg IV), or a titratable dihydropyridine calcium channel blocker such as nicardipine (5 mg/h IV infusion, increased by 2.5 mg/h every 15 min to a maximum of 15 mg/h) may also be helpful for vasospasm or complications of severe hypertension such as aortic dissection. Vasospasm may be recurrent and require prolonged therapy [137]. Nitroprusside (0.25 microgram/kg/min IV infusion, increased by 0.5 microgram/kg/min every 5 min to a maximum of 10 microgram/kg/min) and nitroglycerin (400 microgram sublingual tablet every 5 min or 50 microgram/min IV infusion, increased by 10 microgram/min every 5 min) can be titrated to effect in cases of elevated blood pressure with markers of injury to end organs such as cardiac enzyme elevation, acute kidney injury, neurological deficits, vision changes, or retinopathy or blood pressure $\geq 200/125$ mmHg.

Hypotension, if present, should be treated first with normal saline or lactated Ringer's solution. Hypotension unresponsive to crystalloid infusion requires the use of standard vasopressor agents.

Rhabdomyolysis, if present, should be treated with adequate hydration and maintenance of urine output. Although controversial, some clinicians recommend urinary alkalinization to prevent renal myoglobin deposition. Justification for this in the absence of clinical data showing improved outcomes includes the large quantity of IV fluids required to prevent oliguria in cases of significant rhabdomyolysis, the lack of significant adverse effect of bicarbonate infusion, and the expected development of hyperchloremic metabolic acidosis after significant normal saline infusion [138]. Alkalinization of the urine may impair renal clearance of the amphetamines, though. Given the lack of data suggesting benefit

of alkalinization over IV hydration in the treatment of rhabdomyolysis and decreased amphetamine clearance, we do not routinely recommend urinary alkalinization [138] (Grade III recommendation).

Elimination Enhancement

The enhanced renal elimination of amphetamines by urinary acidification is mentioned only to be immediately condemned. The elimination half-life of amphetamine is 8 – 10.5 h with acidic urine and 16 – 31 h with alkaline urine [139]. Toxicity from amphetamines may be accompanied by rhabdomyolysis, however, and the risk of inducing acute kidney injury due to the precipitation of myoglobin in acidic urine is believed to outweigh any potential benefit from increased drug clearance. Hemodialysis, hemoperfusion, and hemofiltration play no role in increasing drug clearance in amphetamine toxicity.

Criteria for ICU Discharge in Amphetamine and Amphetamine-Derivative Intoxication

- Hemodynamic stability
- Ability to protect airway
- Resolution of hyperthermia and lack of evidence of hyperthermia-related multisystem organ failure
- No requirement for continued intravenous medication infusion for hypertension, cardiac dysrhythmias, or seizures
- No evidence of continued drug absorption in cases of oral exposure
- Clear mental status
- Normal temperature
- No multisystem organ failure

Key Points in the Treatment of Amphetamine and Amphetamine-Derivative Intoxication

1. Rapidly gain control of agitated patients, using physical and pharmacologic restraint as needed.

2. Rapidly assess all vital signs, especially core temperature.
3. Treat hyperthermia aggressively with sedation, physical cooling measures, and paralysis, as clinically indicated.
4. Consider rhabdomyolysis as a complication of toxicity.

Special Populations

Pediatric Patients

Neonatal effects associated with maternal amphetamine use include tachycardia and bradycardia, which typically resolve as the drug is eliminated or as catecholamine homeostasis is restored. Infants born to amphetamine-using mothers may lag behind their peers in various measures of intellectual performance and show abnormal growth and maturation patterns at puberty [140]. Children also may ingest amphetamines unintentionally and may present a diagnostic dilemma to the clinician. In one series describing unintentional methamphetamine ingestion, children commonly manifested tachycardia, irritability, inconsolable crying, agitation, and vomiting [141]. These signs can mimic many serious childhood diseases. A urine toxicologic screen for amphetamines may be a valuable diagnostic tool in these cases, though evaluation of child abuse or parental negligence requires confirmation by gas chromatography mass spectrometry.

Pregnant Patients

Methamphetamine crosses the placenta rapidly in sheep and distributes into fetal tissues with a longer elimination half-life than in the mother. Doses similar to those seen in recreational use caused maternal and fetal hypertension and a decrease in fetal oxyhemoglobin saturation and arterial pH in this model [142]. Amphetamine use during pregnancy is associated with maternal hypertension, tachycardia,

proteinuria, premature labor, and placental hemorrhage in humans. Reported adverse pregnancy outcomes associated with maternal amphetamine use include cleft lip and palate, cardiac defects, growth retardation, cerebral hemorrhage, hyperbilirubinemia, biliary atresia, low birth weight, and reduced head circumference [140]. Preliminary data regarding prenatal exposure to MDMA indicate that there may be increased risk of cardiovascular and musculoskeletal abnormalities [143]. Few data exist regarding the effect of other phenethylamines in pregnancy; however, 2,5-dimethoxy-4-methyl-amphetamine was found to cause significant uterine and umbilical artery vasoconstriction and evidence of fetal distress in sheep [144].

Patients with Drug-Drug Interactions

Monoamine oxidase inhibitors, and possibly tricyclic antidepressants (catecholamine reuptake inhibitors), taken together with amphetamines may result in an exaggerated release of catecholamines and sympathomimetic toxidrome or serotonin toxicity/syndrome [145]. Similarly, antidepressants with serotonergic activity may increase clinical effects and toxicity that occur with MDMA and related drugs. Any drug or dietary change that results in alkaline urine (acetazolamide, antacid therapy, sodium bicarbonate) results in a decrease in the urinary clearance of amphetamine, although this effect is of little significance due to the baseline low urinary clearance of these drugs. Amphetamines are metabolized in part by the CYP2D6 enzyme. Users who are deficient in CYP2D6 activity (7% of Caucasians) or who are taking medications that are CYP2D6 inhibitors (e.g., paroxetine and fluoxetine) may be susceptible to increased toxicity from these drugs. This susceptibility may account for reported cases of toxicity with therapeutic or usual recreational doses of amphetamines and derivatives [67, 146]. In addition, amphetamines may inhibit the metabolism of other drugs that are metabolized by this cytochrome isoform [101].

Common Errors in the Treatment of Amphetamine and Amphetamine-Derivative Intoxication

Failure to rapidly detect and aggressively treat hyperthermia or other significant vital sign abnormalities because of violent behavior on the part of the patient

Failure to consider primary or secondary intracranial hemorrhage as a cause of mental status changes

Common Misconceptions about the Treatment of Amphetamine and Amphetamine-Derivative Toxicity

Alteration of urinary pH is useful in amphetamine toxicity.

All amphetamine compounds can be detected reliably by commonly available urine drug screens.

Legal action can be taken based on the results of an immunoassay screening test without confirmatory testing.

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Arylcyclohexamines: Ketamine, Phencyclidine, and Analogues

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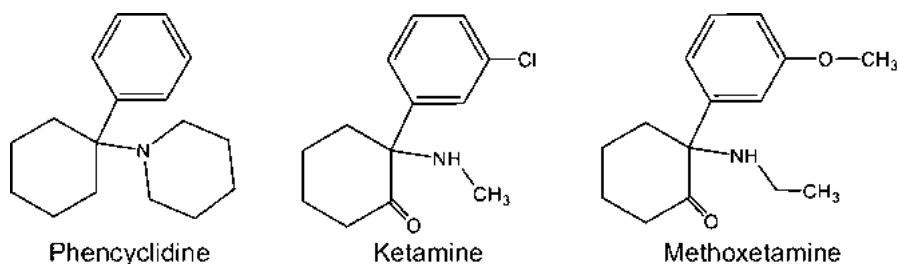


Fig. 1 Chemical structures of the primary arylcyclohexamines: phencyclidine, ketamine, and methoxetamine

Arylcyclohexamines (also known as arylcyclohexylamines) are a group of compounds that contain a cyclohexamine unit with an aryl moiety, typically a phenyl ring, attached to the same atom to which the amine group is linked (see Fig. 1). They all exhibit dissociative effects due to their antagonism of *N*-methyl-D-aspartate (NMDA) receptors, and many have been studied as alternatives to traditional anesthetic agents but subsequently abused recreationally in pursuit of these same effects. The most well-characterized arylcyclohexamines are phencyclidine ((1-(1-phenylcyclohexyl) piperidine; PCP)), ketamine, and, of the novel analogues, methoxetamine.

The main effects of this class of agents are nystagmus, hypertension, and tachycardia in a behaviorally disturbed, and possibly violent, patient. Variation in their potencies, tachyphylaxis in regular users, and the possibility of their misrepresentation as alternative arylcyclohexamines means that prognostication in these patients is difficult. While they can also cause seizures, coma, and death, the majority of patients presenting with acute arylcyclohexamine toxicity will survive with appropriate supportive care.

Historical Perspective

The first arylcyclohexamine to be described was 1-(1-phenylcyclohexyl) amine, in 1907, almost 50 years before the synthesis of PCP [1]. Other analogues reported in the early 1950s included *N*-ethyl-1-phenylcyclohexylamine (PCE) and 1-(1-phenylcyclohexyl)morpholine (PCMo). While many were not explored further by their

initial investigators, chemists at Parke-Davis pursued these and other derivatives in the ensuing years in the hope of developing new anesthetic agents. Compounds such as 1-[1-(thiophen-2-yl) cyclohexyl]piperidine (TCP) were investigated in clinical trials [2, 3]; however, none proved to be effective as an anesthetic due to their prominence of emergence delirium [4].

Phencyclidine, the first well-known arylcyclohexamine, was first synthesized by the Parke-Davis chemist Victor Maddox in 1956. While these experiments were not reported in the literature until nearly 10 years later [5], the pharmacology of phencyclidine had by then already been described [6, 7]. Initially promising human trials appeared to replicate the anesthetic effect observed in earlier animal studies, of potency in anesthesia, and an absence of respiratory depression, and PCP was approved by the US Food and Drug Administration (FDA) in 1957 under the trade name Sernyl [3, 8]. However, its adverse effects – including agitation, psychosis, and catatonia – were soon found to be more frequent and severe than anticipated, and Sernyl was withdrawn from clinical use in 1965 [9], though it was reintroduced to the veterinary market in 1967 as Sernylan [10].

Concurrent research by another Parke-Davis scientist, Calvin Stevens, led to the synthesis in 1962 of 2-chlorophenyl-2-methylamino-cyclohexanone, or ketamine [11–13]. The first human administration of ketamine was conducted in 1964 as part of a trial in 20 prisoner volunteers in the USA; it demonstrated that ketamine was an equipotent anesthetic agent to PCP with a reduced side effect profile, in particular with a reduced incidence of emergence delirium [9, 11]. The

study, led by Edward Domino at the University of Michigan, was the first to propose the use of the term “dissociative” in describing ketamine’s anesthetic effects. It was patented and subsequently marketed as Ketalar, having gained approval from the FDA in 1970 [3].

Since then, ketamine has evolved into a diversely utilized drug. Initially gaining widespread use in both human and veterinary anesthesia, its prevalence of emergence phenomena – though less than with PCP – has still largely restricted its human use to specific populations, in particular pediatric anesthesia and field medicine, where its hemodynamic stability and analgesic properties are highly valued. In veterinary medicine, ketamine remains the most widely used anesthetic across all animal species [14]. As further research into this multifaceted drug has progressed, its spectrum of human clinical use has also expanded. Known for decades as a potent analgesic, its use has recently become more common in the treatment of neuropathic pain, complex regional pain syndromes, and as an adjunct in postoperative pain relief [15–17]. While still somewhat experimental, it is also being researched as a treatment for severe depression and for refractory status epilepticus [18–27], and recent observational studies have suggested a potential role for ketamine as a rescue treatment for difficult-to-sedate patients with severe behavioral disturbance [28].

Recreational Use

Phencyclidine and ketamine appeared on the recreational drug scene at a similar time, with the first reports of recreational use of each drug occurring within a few years of each other in the 1960s [29–33]. First reported on the West Coast of the USA, the use of PCP spread rapidly across the USA such that in 1975 its use was described as an “epidemic of drug-induced schizophrenia,” owing to its overdose being responsible for more psychiatric admissions than alcohol abuse and schizophrenia combined [29, 30]. Between 1975 and 1977, the US Drug Abuse Warning Network (DAWN) reported a doubling in the number of

PCP-related emergencies and deaths, while 1978 data from the US National Institute of Drug Abuse (NIDA) reported that 13.9% of young adults (aged 18–25 years old) had used PCP [34]. Complicating its surveillance was its presence as an adulterant in up to 30 different street drugs, PCP being most commonly represented as marijuana [35]. One report of street drugs found on analysis to be PCP demonstrated less than 10% of samples had actually been sold as PCP [36]; more recently, PCP has been found in tablets sold as methylenedioxymethamphetamine (MDMA or “ecstasy”) [37].

It was not until April 1978, when all manufacture of PCP was prohibited in the USA under the Comprehensive Drug Abuse Prevention and Control Act of 1970, that its use began to decline [10, 38] and the subsequent cocaine epidemic of the 1980s eclipsed PCP use [38, 39]. In 1979, PCP was classed as a Class A drug of the UK Misuse of Drugs Act 1971 (the UK Misuse of Drugs Act 1971 prohibits the activities of Controlled Drugs in relation to their manufacture, supply, and possession; they are graded broadly into three classes, and penalties applied, based on the “harmfulness attributable to a drug when it is misused”) [40]

- **Class A** (includes): cocaine, heroin, lysergic acid (LSD), methadone, MDMA, morphine, PCP, and class B substances when prepared for injection
- **Class B** (includes): oral amphetamines, cannabis, codeine, ketamine
- **Class C** (includes): buprenorphine, benzodiazepines, tramadol, zolpidem

and made a Schedule 2 drug under the UK Misuse of Drugs Regulations 2001 (the UK Misuse of Drugs Regulations 2001 defines the classes of person authorized to supply and possess controlled drugs and defines the conditions under which they may be supplied, possessed, and prescribed [41]),

- **Schedule 1**: possession and supply are prohibited except in accordance with Home Office authority

- **Schedule 2:** are subject to full requirements of controlled drugs, including requirements for prescribing, safe custody, and the need to keep registers
- **Schedule 3:** are subject to prescription and safe custody requirements, however registers do not need to be kept
- **Schedule 4:** are not subject to prescription or safe custody requirements
- **Schedule 5:** are exempt from the above controlled drug requirements

as it was thought at the time that it might retain some medical indications; whilst not currently used as a pharmaceutical, PCP remains in Schedule 2 in the UK.

In 1971, the first account in the literature of ketamine's psychedelic effects was published in the *New England Journal of Medicine* [42]. Though recreational ketamine use was initially highest among healthcare professionals and others who had easy access to the drug [43], this changed in the 1980s and 1990s as it became increasingly popular among clubbers, and in particular on the rave scene, where it initially appeared as an adulterant to ecstasy tablets [44].

Despite early concern from the FDA about the misuse of ketamine, a request for control of its use from the US Department of Health and Services was rejected by the DEA [45], and it was not until 1995 that ketamine was added to the US "emerging drugs" list and eventually placed into Schedule III of the US Federal Controlled Substances Act (CSA) in 1999. In the UK, it was not until 2006 that ketamine was placed into Schedule 4 and added to Class C of the Misuse of Drugs Act, following evidence of continued abuse [40]; in June 2014, it was made a Class B drug and placed into Schedule 2 [46].

In the USA, increased control did not appear to be associated with a decline in ketamine use; this may, at least in part, relate to the burgeoning Internet trade providing a direct supply, particularly from sources in Hong Kong and in Mexico [47]. Today, most illicit ketamine originates from diverted pharmaceutical production or from illicit production in countries such as Mexico, China, India, and European states [48]. Internet trading

sites remain key in its distribution, the now obsolete Silk Road website having hosted numerous ketamine vendors.

First-Generation Arylcyclohexamine Analogues

Between 14 and 30 analogues of PCP have been reported, and while most of these did not reach a wide audience, the use of three became prominent: PCE, TCP, and 1-(1-phenylcyclohexyl) pyrrolidine (PCPy) [3]. PCE and TCP were the first of the PCP analogues to be reported, in street samples from Los Angeles in 1969 and 1972, respectively, with the first report of PCPy from Maryland in 1974 [36, 49, 50]. By 1975, TCP had been reported in 25 US states [30, 36, 51] and was the first of the arylcyclohexamines to be placed into Schedule I of the US CSA (the US Controlled Substances Act encompasses five Schedules of controlled substances (I–V) based on three criteria [52]. In 1975, after it was deemed to be of no medical value and of high abuse potential [45]:

- (a) A drug or substance's potential for abuse
- (b) A drug or substance's role in currently accepted medical use in treatment in the USA
- (c) A drug or substance's potential to lead to psychological or physical dependence

PCE and PCPy followed suit in 1978, both having been associated with increasing use and fatalities [45, 53, 54]. Anecdotal reports suggest that, despite their scheduling, all three analogues remained available throughout the 1980s, with the last reported seizure of PCE in 1991 [3]. The synthesis of TCP, meanwhile, has been described as recently as 2004 on an online drug forum [55]. Though their potencies were thought to be similar, users describe TCP and PCE as more potent than PCP, with TCP having a longer duration of action [3], while PCPy is reported to be roughly equipotent to PCP [4, 56].

The ketamine analogue 2-(ethylamino)-2-thiophen-2-ylcyclohexan-1-one (tiletamine) was developed by Parke-Davis for use in veterinary

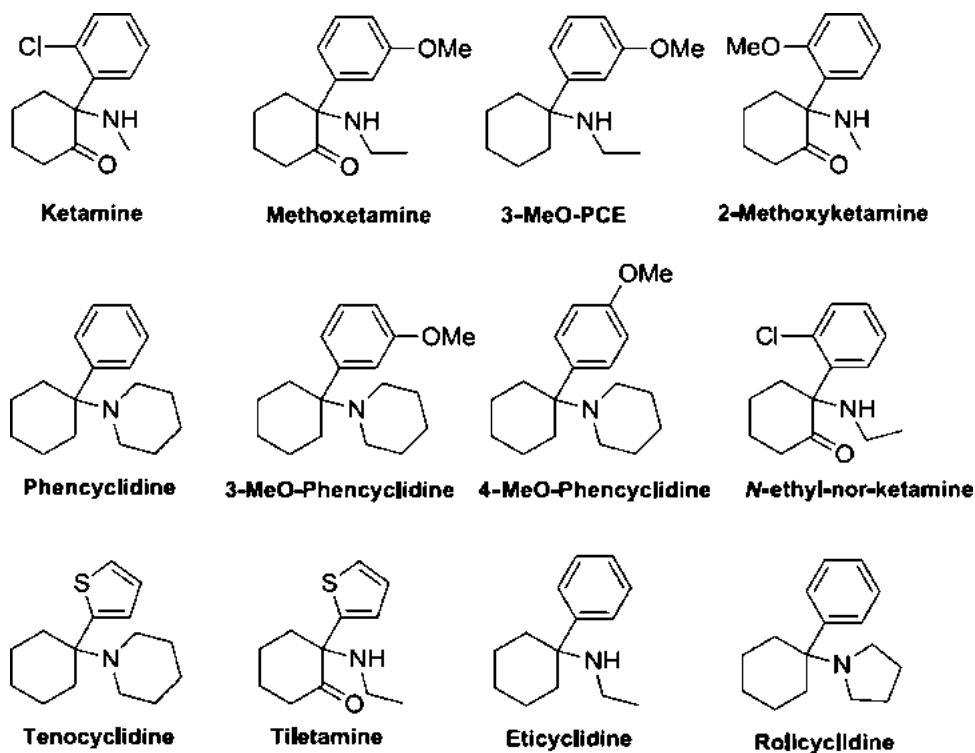


Fig. 2 Chemical structures of the arylcyclohexamine analogues

anesthesia and was patented in 1966 [57]. Despite being placed in Schedule III of the US CSA in 1987, there are reports of tiletamine misuse in the USA and South Korea, including two fatalities from its overdose [58, 59].

Other compounds, such as the PCP precursor 1-piperidinocyclohexanecarbonitrile (PCC), have relevance due to their detection as contaminants. An intermediary in the synthesis of PCP, the presence of PCC indicates an incomplete synthetic process and has been found as a contaminant in up to 33% of illicit PCP samples [49, 60, 61]; reports of an incorrectly synthesized batch of PCP was reported to have caused abdominal cramps, vomiting, coma, and even death [62]. Two studies in mice have shown conflicting data: one showed PCC to be roughly equipotent to PCP, while the other found PCC to be almost twice as toxic as PCP, with an LD₅₀ of 155 µmol/kg compared to an LD₅₀ of 283 µmol/kg for PCP [63, 64]. This toxicity is thought to be due to the release of hydrogen cyanide [61, 63, 65].

Novel Arylcyclohexamine Analogues

More recently, clandestine chemists have been producing novel analogues of phencyclidine and ketamine. A true example of the flourishing “designer drugs” scene, the theoretical effects of the ketamine analogue methoxetamine (MXE), or 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (see Fig. 2), were described on online forums in 2006, at least 3 years before its first known synthesis [3]. It was not until May 2010 that the first public report of MXE’s effects was described online, and only a few months later, it was marketed via “research chemical” websites as a “bladder friendly” alternative to ketamine (see below). First reported to the Early Warning System at the European Monitoring Centre for Drugs and Drugs Abuse (EMCDDA) by the UK in November 2010 [48], availability escalated quickly, with up to 58 websites offering MXE by July 2011 [66]. The first report of MXE toxicity in the scientific literature was published in August 2011 [67], with further reports of acute MXE toxicity and

MXE-related fatalities subsequently reported [68–74]. In April 2012, MXE became the first drug in the UK to be banned under a Temporary Class Drug Order (TCDO) [75, 76]; later that year, the UK Advisory Council on the Misuse of Drugs (ACMD) formally recommended that MXE was controlled, and in February 2013, it was placed into Schedule 1 as a Class B drug under the UK Misuse of Drugs Regulations 2001 and Misuse of Drugs Act 1971, respectively [75, 77].

Further methoxylated arylcyclohexamine analogues have emerged in addition to MXE. While they have appeared on the recreational drug scene only recently, their initial descriptions date back to the first description of PCP, with 2- and 4-methoxy-phencyclidine (2-MeO-PCP and 4-MeO-PCP [also methoxydine]) described by Maddox in his 1965 report [5]; 14 years later, 3-methoxy-phencyclidine (3-MeO-PCP) was described by Geneste et al. [78]. Little was heard of these compounds until their effects were described on an online forum by Beagle in 1999 [79, 80]; however, this site was taken offline in 2004. They reemerged again in December 2008, when 4-MeO-PCP appeared for sale online in the UK, with reports suggesting its varied potency to be due to impurities between batches and leading to re-experimentation with 3-MeO-PCP, which was made available online in April 2011 [3]. 4-MeO-PCP was first reported to the EMCDDA in January 2011 by Finland, with its first involvement in a polydrug intoxication reported in August 2011 from Norway; 3-MeO-PCP was first reported to the EMCDDA in March 2012 by the UK [81].

The ban on MXE left a void in the UK designer drug, or “research chemical,” scene which was quickly filled by other aryl-aminocyclohexanone analogues. In May 2012, 2-(2-methoxyphenyl)-2-(methylamino)cyclohexanone, or 2-methoxy-ketamine, came on to the market followed closely by *N*-ethyl-norketamine (*N*-EK) in August of the same year [3]; they were reported to the EMCDDA in August 2012 by Sweden and in September 2012 by the UK, respectively [82]. Their potency was reported by users to be low, with a wide variation in their effects.

Although other arylcyclohexamine analogues exist (see Fig. 2), including some of those mentioned here, most are poorly characterized and hence not discussed further.

Epidemiology of Recreational Use

Today, recreational use of arylcyclohexamines continues throughout the world. Without clear reason, PCP remains most popular in the USA and Canada – indeed, its use is almost exclusive to North America – with 2013 data showing 6.5 million Americans (2.5%) aged 12 and older to have used it in their lifetime, compared with 2.7 million (1.0%) for ketamine [83]. Ketamine is more widely used in the UK, however, and overall it retains a much more international presence on the recreational drug market; the 2015 UN World Drug Report reported its use in 58 countries [84].

In both the USA and the UK, the use of arylcyclohexamines is more common among males than females [83, 85, 86]: in the UK, 3.6% of males report lifetime ketamine use compared with 1.3% of females; in the USA, this is 1.3% compared to 0.8% [83, 87]. Available data from the UK shows that ketamine use is higher in gay or bisexual males (4.2%) than in gay or bisexual females (1.5%) and heterosexual adults (0.4%) [88]. Like many other recreational drugs and novel psychoactive substances, the use of arylcyclohexamines is more common among nightclub attendees [89–91].

Phencyclidine and Ketamine

Despite the decline of PCP use in the 1980s after its ban in 1978, it has remained a consistently available street drug in the USA, though its use reached a nadir in 1984 [92]. Data from the 2013 US National Survey on Drug Use and Health (NSDUH) shows that lifetime use of PCP in the USA has remained relatively constant over the past decade, at around 2.5% of the population [83]. Of concern, however, is data from the DAWN, which showed a fivefold increase in the number of PCP-related presentations to

emergency departments in the USA between 2005 and 2013, from 14,825 to 75,528 [93]. However, NSDUH data showed a decline in PCP use between 2012 and 2013, with past year initiates and prevalence of last year use falling from 90,000 to 32,000 and 172,000 to 90,000 (0.1% of the population), respectively. In contrast to the diversion of ketamine from overseas suppliers, manufacture of PCP has remained localized, providing one explanation for the sudden decline in use between 2012 and 2013: the discovery and bust of the largest-ever PCP laboratory on US soil in Los Angeles in February 2012 [94]. Of concern, despite the significant fall from 2012 numbers, is that in 2013 more than half (19,000 of 32,000) of past year initiates of PCP use were aged between 12 and 17 years.

Between 2006 and 2013, lifetime ketamine use in the USA has remained steady, at 0.9–1.0% of the population [83], though there was a significant increase in the lifetime use among those 26 years of age and older (0.7–1.1%) and a significant decrease in lifetime use among those aged 18–25 years (2.8–1.5%) and those aged 12–17 years (0.3–0.2%). Despite the overall lifetime use of ketamine remaining steady, there has been a similar increase in US emergency department visits due to ketamine, from 303 in 2005 to 1,550 in 2011 [93]. Further, while lifetime PCP use remains two-and-a-half times higher than lifetime ketamine use in the USA, the most recent data from NIDA's Monitoring the Future Study shows a trend among school-aged users toward ketamine rather than PCP, with 1.5% and 0.8% of 12th graders reporting last year use of ketamine and PCP, respectively, in 2014 [95].

In the UK, data from the Crime Survey of England and Wales (CSEW) showed last year use of ketamine in those aged 16–59 years increased from 0.4% to 0.6% between 2012/13 and 2013/14, with a significant increase in use seen in those aged 16–24 years (0.8–1.8%) [86]. Lifetime use among 16–59-year-olds increased from 1.3% to 2.7% between 2006/07 and 2013/14. Among self-reported substance users in the 2014 Global Drugs Survey, 5.7% of 78,819 global respondents reported last year use of ketamine; this was highest in the UK (19.8% of

7,326 respondents), while it did not make the list of top 20 drugs used in the USA among its 6,500 respondents [96]. Data from the European Drug Emergencies Network showed ketamine accounted for 2.0% of the 5,529 reported presentations of acute recreational drug toxicity to 16 emergency departments in 10 European countries [91]; 0.5% of self-reported ketamine users in the 2015 Global Drugs Survey had sought emergency medical treatment in the past 12 months [97].

In Hong Kong and China, ketamine has for over a decade been the most commonly used psychotropic drug – and second most common drug of abuse overall, behind heroin – since overtaking ecstasy in 2001 [98]. Among reported drug abusers (0.14% of the total population), 28.2% reported ketamine use in 2013, down from a peak of 37.9% in 2009 [99]. Its use is particularly evident among drug abusers under the age of 21 and among newly reported drug abusers; since 2001, in both groups, ketamine has been the most widely reported drug of abuse: in 2013 representing 52.5% (from a peak of 85.5% in 2008) and 46.4% of users, respectively [98, 99]. Similarly to US and UK data, ketamine use was more than twice as common in males, who represented 73% of ketamine users.

Arylcyclohexamine Analogues

There is no population level data on the prevalence of use of MXE from surveys such as NSDUH in the USA or CSEW in the UK. Figures regarding the use of MXE are therefore limited to targeted, nonrepresentative surveys among specific subpopulation groups. In 2011, the annual online Global Drugs Survey reported last year use of MXE in 4.2% of 7,700 UK respondents [100]; in an in situ survey of nightclub attendees in South London, UK, the prevalence of last year use of MXE was 6.4% [90]. Data from the UK National Poisons and Information Service (NPIS) showed a total of 345 inquiries regarding MXE between April 2010 and August 2012. There was a significant decrease in the number of inquiries to the NPIS in the 3 months following

Table 1 Characteristics of the major arylcyclohexamines

	PCP [38, 43]	Ketamine [102]	Methoxetamine [48]
Molecular structure	1-(1-phenylcyclohexyl) piperidine	2-chlorophenyl-2-methylamino-cyclohexanone	2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone
Molecular weight	243 kDa	238 kDa	247 kDa
Presentation	All available as white powder, liquid, tablets, and capsules		
	Often sprayed onto leaf material and smoked	Often adulterated (caffeine, MDMA, heroin, cocaine [CK])	Sprayed on to plant material and smoked
Common street names	Angel Dust, PeaCe Pill, Tic Tac, Supergrass, Hog, Shermans	Special K, Ket, vitamin K	Special M, Mexxy, M-ket, Kmax

MXE receiving a TCDO in April 2012 compared with the 3 months preceding the TCDO, with the total number of inquiries falling from 166 to 35 [85].

The only published data on the use of other novel arylcyclohexamine analogues are for 3- and 4-MeO-PCP, from the Swedish STRIDA project [101]. Between January 2010 and June 2013, only five inquiries were made to the Swedish Poisons Information Centre relating to “PCP” intoxication (none of these were analytically confirmed). In the 21-month period from July 2013 to March 2015, of a total of 2,687 consultations for suspected intoxication with a new psychoactive substance (NPS), 80 cases (3.0%) were registered as 3-MeO-PCP, 4-MeO-PCP, or PCP intoxication. Blood and/or urine samples were available for analysis in 30 (37.5%) of these cases: 27 (90.0%) were confirmed to involve 3- and/or 4-MeO-PCP; none tested positive for PCP. A total of 1,243 cases during the 21-month study period were analyzed for the presence of an NPS. 3-MeO-PCP and 4-MeO-PCP were detected in 56 (4.5%) and 11 (0.9%) of cases, respectively; both substances were found in 8 (0.6%) of cases [101]. The total of 59 cases in which either 3- and/or 4-MeO-PCP were detected suggests there is the potential that, like PCP and ketamine before them, they may also exist as adulterants to other drugs.

Chemistry and Clinical Pharmacology

The structure of arylcyclohexamines consists of a cyclohexamine unit with an aryl moiety, typically a phenyl ring, attached to the same atom to which

Table 2 Structural differences between ketamine and phencyclidine and pharmacodynamic effects

	Modification	Effect
1	Replacement of piperidine ring by a methylamine	Increased nausea
		No effect on potency
2	Addition of chloride to the phenyl ring at the 2-position	Decreases potency
		Increases analgesic effect
3	Addition of carbonyl group to the cyclohexal ring	Increases elimination with subsequent decrease in duration of action

the amine group is linked (see Fig. 1). Their characteristics are summarized in Table 1.

Chemical Structure

Ketamine and methoxetamine differ from phencyclidine in a number of ways (Tables 2 and 3 and Figs. 1 and 2) [76]. Unlike phencyclidine, ketamine has a chiral center and exists as two optical enantiomers that exhibit different properties. The S(+)-enantiomer has more potent analgesic effects, owing to its fourfold greater affinity for the NMDA receptor, while the R(–)-enantiomer is associated with more agitation due to its more prominent postsynaptic effects [103–105]. Studies of ketamine anesthesia for surgery in rats have also demonstrated the R(–)-enantiomer to be responsible for an increased incidence of emergence reactions than either racemic or S(+)-ketamine [106–108]. Differences in the metabolism of the optical isomers and their metabolites’

Table 3 Structural differences between **methoxetamine** and **phencyclidine** and pharmacodynamic effects [76]

	Modification	Effect
1	Replacement of piperidine ring by an ethylamine group	Increased nausea Increased potency
2	Addition of 3-methoxy group to the phenyl ring	Increased μ -receptor affinity Removes mood-altering effects

subsequent biodisposition have also been reported; however, the significance of this has not been well characterized [103]. Methoxetamine also exists as two optical enantiomers; however, it is not known whether there are significant differences in their pharmacokinetic or pharmacodynamic properties.

Although, as discussed earlier, there are many other arylcyclohexamine analogues that have been used recreationally, there is limited data available on their pharmacology.

Pharmacokinetics

Phencyclidine is rapidly absorbed from the respiratory and gastrointestinal tracts, with an onset of action that is quickest after intravenous (i.v.) or inhalational routes (2–5 min) and slowest following oral use (30–60 min) [109, 110]. While oral bioavailability of up to 70% is reported, the typical dose to achieve sedation equivalent to 0.25 mg of i.v. PCP is up to 20 times higher for the oral route (1–5 mg) [38]. Unlike PCP, ketamine is not well absorbed by the oral route and undergoes significant first-pass metabolism, with an oral bioavailability of less than 20% [111–113].

Arylcyclohexamines are weak bases with a pKa of 7.5–8.5 and molecular weights ranging from 238 to 247 kDa. PCP has a larger volume of distribution than ketamine because it is more lipophilic, and this contributes to its longer half-life and duration of action of between 7 and 46 h, compared with a half-life of 3 h for ketamine [38, 109]. Both PCP and ketamine are highly lipid soluble, enabling efficient distribution to the

Table 4 Onset and duration of effects (in minutes, unless specified)

	PCP [109, 110, 115]	Ketamine [102]	Methoxetamine [114, 116]
Time to onset			
IV	½–2	½	1
IM	–	5	5
Nasal insufflation	½–3	30	30–90
Smoking	2–5	–	–
Oral	30	20	90
Duration of effects [48]			
IM	–	30–60	120–180
Nasal insufflation	–	45–60	150–240
Smoking	4–6 h	–	–
Oral	60–180	60–120	180–300

central nervous system (CNS), and water soluble, allowing them to be administered by a variety of routes. The onset of action of ketamine and MXE, as for PCP, is rapid following i.v. and intramuscular (i.m.) administration, with effects apparent after 1 and 5 min, respectively [114]. In contrast to PCP, the onset of action of ketamine following nasal insufflation is up to 30 min, while users report that for MXE, this is as long as 30–90 min [114]. Duration of effect by different routes of administration is shown in Table 4.

All arylcyclohexamines are metabolized by the hepatic microsomal oxidizing system. PCP is metabolized by isoenzymes from the CYP3A and CYP2B subfamilies, primarily by hydroxylation to various inactive metabolites [43, 117, 118]. Metabolism of ketamine is primarily by the CYP2B6 isoenzyme, with contribution from CYP3A4 and CYP2C9 [119].

The main pathway of ketamine metabolism is by *N*-demethylation to norketamine, its major metabolite and also a noncompetitive NMDA receptor antagonist. Norketamine has one-third the potency of ketamine [38, 120] and, like its parent compound, exhibits chiral properties: its S (+)-enantiomer having greater affinity for the NMDA receptor than its R(–)-enantiomer [121]. Norketamine undergoes hydroxylation at the hexanone ring (this hydroxylation also being a minor metabolic pathway of ketamine itself) and subsequent glucuronidation to more water-soluble

Table 5 Pharmacokinetic properties of the arylcyclohexamines

	Phencyclidine [38, 110, 124]	Ketamine [38, 102, 112]	Methoxetamine [77, 100]
Absorption			
Oral Bioavailability	70%	17%	n/a ^a
pKa	8.6–9.4	7.5	n/a ^a
	Highly lipophilic	Water and lipid soluble	Water soluble
Distribution			
Protein binding	70–80%	10–30%	n/a ^a
Vd (L/kg)	5.3–7.5	1.8–2.3	n/a ^a
Metabolism	CYP450, primarily oxidative hydroxylation	Demethylation by CYP450s	Deethylation by CYP450s
Active metabolite	None known	Norketamine	(Normethoxetamine) ^b
Elimination	Hepatic 10% renal	Excretion in bile Glucuronidation and urinary excretion	Glucuronidation and (presumed) urinary excretion
Half-life	7–46 h	3 h	n/a ^a
Notes	No active metabolites In acidic urine, PCP becomes ionized and is not reabsorbed: renal clearance is increased by 23% but overall clearance by only 1.1%	Induction of some CYP450s may explain tachyphylaxis	Unknown activity of metabolites

^aNo data available^bPostulated to be biologically active based on what is known of norketamine [77]

metabolites that are excreted in urine. There does not appear to be significant differences in the pharmacokinetics between ketamine's two enantiomers [104], although some studies have reported a longer elimination half-life for S(+)-ketamine of up to 4–7 h [122].

No human studies have investigated the metabolism of MXE; the little information that is available is based on in vitro studies using liver microsomes and rat models [77, 123]. These showed the predicted metabolism of MXE by CYP 2B6 and CYP3A4, with the main metabolite, normethoxetamine, resulting from *N*-deethylation and accounting for over 70% of metabolites; the other major pathway resulted in *O*-desmethylmethoxetamine and accounted for 14% of metabolites. As with norketamine, normethoxetamine then undergoes hydroxylation and glucuronidation to form the more water-soluble hydroxynormethoxetamine glucuronide. These metabolites are consistent with those found in urine samples of analytically confirmed MXE

ingestions [70, 77, 123]. Like norketamine, normethoxetamine is thought to be pharmacologically active; however, this is unproven.

Known pharmacokinetic properties of the arylcyclohexamines are shown in Table 5.

Pharmacodynamics

All arylcyclohexamines exhibit dissociative effects due to their noncompetitive antagonism of glutamate receptors of the NMDA subtype [125]. They were initially sought after as an alternative to more traditional anesthetic agents but subsequently abused recreationally in pursuit of these same effects. Ketamine has approximately 10% of the affinity for the NMDA receptor than PCP [119, 125, 126], while 3-MeO-PCP has been found to have almost three times the affinity of PCP for the NDMA receptor [127]. In addition, the arylcyclohexamines also have effects at many non-NMDA receptors (Table 6).

Table 6 Receptor binding affinity, K_i (nM)

	PCP	Ketamine	Methoxetamine	3-MeO-PCP
NMDA	59 ^a	659 ^a	259 ^a	20 ^a
SERT	2,234 ^a	19,000 ^d	481 ^a	216 ^a
NET	—	66,800 ^c	—	—
Sigma-1	—	66,000 ^c	—	42 ^a
Sigma-2	136 ^a	—	—	—
5-HT2	5,000 ^d	15,000 ^d	—	>10,000 ^a
D2	37,000 ^d	500 ^d	—	—
Muscarinic	30,000 ^b	—	—	—
Opioid receptors	26,000 ^b	—	—	—

^aFrom [75, 127]^bFrom [157]^cFrom [159]^dFrom [153]

Arylcyclohexamines cause dissociation between the somatosensory cortex and higher brain centers, evoking a cataleptic state in which there is an absence of motor reaction to nociceptive stimuli [128, 129]. Functional magnetic resonance imaging (fMRI) studies have demonstrated a dose-dependent reduction in pain-induced cerebral activation at the secondary somatosensory cortex (S2), the insula, and the anterior cingulate cortex [130, 131]. While cortical effects are predominant, arylcyclohexamines also have significant effects at the spinal level, blocking afferent spinoreticular pathways and enhancing descending inhibitory serotonergic pathways [132–135].

Glutamate-Dependent Mechanisms

Glutamate is the major excitatory neurotransmitter in the mammalian CNS, acting on pre- and postsynaptic receptors located on ion channels [102]. Ionotropic glutamate receptors are classified as either NMDA, activated specifically by *N*-methyl-D-aspartate, or non-NMDA, activated by other neurotransmitters such as AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) or kainate [136, 137]. NMDA receptors are located on nearly all CNS cells, and in particular on those structures involved with nociception [102]. A specific “PCP binding site” has been identified; of the major arylcyclohexamines, PCP displays the highest

affinity for this site, followed by methoxetamine and then ketamine [127] (Table 6).

Activation of NMDA receptors occurs after calcium-dependent exocytosis of glutamate-containing synaptic vesicles [138, 139]. Glutamate is released into the synaptic cleft where it binds postsynaptic NMDA receptors, opening ion channels, and leading to membrane depolarization [140].

The NMDA Receptor

Present on nearly all cells of the CNS, the NMDA receptor is a tetrameric structure consisting of two subunits, of which there are three types: NR1, NR2, and NR3 (alternatively known as GluN1, GluN2, and GluN3, respectively) [102]. Each subunit possesses four hydrophobic segments, M1 to M4, which form the transmembrane domain (TMD); three of these segments (M1, M3, and M4) are truly transmembrane, while the M2 segment faces the cytoplasm and forms the receptor’s ion channel (Fig. 3). As well as the TMD, the NMDA receptor is comprised of two extracellular domains: the N-terminal domain (NTD, or amino terminal domain [ATD]) and the ligand-binding domain (LBD) [102, 139, 141].

The NMDA receptor is typically comprised of two NR1 and two NR2 subunits, of which seven and four subtypes of each subunit have been identified: NR1 a-g and NR2 A-D. The NR2 subtypes appear to be responsible for the variation in potency between arylcyclohexamines and the

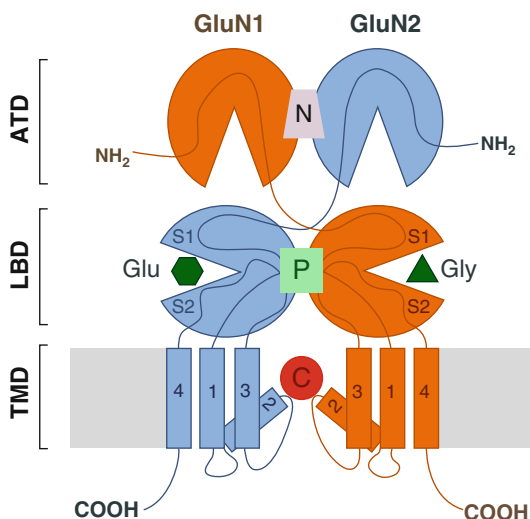


Fig. 3 Structure of the tetrameric NMDA receptor. Each of the two subunits (in this case NR1 and NR2) comprise a transmembrane domain (TMD), containing segments 1–4, and two extracellular domains: the ligand-binding domain (LBD) and the amino terminal domain (ATD). The channel-blocking domain (C; site of Mg^{2+} ion voltage-dependent block) and sites of glutamate (Glu) and glycine (Gly) binding are also shown. The PCP binding site is not shown but is located close to the Mg^{2+} binding site (C) within the ion channel [102, 139] (Figure reproduced with kind permission from Prof. David Lodge)

pathological processes associated with abnormal NMDA channel function [102, 142–144]. While the NR2A subtype is ubiquitous, the locations of the other subtypes are more localized. The NR2B subtype is found in the anterior parts of the brain, especially the cingulate cortex, hippocampus, amygdala, and olfactory bulb, and is also involved in nociceptive transmission to the thalamus, spinal cord, and extrasynaptic areas such as the primary afferents. The NR2C subtype is prominent in the cerebellum, while the spinal cord is rich in the NR2D subtype. Studies of PCP and ketamine have shown that they are, respectively, four and nine times more potent at NR2B-D receptor subtypes compared with the NR2A receptor subtype [142]. While there are no receptor studies of MXE, there is the potential that, given reports of cerebellar features in patients with acute MXE toxicity [69], it has greater specificity for the NR2C subtype.

NMDA receptors are coupled to calcium ion channels, which are activated by synaptic glutamate binding to the LBD of the NR2 subunit and require co-activation with either glycine (or D-serine) binding to the LBD of the NR1 subunit. The main inhibitory mechanism is the voltage-dependent block of the ion channel by magnesium ions [145]. At resting membrane potential, extracellular magnesium is held within the ion channel by negative electrostatic forces; neuronal depolarization causes magnesium to be released, and in the presence of the co-agonists glutamate and glycine, calcium influx ensues. Predictably, ketamine and magnesium have been shown to have a synergistic antagonistic effect at NMDA receptors [146].

The effects of NMDA receptor antagonism by arylcyclohexamines result in modulation of glutamatergic transmission [147]. Their primary effects, including anesthesia, analgesia, and psychotomimetic properties, relate to this action (see Pathophysiology, below). Other effects thought to be related to the NMDA receptor include antidepressant activity [148] and specific analgesic effects due to action at NMDA receptors in dorsal horn neurons [149].

Non-glutamate/NMDA-Dependent Mechanisms

Arylcyclohexamines also display affinity for a host of other receptors (Table 6). They bind to and inhibit biogenic amine transporters at approximately 10–20% of their affinity for the NMDA receptor [150], with resultant sympathomimetic and psychomotor effects due to inhibition of catecholamine, serotonin, and dopamine reuptake. It is thought that the effect on dopamine release is especially prominent in the nucleus accumbens [151], with subsequent implications for addiction [152]. In addition to inhibition of amine transporters, arylcyclohexamines have been demonstrated to have varying affinity for D_2 and 5-HT_{2A} receptors, where they are thought to exert agonist activity [153]. PCP and MXE have greater affinity than does ketamine at the 5-HT_{2A} receptor, thought to be related to the more

pronounced perceptual disorders and hallucinations seen with their use [154].

In overdose, the arylcyclohexamines also stimulate sigma receptors [155], causing an inhibitory effect on cholinergic pathways. It is thought that binding of sigma receptors may play a role in their antidepressant activity [156]. While ketamine has also been shown to bind to opioid receptors, its binding affinity at usual recreational or anesthetic doses is too low to contribute to its analgesic effects [157, 158]. Arylcyclohexamines also display weak affinity for nicotinic and muscarinic cholinergic receptors [157], though their role here is uncertain.

Analgesic Effects

As mentioned, the arylcyclohexamines are weak agonists at opioid receptors; however, at usual anesthetic and recreational doses, this is not thought to contribute to their analgesic effect; further, their analgesic effects are not reduced by the administration of naloxone [160, 161]. Rather, their analgesic properties are modulated by NMDA receptor antagonism in the CNS and in the spinal cord, by decreasing the amplification response to repeated stimulation, or “windup,” that causes CNS sensitization to nociceptive stimuli [102, 122]. Studies of ketamine have also suggested a non-NMDA-dependent role in directly inhibiting nitric oxide synthase, contributing to its analgesic effect [162, 163]. Further, both NMDA- and nitric oxide-dependent mediation of opioid receptors, and in particular the μ -receptor, appear to attenuate analgesic tolerance [164].

The Pharmacology of Tolerance, Dependence, and Withdrawal

The stimulatory effects of the arylcyclohexamines on dopaminergic and serotonergic transmission in the central nervous system, via both inhibition of amine transporters and via direct agonist activity at D_2 and 5-HT_{2A} receptors, are responsible for their addictive properties [151–153].

While it was initially thought that PCP did not have dependence potential, subsequent animal studies found that monkeys self-administered PCP and appeared to develop withdrawal [165]. These studies have since been replicated, demonstrating the development of dependence and the presence of withdrawal in multiple animal species [166–171]. In a case series of 68 chronic PCP users seeking treatment who had used PCP for a mean of 3.0 years, it was found that both psychological and physical dependence and withdrawal occurred [172]; 25 (36.8%) had considered themselves to be addicted to PCP. The most commonly reported symptoms were craving (51.5%), increased need for sleep (48.5%), poor memory (45.6%), depression, and laziness (both 44.1%). Irritability was reported by 30.9%, increased anxiety by 22.1%, and headaches and insomnia by 16.2% and 14.7%, respectively. However, no details regarding the length or severity of these symptoms were reported.

Ketamine use has been reported to be characterized by bingeing, often with repeated dosing until exhaustion of a user's supply [173, 174], and is generally associated with psychological dependence characterized by craving, rather than any physical dependence or withdrawal state [175–177]. In an online survey of 506 mostly Spanish self-reported ketamine users, 40.5% reported tolerance with ketamine use [178]. The observed tolerance in repeat and chronic ketamine users is thought to be as a result of auto-induction of CYP450 enzymes [177, 179–181].

No studies have examined the dependence or abuse potential of MXE; however, self-reports from users suggest compulsive re-dosing is an issue [48]. Reported withdrawal symptoms of MXE include low mood and depressive thoughts, while one user reported 48 h of insomnia after nasal insufflation of 1,000 mg of MXE [114].

Pathophysiology of Toxic Effects

The effects of the arylcyclohexamines are varied owing to their interactions with numerous receptors, as detailed above. Their predominant effects are on the central nervous system, and their

induction of a state akin to catatonia has led to advancements in the pathophysiology of schizophrenia, with NMDA receptor dysfunction as the foundation of the glutamate hypothesis of schizophrenia [147, 182, 183].

Neurological Effects and Pathophysiological Similarities with Schizophrenia

While the clinical effects of the arylcyclohexamines have been apparent from their outset, it has been only recently that their effects on the NMDA receptor have been fully characterized, their schizophrenia-like effects noted, and the glutamate hypothesis of schizophrenia advanced.

In the 1960s and 1970s, observations of dopamine D₂ antagonists, such as chlorpromazine, causing reduced psychotic features led to the development of the dopamine hypothesis of schizophrenia [184]. Characterized by positive symptoms – including delusions, hallucinations, and catatonia – and negative symptoms – of alogia, avolition, and flattened affect – there has been ongoing debate as to the ability of a hypodopaminergic state to account for all these effects [185].

More recently, the hypothesis of glutamate dysfunction as an explicable mechanism for both the positive and negative symptoms of schizophrenia has gained support [182]. While the schizophrenia-like effects of PCP were noted early in its use [11, 29, 186–188], the subsequent elucidation of the mechanisms of the NMDA receptor function has led to further interest in the role of this receptor and its antagonists as a model for studying schizophrenia and possible therapeutic interventions [185, 189]. Studies have shown that arylcyclohexamines produce a dose-dependent transient psychosis-like state closely resembling schizophrenia [147, 183, 190–192], which in some cases is indistinguishable from it [193] and indeed can exacerbate symptoms in those with schizophrenia [191, 194, 195].

These effects appear to be mediated by changes in blood flow seen in the prefrontal, medial frontal, and inferior frontal cortices [196, 197]. Though

the fundamental action of arylcyclohexamines in their antagonism of NMDA receptors is reduction in glutamatergic transmission at this receptor site, it has been shown that many of their effects are actually affected by an *increase* in non-NMDA-mediated glutamatergic activity. This goes some way in explaining the behavioral and neurochemical dysfunctions of arylcyclohexamine use while also providing an explanation for the apparently paradoxical pro-convulsant properties of high doses of PCP despite decreased NMDA-associated glutamatergic activity [198]. That is, the primary antagonism of NMDA receptors leads to decreased stimulation of inhibitory GABAergic interneurons (causing decreased GABA release), with subsequent increase in not only downstream glutamate release but also increased cholinergic and serotonergic activity [199–201]; these effects are seen primarily in the frontal cortex, anterior thalamus, and the superior temporal, posterior cingulate, and parahippocampal gyri. These effects on the pyramidal cells of the posterior cingulate cortex, in particular, may account for the focal neurodegeneration seen with chronic ketamine use due to this over-excitatory effect [199].

Further sequelae of chronic use include dose-dependent loss of gray matter volume and white matter abnormalities in the frontal lobes [202, 203]. Chronic use has also been found to induce regionally selective upregulation of dopamine D₁ receptors in the dorsolateral prefrontal cortex [43]. Further, consistent with the alternate dopamine hypothesis, acute ketamine administration has also been shown to alter the firing of mesocortical and mesolimbic dopaminergic neurons, leading to increased extracellular dopamine in both the striatum and in the prefrontal cortex [204, 205].

Other mechanistic links between the NMDA receptor and schizophrenia have been demonstrated in the signal transduction cascades that mediate cellular growth, differentiation, and survival in proliferating mammalian cells. In particular, the Ras–MAPK pathway has been shown to be involved in NMDA receptor signaling, providing a regulatory role in the synaptic plasticity related to long-lasting changes on memory and

addiction [206]. While formal studies of the molecular mechanisms of cognitive deficits due to arylcyclohexamine use are lacking, the similarity between the memory impairment seen in chronic users of ketamine and in schizophrenics suggests that the dysfunction of the MAPK pathway and decreased MAPK1 gene expression in schizophrenic brains [206–208] may also play a role in the cognitive and memory deficits seen with chronic arylcyclohexamine use [209, 210].

Differences Between Acute and Chronic Use

While there have been many reports of the psychotic effects attributable to acute arylcyclohexamine use, differences in the neuropathophysiology in repeated and chronic users have been shown to induce more persisting schizophreniform symptomatology [147].

As mentioned above, increase in blood flow to the frontal cortex is seen after acute ketamine exposure in both healthy volunteers and in schizophrenic patients [196, 197]; in contrast, a reduction in frontal lobe blood flow is seen in long-term abusers of PCP [211, 212], more consistent with the “hypofrontality” observations of cognitive dysfunction associated with reduced blood flow to the frontal cortex in schizophrenia [213–216].

Similarly, there is a difference in the effects on dopaminergic transmission associated with acute and chronic arylcyclohexamine use. Where their acute administration resulted in a dramatic increase in frontal lobe dopaminergic activity [204, 217, 218], long-term administration caused the reverse effect [219, 220], again consistent with effects seen in schizophrenia [221, 222]. The increase in dopamine in the forebrain is responsible for the cognitive dysfunction seen after acute arylcyclohexamine ingestion due to impairment of spatial working memory [223, 224]. Alongside this, the disinhibition of prefrontal glutamatergic transmission caused by NMDA receptor blockade leads to increased downstream glutamatergic stimulation of mesocorticolimbic dopaminergic transmission and of locomotor behavior [225].

The subsequent reduction in dopaminergic activity seen with chronic use of arylcyclohexamines also plays a role in decreased working

memory function of the prefrontal cortex [226]. In addition to the cortical effects of NMDA receptor antagonism, studies of subcortical striatal dopamine dysfunction have revealed more about dopamine’s role in the impaired cognitive function seen in schizophrenia and in chronic arylcyclohexamine use. In subcortical areas, it is thought that dopaminergic hyperactivity is in fact associated with chronic use [147]; this has previously been suggested for schizophrenia and would be consistent with the original dopamine hypothesis [227–229].

While the acute administration of arylcyclohexamines increases serotonergic and catecholamine activity via both biogenic amine reuptake inhibition and direct receptor agonism, no changes in their metabolism have been observed after long-term use of PCP [219, 220]. The effects of chronic arylcyclohexamine use on cholinergic pathways are less well studied, though it is thought that a degree of tachyphylaxis occurs [230].

Cerebellar Effects

While the effects of PCP and ketamine on the cerebellum have been demonstrated *in vitro* in rats, this clinical effect has not been demonstrated in humans [177]. In contrast, cerebellar toxicity was a prominent feature in a three cases of acute MXE toxicity, who presented with incoordination and severe cerebellar signs of ataxia, dysidiadokinesis, and nystagmus [69]. In all of these cases, the route of administration had been by nasal insufflation, with cerebellar toxicity reported within 20–30 min; in two of these, cerebellar features resolved after 16 h; however, in one case, ataxia and nystagmus persisted for 4 days. Toxicological analysis of serum samples of these patients showed methoxetamine concentrations of between 0.16 and 0.45 mg/L; no other drugs, including ethanol, were detected in any of these cases.

Effects on the Cardiovascular System

Pressor Effects

The pressor response typical of arylcyclohexamines has long been observed, with positive

effects on blood pressure as well as potentiation of the response to catecholamines, though tachyphylaxis was noted with repeated dosing [6, 7, 231]. While the mechanisms were not known at the time, this led Ilett et al. to postulate a role of PCP on catecholamine stores – rather than direct receptor agonism – which has since shown to be the case [38]. Interestingly, while the direct effect of arylcyclohexamines in isolation is to increase heart rate and blood pressure, some studies have shown that coadministration of other stimulant drugs, in particular cocaine, may ameliorate the sympathomimetic effects of subsequent arylcyclohexamine use [231], further complicating the clinical presentation of those intoxicated with these drugs. Since then, the effects of PCP and ketamine on the cardiovascular system have been well characterized, displaying modest rises in heart rate and blood pressure at usual recreational doses [232–235]; in one case series, the mean heart rate and blood pressure in PCP intoxicants were 101 bpm and 146/87 mmHg, respectively [235].

It should be noted, however, that arylcyclohexamines may exert cardiodepressant effects in the critically ill. Commonly overshadowed by the stimulant effects exerted by their effect on catecholamine reuptake inhibition, depletion of catecholamine stores in unwell patients can lead to the unmasking of the intrinsic negative inotropic effect of arylcyclohexamines caused by decreased intracellular calcium availability [231, 236–238].

In contrast to PCP and ketamine, MXE is associated with significantly greater cardiovascular pressor effects. In 2012, the first analytically confirmed case series of methoxetamine use provided confirmatory data of these effects [70]. Three individuals from London – two of whom had used only methoxetamine – were found to have tachycardia ranging from 113 to 135 bpm and to be hypertensive (systolic BP 187–201 mmHg, diastolic BP 78–104 mmHg); their serum MXE concentrations were 0.09, 0.12, and 0.20 mg/L. A second case series of three individuals from York also presented with mild cardiovascular stimulation [69]. Interestingly, though the observed effects were milder than those observed in the London group (heart rate 67–107 bpm, systolic

BP 148–194 mmHg, and diastolic BP 104–112 mmHg), their blood MXE concentrations were generally higher (0.16, 0.24, and 0.45 mg/L).

Other Cardiovascular Effects

There is little evidence as to the effects of PCP and ketamine on cardiac rhythm, while there are no data for MXE. Further, the paucity of experimental data in this area is somewhat contradictory, with ketamine having been observed to both enhance and diminish adrenaline-induced dysrhythmias in animal models [239–242].

In a series of 233 cases of acute recreational ketamine toxicity, despite palpitations being a common presenting symptom (likely to be related to sinus tachycardia), no cases of significant arrhythmia were recorded [234]; there were also no reports of myocardial infarction. Further supporting this is the considerable experience of ketamine in the setting of cardiac catheterization and as an anesthetic, which have not demonstrated proarrhythmic effects [243, 244].

However, a recent study in rabbits has suggested that chronic use of ketamine may result in remodelling of the myocardium, with ventricular myocardial apoptosis, fibrosis, and increased sympathetic sprouting leading to alteration of underlying cardiac electrophysiological properties and possible arrhythmogenesis [245]. Chronic ketamine use has also been shown in mice studies to cause hypertrophy of cardiac muscle with subsequent lysis and coagulative necrosis, with subsequent ECG tracings showing signs of myocardial ischemia [43].

Effects on the Respiratory System

The introduction of PCP and ketamine as dissociative anesthetic agents was based on the observations that they produced markedly less respiratory depression than traditional anesthetics [3]. In reality, they exhibit mild dose-related respiratory depression [246], though usually only in high or overdose [6, 103, 247]; an animal study using doses of 20 mg/kg of PCP successfully produced respiratory depression. The pattern of

respiratory depression differs from that of other anesthetic agents in that they have no effect on the slope of the CO₂-response curve; however, it shares similarity with opiates in shifting the curve to the right; that is, respiratory response to hypercarbia remains intact [248]. This also suggests that at the high doses required to cause respiratory depression, this action is via opioid and sigma receptors [38, 246]; this is supported by the observation that at sub-anesthetic doses the role of opioid receptor-mediated analgesia is minimal [158].

However, at usual recreational doses, the effect on respiratory depression is minimal, with clinical studies demonstrating maintenance of, or even an increase in, minute ventilation, tidal volume, and respiratory rate [8, 249]. In a review of 1,000 cases of acute PCP intoxication, tachypnea was much more commonly observed than was bradypnea [232]. Protection of airway reflexes and maintenance of airway muscle tone has also been demonstrated [250]. Further, ketamine has been noted to have a bronchodilatory effect, postulated to be via two mechanisms: (1) indirect stimulation of β_2 adrenergic receptors via catecholamine reuptake inhibition and (2) direct anticholinergic effect on bronchial smooth muscle [112, 251].

Arylcyclohexamines increase tracheobronchial mucus gland secretion [112], which may be of significance in overdose in conjunction with the potential for respiratory depression at high doses.

Effects on the Urogenital System

The toxic effects of arylcyclohexamines, and ketamine in particular, on the urogenital system have only been described relatively recently [252–254]. Only one study has investigated the effects of ketamine on the kidney after acute administration; after a 50 mg/kg administration of ketamine, rats demonstrated decreased glomerular filtration rate and renal plasma flow lasting 2 days [255]. Most studies and reports describe the effects of chronic ketamine use on the urogenital system; the following relates to chronic use.

Urogenital toxicity from ketamine displays a dose–frequency relationship, with cessation of use correlating with improvement in symptoms; however, severe fibrotic changes in the bladder are irreversible, and cessation of ketamine only prevents worsening of pathology in those with early bladder effects [256]. Common symptoms of urogenital toxicity include dysuria, hematuria, urinary urgency, urge incontinence, frequency, and nocturia [254]. In self-reported ketamine users, the frequency of lower urinary tract symptoms and cystitis has been documented to be as high as 27.0% and 32.0%, respectively [178, 254]. The mechanism of urogenital toxicity is unknown. However, it is clear that the lower urinary tract is more commonly affected, with the upper urinary tract usually affected after only more prolonged ketamine use.

It is thought that ketamine in particular, and its metabolites, may be directly toxic to the mucosa of the lower urinary tract, owing to their accumulation in urine. This may be due to effects on the microvasculature leading to ischemia and fibrosis [252, 253].

Bladder Effects

The first stage of effects on the bladder is stasis, resulting from a functional disturbance caused by infiltration of mononuclear cells into the bladder and the kidney, with a resultant increase in the risk of infection [257]. The second stage shows degeneration of nerves and the neuromuscular junction, with subsequent muscle thinning. In the third stage, bladder muscle degeneration is distinct, with replacement by fibrous tissue. The resulting small and rigid bladder causes frequent voiding [43], with bladder volumes reported to be as low as 30–100 mL in severe cases [252]. Bladder biopsies taken from chronic ketamine users have shown chronic inflammatory changes similar to those seen with other forms of interstitial cystitis [253, 258].

MXE was initially marketed as a “bladder friendly” alternative to ketamine. While there have been no human case reports of bladder or renal toxicity with methoxetamine use, animal models have shown that methoxetamine does cause inflammatory changes and fibrosis in the

bladder and both tubular and glomerular changes in the kidney, which are comparable to those in similar animal models of chronic ketamine administration [259].

Renal Effects

There is evidence that ketamine causes interstitial changes in the ureters and kidneys similar to those seen in the bladder, with mononuclear cell infiltration in the kidneys seen after between 1 and 3 months of ketamine treatment in mice [260]. It is unclear at this stage whether these chronic changes lead to ureteric or kidney tumors [261].

Hydroureter and hydronephrosis are reported in up to half of chronic users presenting with lower urinary tract symptoms [252]. In some of these cases, this was found to be due to renal papillary necrosis, with sloughing of the papilla into the ureter causing ureteric obstruction. In the majority of cases, however, proximal dilatation of the urinary tract is likely to be a result of the bladder changes described above.

There has been one case report in the literature of ketamine-induced renal infarction in an otherwise healthy 20-year-old female, who had presented with persisting left flank pain for 3 weeks [262]. It is thought that decreased nitric oxide synthesis might be the mechanism in this case, with vasospasm from decreased nitric oxide leading to hypoperfusion and subsequent infarction.

Effects on the Gastrointestinal System

There is little published on gastrointestinal (GI) effects of the arylcyclohexamines. User reports have described nausea, vomiting, and abdominal pain with ketamine use; however, there is no description of GI symptoms associated with use of PCP, MXE, or 3-/4-MeO-PCP in the major published case series [70, 101, 232, 235]. An early report of prominent GI symptoms with PCP use was thought to be due to the presence of a contaminant [263].

Users' reports of ketamine have commonly described nausea, vomiting, and abdominal cramps ("K-cramps"); however, there is limited

data on the frequency of these symptoms. In a study of ketamine users from the UK, the incidence of nausea was as high as 42.2%, while K-cramps were the most common reason for frequent users to seek medical attention [180]. In the largest case series of ketamine use, the incidence of abdominal pain and nausea was found to be 21% and 9.9%, respectively [234]. This study also noted abnormal liver function tests and/or dilatation of the common bile duct in 16.3% and 5.7% of users, respectively. In another case series, 12 of 14 users (85.7%) with GI symptoms who had an endoscopy performed were found to have gastritis [264]. While the pathophysiology of these effects is not characterized, improvement in GI symptoms was noted on follow-up after abstinence from ketamine use [264, 265]. A recent online survey advertised at clubs, festivals, underground raves, and on social media found 25.3% of 506 Spanish respondents to have experienced "frequent" abdominal pain [178].

Clinical Presentation and Life-Threatening Complications

The toxidrome of acute arylcyclohexamine toxicity has been described as including violent behavior and/or agitation, nystagmus, hypertension, tachycardia, and analgesia [266], and these are certainly their most common acute effects (see Table 7 for most common effects). Their toxidrome is not, however, specific, and therefore discerning these patients from users of other recreational substances can be difficult not only because of the varied effects of the arylcyclohexamines but also due to their rare use in isolation [3, 14, 48, 235]. Further, variation in dose, routes of administration, and even purity of the drug makes true description of a "typical" presentation impossible. PCP and ketamine have also been known to be adulterants to other drugs, such as MDMA, cocaine, and even cannabis [3, 14], while MXE may be confused by both dealers and users for its weaker parent drug ketamine [69].

The most serious of effects appear to be neurological, including seizures and coma, while

Table 7 Frequency of signs and symptoms of arylcyclohexamine toxicity (%)

	PCP [232, 235]	Ketamine [234]	MXE [48, 85]
Neurological			
Impaired conscious level (reported)	21.7–54.1	45.0	17.0
GCS <15 (recorded)	–	14.0	27.3
Unconscious	10.6	–	7.1–18.2
Agitation ^a	34.0	–	28.6–42.6
Amnesia	25.0	4.3	27.3
Hallucinations/delusions	18.5	0.9	22.2–27.3
Seizures	3.1	–	2.1
Nystagmus ^a	57.4–64.1	–	6.4–27.3
Cardiovascular			
Hypertension ^a	47.0–57.0	40.0	36.2–48.1
Tachycardia ^b	30.0	39.0	36.2–44.4
Chest pain	–	5.6	7.1
Palpitations	–	5.1	–
Cardiac arrest	0.3	–	–
Respiratory			
Respiratory depression	(Apnea) 2.8	–	0.0–9.1
Gastrointestinal			
Abdominal pain	–	21.0	–
Nausea/vomiting	–	9.9	–
Hyperthermia	2.6	14.0	–
Anticholinergic effects			
Mydriasis	–	–	27.3–29.6

^aClassic triad of PCP intoxication, first described by Burns et al. [35]

^bAdditional effect included in toxidrome of arylcyclohexamine use (plus analgesia) described by Bey et al. [266]

–No data/not reported

reports of cardiac arrest have also been noted with PCP use. All have been associated with mortality, and this is discussed further below.

Typical doses of arylcyclohexamines for recreational use are shown in Table 8; ketamine, in particular, has a wide therapeutic index. Its doses can be compared to its therapeutic use, where an intravenous dose of 1–2 mg/kg (4–10 mg/kg i.m.) is usually sufficient to induce anesthesia and 0.2–0.75 mg/kg i.v. (2–4 mg/kg i.m.) provides sedation and analgesia [267].

Phencyclidine

The first classification of PCP intoxication was proposed by Burns et al. in 1975, who described three progressive stages that were associated with increasing dose (Table 9) [35]. It was here that a “diagnostic” triad of nystagmus with

hypertension in an agitated, or comatose, patient was first described. Limitations of their categorization included a small sample size of 55 patients, in whom only 10 had confirmatory analysis of PCP use by detection in urine. The route of ingestion was also different between categories – inhalation or insufflation for low and moderate doses and oral for high doses – although it is also important to note that the high-dose category consisted of only one patient from their cohort combined with data from four additional case reports [35]. In 1979, Rappolt et al. drew from their clinical experience of 250 cases to elaborate upon Burns et al.’s work, proposing treatment for the differing stages of PCP intoxication [10].

The largest clinical case series of PCP intoxication was published by McCarron et al. in 1981 and described 1,000 patient episodes [232]. Of these 1,000 episodes, 59.7% were due to PCP ingestion only; the most common co-ingestants

Table 8 Typical recreational doses of arylcyclohexamines, by route of use

	PCP [115]	Ketamine [48]	Methoxetamine [48]
Oral	2–6 mg	75–300 mg	20–60 mg
Insufflation		30–75 mg	40–60 mg
Smoked	1.5–3.5 mg (typical PCP-laced cigarette contains 1–10 mg)		
IM		25–50 mg	15–30 mg
IV	5–10 mg [73]	100–200 mg [73]	5–40 mg [68]

Table 9 Clinical categorization of acute PCP toxicity, adapted from Burns et al. and Rappolt et al. [10, 35]

Stage	Dose (mg)	Serum PCP concentration (ng/mL)	Features		Time to recovery (hours)
			Specific	Common to all Stages	
I: Low dose	<10	25–90	“Behavioral toxicity”: agitation, excitement, incoordination Analgesia/dissociation of somatic sensation	Nystagmus, tachypnea, tachycardia, hypertension (common across all stages of intoxication)	4–8
II: Moderate dose	10–20	90–300	Light coma, or stupor		8–24
III: High dose	>100	>300	Prolonged coma		48–96

were alcohol (55.3%) and cannabis (37.5%). Most (72%) had smoked PCP – either by lacing cannabis or mint leaves with the powder or by soaking cigarettes in liquid – 13% had either snorted or sniffed PCP, 12% had ingested it orally, and 1.6% had injected it intravenously; the remainder had used either multiple routes or had been exposed to accidental inhalation of fumes following a laboratory explosion.

McCarron et al. noted the difficulty in correlating the signs and symptoms of PCP intoxication with the ingested dose; in particular, they acknowledged difficulty both in the accurate determination of the dose taken and the timely receipt of serum concentrations [268]. A later quantitative study by Walberg et al. did not show any significant correlation between serum PCP concentrations and degree of intoxication with PCP [269].

From their case series, McCarron et al. proposed a clinical classification of PCP intoxication based on patients’ sensorium and behavior and described four major and five minor patterns of intoxication (Table 10)

[268]. These patterns of intoxication were not mutually exclusive, and the authors found that patients often transitioned through more than one pattern during their clinical course. Patients with one of the major patterns of intoxication were more likely to require hospitalization, while those with minor syndromes could be expected to improve more rapidly.

Since then, there has been a paucity of large case series of acute PCP intoxication. However, the most recent case series by Dominici et al. [235] showed similar trends to those observed by McCarron et al. three-and-a-half decades earlier. The most common route of administration was still smoking, in 83.2% of the 184 patients reviewed from June 2011 to March 2013. Two-thirds of patients were male, with a mean age of 32.5 years, and more than half (53.8%) had co-ingested at least one additional substance, the most common being cannabis and benzodiazepines (see Table 11).

Overall, the most common clinical findings were nystagmus (57.4–64.1% of patients) and hypertension (47.0–57.0% in McCarron et al.,

Table 10 McCarron clinical classification of PCP intoxication [268]

		Definition/features	Frequency (%) ^{a b}
Major patterns	Coma	Loss of consciousness with no response to verbal or tactile stimuli	9.2
	Catatonic syndrome	Motor signs (posturing, catalepsy, rigidity), psychosocial withdrawal (mutism, staring, negativism), excitement (nudism, impulsiveness, agitation, violence), stupor	14.6
	Toxic psychosis	Hallucinations and/or delusions, with or without acute brain syndrome, but without signs of catatonic syndrome	16.8
	Acute brain syndrome	Disorientation, with any combination of confusion, impaired judgment, inappropriate affect, or recent memory loss	26.6
Minor Patterns	Lethargy/stupor		2.3
	Bizarre behavior		10.6
	Violent behavior		9.7
	Agitation		3.5
	Euphoria		3.0

^aIn those with lone PCP ingestion ($n = 597$); an additional 3.7% were asymptomatic

^bFrequency of most patterns of intoxication was similar between those with lone PCP ingestion and those who had also ingested other drugs. Catatonic syndrome was more common in lone PCP use (7.4% in those with other ingestions), while violent behavior and agitation were more common in polydrug use (14.1% and 7.4%, respectively)

Table 11 Co-ingestions in patients presenting with acute arylcyclohexamine toxicity (%)

	PCP [235]	Ketamine [234]	MXE [85]	3-/4-MeO-PCP [101]
Lone use	46.2	72.2	80.9	11.9
Polypharmacy	53.8	27.8	19.1	88.1
Most common drugs co-used				
Cannabis	41.2	^b	^a	34.6
Benzodiazepine	25.5	4.3	^a	48.1
Alcohol	20.1	10.3	^a	32.7
Cocaine	9.1	3.9	^b	1.9
Amphetamine	0.7	6.0	^b	9.6

^aDetection of drug reported, but no data provided

^bDetection of drug not reported

systolic BP >140 mmHg or diastolic BP >90 mmHg; not defined in Dominici et al.). Tachycardia (heart rate >100 bpm) was seen in 30% of cases in McCarron et al.'s series; however, it was reported that heart rates greater than 120 bpm were unusual, with the highest heart rate recorded being 140 bpm. Interestingly, the series from Dominici reported only two cases (1.1%) of tachycardia; however, they did not report their definition of this.

Agitated behavior was reported in just over one-third of PCP-intoxicated patients [205,

235]. Between 45.9 and 78.3% of PCP-intoxicated patients were alert at the time of their presentation to emergency services, one-quarter of whom were found to have retrograde amnesia – 11 of these 46 had co-ingested benzodiazepines [235]. Coma was seen in 106 (10.6%) cases involving PCP intoxication, with the typical history featuring sudden onset of violent or bizarre behavior, or what McCarron et al. termed “acute brain syndrome” (see Table 10), followed by, an occasionally abrupt, loss of consciousness [268]. Coma was

differentiated by length of unconsciousness into mild (<2 h), moderate (2–24 h), or severe (>24 h); 55 of those with coma had lone PCP ingestion, of whom 26 (47.3%) were classified as mild, 17 (30.9%) moderate, and 12 (21.8%) severe. Other neuromuscular effects seen with PCP intoxication were generalized tonic-clonic seizures (3.1%), posturing (2.8%), dystonic reactions (2.4%), tardive dyskinesia (1.7%), athetosis (1.3%), and catalepsy (1.3%) [232]. Muscle spasms mimicking extrapyramidal features were seen in 5.9% of cases, none of whom were known to have received neuroleptic medications prior to onset of the dystonic reactions; in 80% of these cases, PCP was the only drug ingested [232].

In McCarron et al.'s case series, tachypnea (respiratory rate >30 breaths per minute) was recorded in 4% of cases; conversely, apnea occurred in 28 patients (2.8%), of whom three displayed Cheyne–Stokes respirations and three suffered respiratory arrest. In 17 of the 28 episodes, apnea was associated with a generalized tonic-clonic seizure. The effects of PCP on respiration were not specifically reported by Dominici et al.

Hyperthermia (temperature >38.9 °C) was seen in 26 patients (2.6%) with acute PCP intoxication; 20 of these were lone PCP ingestion, while no details of the co-ingestants in the other 6 patients were provided [232]. Hypothermia was also reported in 64 patients (6.4%); 41 had co-ingested another drug, but these were not specified. Further, their definition of hypothermia was a temperature <36.6 °C, while no further breakdown of the clinical data was provided [234, 270].

The autonomic effects reported were diaphoresis (3.9%), bronchospasm (2.1%), urinary retention (2.4%), miosis or mydriasis (2.1% and 6.2%, respectively), hypersalivation (1.7%), and bronchorrhea (0.6%).

Ketamine

A case series of 116 presentations associated with ketamine use found similar rates of hypertension (38.8%; systolic blood pressure \geq 140 mmHg)

and tachycardia (29.3%; heart rate \geq 100 bpm) to those seen with PCP intoxication [271]; however, only 13 of these were due to lone ketamine use.

Data from Hong Kong, where ketamine remains the most abused psychotropic drug, has provided the largest case series, of 233 patients, with acute ketamine toxicity [234]. In this series from July 2005 to June 2008, twice as many males as females – with a median age of 22 years – presented to an emergency department after nasal insufflation (88%) or oral (5%) use of ketamine (unknown route of ingestion in 7%). Of those in whom toxicological screening was performed (126 of 233 patients), 72% of samples were positive only for ketamine; the most commonly co-ingested drugs were alcohol (10.3%), ecstasy (6.4%), and methamphetamine (6.0%).

As for PCP, the majority (54.5%) of patients presenting to emergency services after acute ketamine use were alert. However, the most common symptom reported in this cohort was still impaired consciousness (45.5%), although only 14.0% had a recorded GCS of less than 15 on examination in hospital. The most common clinical signs were hypertension (4%; not defined) and tachycardia (39%; heart rate >100 bpm). Forty-nine patients (21.0%) reported abdominal pain, 23 (9.9%) had nausea or vomiting, and 20 (8.6%) reported dysuria; on examination, 41 (17.6%) had abdominal tenderness and 32 (13.7%) were recorded to be hyperthermic (not defined). As mentioned previously, abnormal LFTs (16.3%) and dilatation of the CBD (5.7%) were observed among ketamine users, and while these both demonstrated improvement upon cessation of ketamine use, their significance is uncertain [234, 265]; gastritis appeared to have a similar temporal association with ketamine use in a subgroup of 14 ketamine users who underwent endoscopy [264].

In 96 cases of chronic ketamine use from Hong Kong, the most common features on presentation to outpatient clinics were of cystitis (91.7%) – such as dysuria, urgency, and frequency – while 63 (65.5%) reported chronic abdominal pain, and 15 (15.6%) had psychiatric concerns (not further defined) [272].

Methoxetamine

While no animal or human studies have examined the toxicity of MXE, limited data is available from three small series of acute MXE intoxication, two case series of user reports of MXE use, and data from the EMCDDA–Europol Joint Report on MXE and the NPIS [48, 69, 70, 85, 114, 270, 273]. In one report, males accounted for three times as many users as females, with an overall median age of 24 years [85]. It was most commonly taken by nasal insufflation (37%) or orally (38%) – either by “bombing” or dissolved in water – other routes included i.m. or i.v. injection (total 7%), sublingually, or rectally [270].

A total of 110 nonfatal intoxications and 20 deaths have been associated with MXE use. Collectively, the data suggest that the clinical toxicity of MXE is akin to that of PCP and of ketamine. The first report in the literature of MXE use was published in 2011 [67]. A 32-year-old male was brought to the emergency department after he was found by police and paramedics to be agitated; he had used an unknown amount of MXE by i.m. injection and denied any co-ingestion. On arrival, he had a heart rate of 105 bpm, blood pressure of 140/95 mmHg, respiratory rate of 16, temperature of 37.2 °C, and pupils of 6 mm. He intermittently appeared in a dissociated state and was noted to have rotary nystagmus; the remainder of his neurological examination was normal, and he returned to his baseline mental status after 8 h [67].

Initial reports suggested that the cardiovascular pressor effects of MXE were greater than those of either PCP or ketamine [70, 274]; however, the incidence of hypertension and tachycardia appears to be comparative based on the limited data available [48, 85]. Data from case reports are mixed. One male, presenting within half an hour of i.v. injection of an unknown dose of MXE, was both hypertensive (168/77 mmHg) and tachycardic (134 bpm), and his serum was positive for MXE; however, this was not quantified [68]. Another male who presented agitated and aggressive was tachycardic (120 bpm) but had a normal blood pressure (130/80 mmHg), while a third was hypertensive (167/110 mmHg) with a

heart rate in the normal range (not reported) [275, 276]. In the case presenting with tachycardia, serum MXE concentration was 0.27 mg/L [275]; blood samples were not taken in the hypertensive case. GI symptoms of nausea and vomiting have also been described in user reports; however, no data is available on their frequency [114, 277].

In those with objective recording of conscious state, MXE caused almost double the number of those with impaired conscious state (27.3%) as compared to ketamine (14.0%) [48, 85]. Two reports have associated seizures with MXE use (see section “[Life-Threatening Complications](#)”, below) [85, 278], while other common neurological features of MXE toxicity include agitation in around one-third of users – similar to the rate seen with PCP use – and muscular symptoms in up to 18% of cases [270]. In contrast to PCP and ketamine, a case series of three MXE users reported significant cerebellar toxicity, with their serum MXE concentrations being 0.16, 0.24, and 0.45 mg/L [69].

Methoxylated Arylcyclohexamines

The only case series of other arylcyclohexamine analogues comes from the Swedish STRIDA project, which reported 59 cases of acute 3- and 4-MeO-PCP toxicity [101]; 86.4% were male and the median age was 26 years. Fourteen cases described route of administration: oral was the most common (9 cases; 64.3%), while nasal, i.v., and rectal routes were also reported. As with the other arylcyclohexamines, polydrug use was common. Additional substances were detected in the majority of cases (52 of 59; 88.1%), the most common being cannabis and ethanol (see Table 11); all 7 of the single-substance cases involved 3-MeO-PCP.

The most frequent clinical signs observed with methoxylated arylcyclohexamine use were akin to those observed with PCP, ketamine, and MXE use (see Table 7); altered conscious state (57.6%), tachycardia (54.2%), and hypertension (45.8%) are the most commonly reported, while nystagmus was seen in 30.5% of cases. In the 7 cases of lone 3-MeO-PCP use, there was a greater

incidence of hypertension (100%; systolic BP ≥ 140 mmHg) and tachycardia (71%; heart rate ≥ 100 bpm), with similar rates of altered conscious state (57.1%) and nystagmus (28.6%) [101]. There were no reports of seizures or of altered thermoregulation associated with lone 3-MeO-PCP use.

Emergence Phenomena and the “K- and M- Holes”

The emergence phenomena observed during the recovery phase of anesthesia with arylcyclohexamines has limited their clinical use and was one of the main reasons that PCP was withdrawn less than 10 years after being introduced [9]. Characterized by a confusional state, vivid dreams, and hallucinations, these reactions occurred most frequently in middle-aged males, with an incidence of 17–30% with use of PCP in clinical anesthesia [38]. Following ketamine anesthesia, studies have shown varying incidences of emergence phenomena, from less than 5% to more than 30% of subjects [279–284]. Collectively, the experiences of recreational users during their dissociated state have been commonly referred to as the “K-Hole” and “M-Hole” when associated with ketamine and methoxetamine use, respectively [114, 285]. Other descriptions have included a sensation of feeling light, body distortion, experiences of cosmic oneness, and out-of-body and near-death experiences [103, 286].

The underlying mechanism of the emergence phenomena caused by arylcyclohexamines appears to be due to their depressive effects on visual and auditory relay nuclei in the medial geniculate and inferior colliculus, respectively, leading to misperception and/or misinterpretation of visual and auditory stimuli [287, 288]. Further, the loss of proprioceptive sensation results in decreased sensitivity to gravity, providing an explanation for the out-of-body and floating experiences described by recreational users and by those recovering from general anesthesia [76, 114, 286, 289].

In McCarron’s study of 1,000 cases of PCP intoxication, the incidence of emergence patterns

was described for each category of coma [268]. A total of 106 cases of coma were described, of whom 55 (51.8%) had only ingested PCP; of these, 26 (47.3%) were classified as mild, 17 (30.9%) as moderate, and 12 (21.8%) as severe coma. In the 12 patients with severe coma (>24 h) due to lone PCP intoxication, the emergence patterns included five with acute brain syndrome (defined by McCarron et al. as “disorientation with any combination of confusion, lack of judgment, inappropriate affect, or loss of recent memory (with or without bizarre behavior, violence, or agitation)”) (see Table 10) lasting up to 7 days, one with stupor for 10 days, one with catatonia lasting 3 days, one with lethargy for 24 h, three with agitation, and one with psychosis requiring transfer to a psychiatric hospital. In those emerging from moderate coma, eight developed acute brain syndrome for up to 8 days, three were agitated for up to 14 days, one was psychotic for 7 days, and one displayed bizarre behavior for 4 days; only 4 of the 17 (23.5%) were mentally clear on awakening from coma. For those with mild coma, a majority (14, 53.8%) displayed acute brain syndrome, which lasted less than 24 h in all cases; four were stuporous; two were agitated; two were psychotic for 34 h and 3 days, respectively; one was catatonic; and one displayed violent behavior. Two (7.7%) displayed mental clarity on emergence from coma [268].

Aside from this case series by McCarron et al., there is no other data on the incidence or severity of emergence reactions following acute toxicity and coma associated with PCP or other arylcyclohexamine analogues. The availability of pharmaceutical non-racemic ketamine and reports of its recreational use [290], in particular the S(+)-enantiomer, may impact the prevalence of emergence reactions given the evidence supporting a decrease in the incidence of these reactions with its use, as compared with racemic or R(–)-ketamine [106–108].

Life-Threatening Complications

Massive overdoses, of up to 1 g orally of PCP, have resulted in coma for up to 5 days’ duration [115]. McCarron et al. found that, of those with

coma, almost one-quarter had prolonged, or “severe,” coma lasting more than 24 h, with the possibility of delayed and prolonged hypoventilation and apnea as a result [268]. Burns et al. also noted that such cases were marked by sustained hypertension, tachycardia, and more prominent neurological features, including seizures [291, 292]. These findings were consistent with McCarron et al.’s results demonstrating increased frequency of almost all clinical features of PCP intoxication with increased duration of coma – with the exception of nystagmus and hypertension, which were uniformly present in around 60% and 50% of all PCP intoxicants, respectively, regardless of duration of coma [268].

There is conflicting data regarding the association between serum PCP concentration and clinical findings. Most demonstrate no correlation between the two, with the exception of the finding of a moderate correlation ($r = 0.60$, $p < 0.05$) between plasma PCP concentration and hypertension in a series of 5 patients with acute PCP toxicity [293]. It was also noted in the series by Walberg et al. that, of the 183 patients whose blood tested positive for PCP, all 14 of those with coma had uniformly higher serum PCP concentrations (>0.1 mg/L) [269]. One explanation for the lack of association is the high protein- and tissue-bound fraction of PCP, meaning blood PCP concentrations do not reflect total body load [293, 294]. There is also some evidence to suggest that chronic users develop tolerance to PCP, and, as a result, their toxic blood concentrations are significantly higher than for casual users [295, 296].

In the largest case series of 1,000 acute PCP intoxications, there were three cases of cardiac arrest, all of whom were successfully resuscitated; however, no further details were provided [232]. One additional patient died post-cardiac arrest, found on autopsy to be due to pulmonary embolism. Three patients suffered respiratory arrest, from a total of 28 in whom apneas were noted; 16 (57.1%) had co-ingested a sedative—hypnotic or narcotic drug in addition to PCP. Of the 28 in whom apneic episodes were seen, 17 were associated with seizures, with some requiring intubation and ventilation for prolonged

apnea; it was not reported how many of those who had seizures had also co-ingested other substances. A total of 26 patients suffered from one or more generalized tonic–clonic seizures, while a further 5 patients had status epilepticus; in all cases, status epilepticus was terminated by administration of intravenous diazepam [232]. Two cases of seizure have been reported with MXE use: one had multiple seizures terminated by administration of i.v. clonazepam, after inhaling the vapor of 50 mg of MXE powder over a couple of minutes – his serum MXE concentration was 0.03 mg/L [278]; a further case is mentioned in a series of MXE intoxications, but no further details were reported [85].

Rhabdomyolysis (creatinine phosphokinase [CK] $>16,000$ IU/L) was seen in 2.5% of 1,000 patients with PCP intoxication; of these, 40% had acute kidney injury (defined as one of (a) rising serum creatinine or urea despite i.v. rehydration, (b) serum urea/creatinine ratio between 9 and 11, or (c) oliguria [urine output <500 mL day] persisting for several days) [297].

The vast majority of patients with acute arylcyclohexamine intoxication will survive with supportive care. However, it is the group that is particularly behaviorally disturbed in whom additional significant harm can occur and who can pose a significant management challenge requiring critical care admission. Owing to the dissociative and analgesic effects in combination with acute behavioral disturbance and agitation, patients may self-inflict significant damage while under the influence of arylcyclohexamines; cases as marked as nuclear evisceration and genital mutilation have been reported [298–300].

Other Considerations

A concern with regard to the potential for serious toxicity and/or mortality associated with recreational arylcyclohexamine use is the prevalence of their misrepresentation, either intentionally or accidentally, as a contaminant. Historically, PCP has a long history of this. Early in its use, it was often found to be adulterated by, or an adulterant of, other arylcyclohexamines. While some were

thought to be less potent than PCP, others with increased potency, such as TCP, PCE, and PCPy, had the potential to cause significant inadvertent toxicity. The precursor to, and sometime contaminant of, PCP – PCC – was reported to cause serious toxicity, including coma and death; however, there is little further detail about its clinical effects [3, 62, 64].

More recently, there have been reports of ketamine and MXE being interchanged for each other. Given the binding affinity of MXE for the NMDA receptor is significantly higher than that of ketamine [127], there is the potential for inadvertent overdose. With the marketing of MXE as an “alternate” form of ketamine, the risk of significant toxicity with the use of MXE by those inexperienced in its dosing is compounded by its longer time to onset than ketamine, of up to 90 min, which has caused some users to prematurely re-dose [114].

Further, there are reports of ketamine being sold on the street in its non-racemic form. Given the S(+)-enantiomer is four times more potent in its dissociative effects than its R(–)-enantiomer, this presents further risk to those not aware of the difference in effects between racemic and non-racemic mixtures [40].

Deaths

Throughout its decades of use, PCP has been associated with hundreds of deaths. This is, however, more commonly due to the acute behavioral disturbances associated with mild intoxication [35, 115, 301]. After significant PCP ingestion, coma is protective from potential self-harm in these patients, while risk of death from accidental overdose is minimized by provision of adequate supportive care.

Data from a recent 5-year retrospective review from the New York City Medical Examiner’s Office documented a total of 138 autopsy cases, from 2003 to 2007, in which PCP was detected in postmortem blood samples [296]. Of these, the majority (80; 58.0%) were involved in violent deaths in which PCP was detected but not thought to be directly related to the cause of death;

52 (37.7%) were deemed to be as a result of mixed drug intoxication, 5 (3.6%) were nonviolent deaths in which only PCP was detected, and in one (0.7%), the cause of death was indeterminate.

Previous case reports have reported lethal serum PCP concentrations of greater than 2.0–2.5 mg/L [302]. However since then, deaths have been reported where the serum PCP concentration was much lower. In one case, a 30-year-old man without any medical comorbidities died from a nonviolent cause [296]. Urine toxicology screen on presentation to the emergency room was positive only for cannabinoids, and serum was negative for ethanol, paracetamol, and salicylates; serum PCP concentration at autopsy was 0.07 mg/L; however, this was 5 days after his initial presentation. A quantitative study by Walberg et al. did not show any significant correlation between serum PCP levels and degree of intoxication with PCP [269]. However, of the 183 patients whose blood was positive for PCP, all of those with coma had a serum PCP level greater than 0.1 mg/L. Indeed, significantly raised serum PCP concentrations are usually seen after massive overdose resulting in death attributable to PCP toxicity, rather than consequences of behavioral disturbance. A serum PCP concentration of 7.0 mg/L was reported in a case of status epilepticus with resultant cardiopulmonary arrest and death [115, 303].

Ketamine

Despite its widespread use, there is little recent data on the number of deaths relating to ketamine use. The first documented blood ketamine concentration in a fatality was reported in 1988, in a 31-year-old female who died after an accidental injection (not reported whether i.v. or i.m.) of up to 900 mg of ketamine; she had a blood ketamine concentration of 7.0 mg/L [304]. A comparison case also detailed in this report, of a 46-year-old man given 100 mg of ketamine (route of administration not documented) during anesthesia for surgery post-gunshot wound, showed a postmortem blood ketamine level of 3.0 mg/L. He suffered

cardiac arrest and was pronounced dead 40 min after receiving ketamine; the final cause of death was not reported. A review by the authors of 27 other cases in which ketamine was detected postmortem over a period of 2 years showed blood concentrations of between 0.1 and 9.5 mg/L, in which 15 were less than 1.0 mg/L [304]. No comment was made about the cause of death in these 27 cases or whether other drugs or alcohol were detected; however, their report highlights the issue of timing of postmortem blood and tissue samples and the importance of considering the time of death in interpreting these results.

A review of ketamine-associated deaths examined at the New York City Office of the Chief Medical Examiner between 1997 and 1999 identified 12 nonhospital deaths due to acute intoxication, none of which were due solely to ketamine [305]; of the 87 total ketamine-associated deaths, the vast majority, 72, were inhospital deaths in the setting of treatment with ketamine for burns or surgery.

In 2008, Schifano et al. presented data on 23 ketamine-associated deaths in the UK from 1993 to 2006; of these, only four cases were identified in which ketamine was the only drug found, three of which were deemed to be accidental overdoses, with the other being a case of suicide [306, 307]. Ketamine concentrations were not reported in these cases. Since then, data from the UK's National Programme on Substance Abuse Deaths (NPSAD) showed a peak of 23 deaths related to ketamine use in 2009, with a subsequent decline to 12 and 8 deaths in 2011 and 2012, respectively [308]. A total of 93 deaths in which ketamine was mentioned on the death certificate were identified from the NPSAD database; in most (70; 75.3%), other drugs and/or alcohol were also detected [40]. In the remaining 23 cases, where ketamine was the only substance detected, it was not possible to determine whether ketamine was the actual cause of death [40].

Reports of lone ketamine toxicity leading to fatality have reported blood ketamine concentrations varying from 1.8 to 27.4 mg/L [304, 309, 310], while previous studies in squirrel monkeys investigating anesthetic and lethal ketamine doses have led to the estimate of a lethal i.v. dose in

humans of 11.3 mg/kg [307, 311]. In comparison, anesthetic studies have demonstrated that i.v. loading doses of 2 mg/kg of ketamine, followed by continuous ketamine infusion, were able to achieve a targeted blood ketamine concentration of between 2 and 3 mg/L, which maintained stable anesthesia [312, 313]. Subjects were found to be rousable to deep stimulus at blood ketamine concentrations of between 1.0 and 1.5 mg/L, while recovery from anesthesia was seen at blood ketamine concentrations between 0.50 and 0.64 mg/L [312–315]. Apart from the limited case reports of fatalities documenting blood ketamine concentrations, there are no other published data for ketamine concentrations in recreational use or overdose.

Methoxetamine

In 2012, no confirmed deaths were attributable solely to the use of MXE [75]. By 2014, 20 deaths associated with MXE use had been reported to the EMCDDA [48, 116]; in 8 cases, MXE was the only psychoactive substance reported. Of those reporting a cause of death, four cases listed MXE in the cause of death, 2 cases were due to mixed overdose, while three cases listed MXE as contributing to death [48]. Interestingly, 4 of the 20 deaths were from drowning, perhaps highlighting the theoretically increased potential for accidental self-harm with MXE given its prominent cerebellar toxicity alongside the dissociation associated with other arylcyclohexamines [69]. Postmortem MXE concentrations in blood were highly variable, ranging from 0.03 mg/L (cause of death: mixed overdose) to 5.2 mg/L (cause of death: drowning) [48, 72, 316]; there was overlap in MXE concentrations with acute toxicity, which in one case series ranged from 0.16 to 0.45 mg/L [69].

The first case report of death involving MXE, published in 2013, was that of a 26-year-old male found deceased in his home, whose postmortem blood MXE concentration was 8.6 mg/kg; three synthetic cannabinoids were also detected (concentrations not reported), as was tetrahydrocannabinol [71]. A year later, a case of death where

clinical features were recorded was reported from Poland [73]. A 31-year-old man presented to the emergency department in deep coma; he was tachycardic (heart rate 120–140 bpm) and hyperthermic (temperature 39 °C) and had rhabdomyolysis with a peak CK of 220,531 IU/L. He was also reported to have had seizures, required mechanical ventilation for respiratory failure, and developed acute liver and renal failure; he was admitted to intensive care but died 28 days after his presentation. Serum MXE concentration taken 8.5 h after presentation was 0.32 mg/L; amphetamine was also detected (0.06 mg/L). The first report of fatality from lone MXE use was also reported from Poland, in 2015, of a 29-year-old man who was found deceased in his home [73]; his estimated serum MXE concentration was 5.8 mg/L.

Diagnosis

Clinical

As with all patients who present with recreational drug overdose, collateral history where available provides important information about the dose and route of exposure, co-ingestant(s), and previous drug use. The most common clinical signs in arylcyclohexamine intoxication are nystagmus and hypertension; in the presence of an altered sensorium – either agitation or coma – these patients have been described to have a classic triad of PCP intoxication.

Serum and Urine Arylcyclohexamine Testing

Testing for arylcyclohexamines is not part of routine toxicological screening, and samples are often required to be sent to specialist laboratories for their identification.

Phencyclidine can be qualitatively detected using enzyme-linked immunoassay techniques with a sensitivity of 0.01 mg/L; however, false-positive results are possible due to cross-reactivity with molecularly similar substances such as

dextromethorphan [38]. No commercially available immunoassay exists for ketamine; its detection is by gas chromatography and mass spectroscopy. Rapid-detection urine assays have recently been developed and are reported to be sensitive and specific, with a limit of detection of 0.005 mg/L [317, 318]. However, there have been case reports of false-positive results for PCP in those patients also on venlafaxine, with its active metabolite *O*-desmethylvenlafaxine cross-reacting with the PCP assay reagent [319–321]. Other drugs that have been shown to cause false-positive results in urine PCP assays include dextromethorphan and diphenhydramine [322, 323].

Methoxetamine is tested for using either calorimetric or immunoassay kits and analyzed by gas chromatography–mass spectrometry (GC–MS) techniques. Newer techniques for methoxetamine and other arylcyclohexamine analogues have recently been developed, with the use of high-pressure liquid chromatography (HPLC) able to detect these compounds in both blood and urine [324]. With the rapid appearance of novel arylcyclohexamine analogues, interpretation of immunoassay results must be made with caution. Cross-reactivity between the methoxylated arylcyclohexamines and PCP has been described after confirmatory MS analysis [101].

While toxicological screening for these compounds is not required routinely, it can be useful academically, particularly to help confirm the pattern of toxicity associated with novel arylcyclohexamines. This has been shown in the recent case series of 3- and 4-MeO-PCP as well as the earlier case reports of MXE use [68, 69, 71–73, 101, 275].

Other Investigations

Patients with significant clinical features should have routine hematology and biochemistry testing. Nonspecific laboratory findings include leukocytosis, hypoglycemia, and elevated CK, urea, and creatinine [232, 234]. In the case series of 1,000 patient episodes by McCarron et al., 22% of those tested had hypoglycemia of less than

70 mg/dL (3.9 mmol/L). Creatinine kinase was elevated above 300 IU/L (reference range 5–200 IU/L) in 70% of cases, of whom roughly one-third each were violent, agitated, and calm; the highest recorded CK was 423,045 IU/L [232]. Of those who had no other reason to have an elevated white blood cell count (e.g., trauma, rhabdomyolysis, or infection), 39% were shown to have white blood cell counts of greater than 12,000/ml³. The number of those with leukocytosis (36%) was similar in a case series of acute ketamine toxicity, while raised creatinine kinase was seen in 32% of cases [234]

An ECG is an essential investigation in patients with acute recreational drug toxicity in the critical care setting; however, there are no findings specific to arylcyclohexamine toxicity. In one study of anesthesia during electroconvulsive therapy, ketamine was found to cause QTc prolongation from a mean of 410.9 ms at baseline to a mean of 431.6 ms after induction with a 1 mg/kg bolus [325]; there were no episodes of torsade de pointes, and this is therefore of doubtful clinical significance. Isolated reports of ST-segment and T-wave changes with ketamine use also exist. One case of broad-complex arrhythmia with peaked T-waves in the setting of PCP intoxication was likely caused by hyperkalemia of 9.35 mmol/L rather than arylcyclohexamine-specific effects [326]. There has also been a single case report of transient Brugada syndrome in a 31-year-old Caucasian male who had nasally insufflated ketamine [327]. Resolution of the Brugada pattern and subsequent testing demonstrated no other reason for the ECG findings, and it was determined that ketamine’s inhibition of I_{Na} and I_{Ca} channels was the cause of the ST elevation [327, 328]. Reports of propofol also causing a transient Brugada syndrome with subsequent malignant arrhythmias is of importance due to its use as a sedative agent in the critical care setting, especially when used to sedate patients with recreational drug toxicity [329].

An electroencephalogram (EEG) may be useful in the undifferentiated comatose patient to exclude ongoing seizures or status epilepticus as a cause for unconsciousness or neuromuscular excitation. Findings seen in arylcyclohexamine

Table 12 Differential diagnoses for arylcyclohexamine intoxication

Other intoxicants	Gamma hydroxybutyrate, stimulant drugs, other hallucinogens Anticholinergic drugs Neuroleptic malignancy syndrome Withdrawal syndromes
Mental health disorders	Schizophrenia Acute manic episode, exacerbation of bipolar affective disorder
Metabolic	Hyponatremia Hypoglycemia Hypoxemia Hyperthyroidism
Infective	Sepsis Meningitis/encephalitis
Intracranial pathology	Intracranial hemorrhage

toxicity include diffuse slowing with θ and δ waves, which may return to normal prior to clinical improvement [38, 263, 330, 331].

Differential Diagnoses

The varied signs and symptoms seen with arylcyclohexamine intoxication, and indeed the frequency of co-ingested drugs, make for a wide list of differential diagnoses (Table 12). Arylcyclohexamine intoxication therefore requires a high index of suspicion and gathering of as complete a collateral history as possible.

Management

Conservative and supportive management is the mainstay of treatment in arylcyclohexamine toxicity, with the focus on maintaining a clear airway, adequate respiration, and oxygenation; providing circulatory support where necessary; and being mindful of thermoregulation due to the potentially significant psychomotor agitation and bioamine reuptake inhibition. Restraint and sedation may also be necessary in the most acutely disturbed patients to avoid harm to both the patient and clinical staff tasked with their care; this is described in more detail in the next section. There is no specific antidote for

arylcyclohexamine toxicity, and most patients will survive with purely supportive measures.

Intravenous access is required for all patients who present with significant acute arylcyclohexamine toxicity, with blood taken for electrolytes, glucose, lactate, urea, and creatinine. In the significantly agitated patient, rhabdomyolysis may be a feature, with myoglobin-associated acute kidney injury as a cause of high morbidity and mortality associated with PCP intoxication in particular [332, 333]. When present, it should be treated aggressively with intravenous fluids (see ► Chap. 32, “Toxicant-Induced Rhabdomyolysis”).

Seizures can be treated initially with benzodiazepines. In the setting of status epilepticus, or in a patient with an otherwise compromised airway, sedation with a barbiturate or propofol, paralysis, and endotracheal intubation is indicated. In patients requiring critical care intervention and management, significant hyperthermia is associated with poor prognosis [334–336]. Therefore, particularly in the setting of hyperthermia, prompt anticonvulsant therapy should also be instigated to minimize additional thermogenesis from seizure activity. In those patients with significant hyperpyrexia (>39 – 40 °C), aggressive cooling methods should be employed, including the use of cold intravenous fluids, packing of the axillae/groin with ice, and, if necessary, immersion in an ice water bath or the use of an intravascular cooling device (Grade III recommendation).

Patients should have continuous cardiac monitoring, due to the prevalence of tachycardia and reports of arrhythmias. While hypertension is common, it is usually short-lived, with most cases resolving without the need for specific antihypertensive treatment. Those that require medicating for behavioral disturbance, agitation, or seizures – such as benzodiazepines – are likely to see a beneficial effect of this on blood pressure. In 563 patients with PCP-induced hypertension, only one required specific antihypertensive medication; seven additional patients had known essential hypertension, of whom five received antihypertensives [232]. If hypertension is persistent and severe (systolic BP >200 mmHg or diastolic BP >120 mmHg), we recommend treatment

with intravenous glyceryl trinitrate as its short half-life enables it to be readily titrated (Grade III recommendation). While this is also true of sodium nitroprusside, it has the potential to increase catecholamine secretion and worsen tachycardia [337, 338]. The longer half-lives of calcium channel blockers make them impractical for rapid titration in the critical care setting, while beta-blockers are generally not recommended in the setting of acute stimulant toxicity as they can result in unopposed alpha activity and worsen hypertensive crises.

Agitation and Behavioral Management

As the psychotomimetic features of acute intoxication are similar to those seen in emergence reactions, it is useful to be mindful of the importance of non-pharmacological modalities of treatment in caring for the patient intoxicated with arylcyclohexamines. However, the spectrum of behavioral disturbance is wide. Indeed, the major toxicity of arylcyclohexamines is related to these effects, with unawareness of surroundings and oblivion to pain due to their dissociative and analgesic effects leading to the potential for self-inflicted injuries and extreme overexertion. The potential for accidental self-harm is theoretically exacerbated with MXE given its reported cerebellar toxicity [69].

In mild intoxication, management may involve maintaining an environment of relative sensory deprivation [339]; however, this has not been formally studied (Grade III recommendation). Patients with more severe toxicity and acute behavioral disturbance may initially require physical restraint in order to establish intravenous access to facilitate chemical sedation. Overall, chemical restraint is preferred, as physical restraint may exacerbate underlying rhabdomyolysis. Benzodiazepines are the preferred sedating agent, as antipsychotic medications may exacerbate hyperthermia, lower the seizure threshold, or worsen dystonic and anticholinergic reactions [266].

If an antipsychotic medication is required, atypical agents offer a better choice than

traditional antipsychotics due to their more favorable side effect profile, in particular their less pronounced extrapyramidal side effects [340]. In one series of PCP intoxication, 168 patients received haloperidol and 66 received chlorpromazine for agitated behavior, in whom 10 (6.0%) and one (1.5%), respectively, developed dystonic reactions [268]. There is limited published experience with newer sedatives, such as dexmedetomidine, or newer atypical antipsychotics. In our opinion, therefore, benzodiazepines should remain first line in these patients (Grade III recommendation). Initial intramuscular dosing, using an agent with good systemic absorption by this route such as lorazepam, may be required in those with very severe behavioral disturbance; however, i.v. administration is the route of choice as it allows for more titrated dosing.

Decontamination and Elimination

Activated Charcoal

There are no human studies investigating the role of activated charcoal (AC) administration on arylcyclohexamine toxicity; data on the use of AC is limited to a single study investigating PCP in dogs [341]. Patients with significant arylcyclohexamine toxicity generally have significant behavioral disturbance and/or drowsiness which would limit AC administration and routine use of AC is not recommended.

Urinary Acidification

As the arylcyclohexamines are weak bases, acidification of urine theoretically enhances their elimination; indeed, the use of ammonium chloride was previously advocated for this purpose [342]. However, the risk of inducing systemic acidemia outweighs the potential benefits (Grade III recommendation). Urinary acidification also has the potential to increase the risk of acute tubular necrosis in patients with rhabdomyolysis [333, 343]. Furthermore, while renal clearance of PCP has been shown to be increased by up to 23% following urinary acidification, this accounts for only 1% of total PCP clearance due to the majority of its clearance being via hepatic metabolism

[109, 344]. Given these concerns, coupled with the fact that the majority of patients with arylcyclohexamine intoxication will survive with supportive care, urinary acidification is not recommended.

Hemoperfusion and Hemodialysis

Due to the large volume of distribution of PCP and the other arylcyclohexamines, along with their high lipid solubility, hemodialysis and hemoperfusion are not effective in managing arylcyclohexamine toxicity [345].

Emergence Reactions

As described above, McCarron et al. reported a high incidence of emergence reactions following acute PCP toxicity, with more than 75% of those with moderate or severe coma displaying confused, agitated, or psychotic behavior [268]. In those with mild or moderate coma, only 13.9% emerged from their altered conscious state with clear sensorium, while none of those with severe coma did so.

There are no data for the treatment of emergence reactions following acute arylcyclohexamine toxicity causing coma. Indeed, apart from the study by McCarron et al., there are no data on the frequency of emergence reactions following arylcyclohexamine toxicity in the recreational setting. Anesthetic studies demonstrate that the incidence of emergence phenomena after general anesthesia with PCP and ketamine ranges anywhere from less than 5% to more than 30% [38, 103]. While the incidence of emergence reactions following anesthesia with PCP has been reported to be higher in males [38], it appears to be higher in women after ketamine anesthesia [104, 267, 346].

The role of preanesthetic medication in reducing the incidence and/or severity of emergence reactions following ketamine anesthesia was acknowledged even after its first report; however, it was not investigated at that time [11]. Initial studies investigating various premedications offered conflicting results about the beneficial effect of agents such as droperidol, chlorpromazine, and opiate-containing

regimens [346–351], and these are not recommended [103, 351].

Benzodiazepines have been shown to reduce the incidence of emergence reactions following ketamine anesthesia, with initial studies suggesting lorazepam to be superior to other benzodiazepines, including diazepam (Grade II-I recommendation) [351–353]. However, the introduction of midazolam has since superseded their use due to its shorter half-life and water solubility and has been shown to be superior to diazepam in reducing the incidence of emergence reactions (Grade I recommendation) [354–356]. In one randomized, double-blinded study of those induced to anesthesia using 250 mg i.v. ketamine, only 4% of those who also received 12.5 mg i.v. midazolam had emergence reactions compared to 36% of those who received 20 mg i.v. diazepam in addition to ketamine [355].

While these data provide good evidence of the efficacy of benzodiazepines, and in particular midazolam, for reducing the incidence of emergence phenomena, they must be interpreted with some caution in managing the patient with acute arylcyclohexamine toxicity. Not only are they based on controlled anesthetic studies, most studies administered benzodiazepines as a premedication or at the time of induction of anesthesia, though other studies have suggested that they are equally effective administered at the completion of a procedure [280, 357]. A study by Levänen et al. comparing dexmedetomidine (2.5 µg/kg) with midazolam (0.07 mg/kg) noted a significant reduction in CNS effects in the dexmedetomidine group; however, these were mostly unpleasant dreams, with no reports of agitated or psychotic behavior [358]. A more recent study comparing dexmedetomidine (1 µg/kg) and midazolam (0.02 mg/kg) also demonstrated less subjective CNS effects in the dexmedetomidine group; however, their findings were not significant [359]; similarly, most of the described effects were mild or moderate dream states, without any significant behavioral changes reported.

As an aside, there is also evidence that the S(+)-enantiomer of ketamine is responsible for less emergence phenomena than either the racemic mixture or, in particular, the R(–)-enantiomer

[106–108]. As the S(+)-enantiomer is now available in a pharmaceutical preparation [267], its use would be recommended above the racemic mixture for anesthesia and for sedation in the critical care setting.

Disposition

Most patients with mild intoxication with arylcyclohexamines will be able to be discharged from the emergency department after a period of monitoring that has demonstrated normal cognition, normal and stable vital signs, normal ECG, and normal biochemical markers. Those with persisting signs of mild arylcyclohexamine toxicity or requiring repeat blood tests, and who do not have significant behavioral disturbance, may be managed in an observation unit or with standard ward-based care.

Patients with severe toxicity, as highlighted in Box 1, will require critical care admission for further targeted management as discussed in the sections above.

Special Populations

Dependants

The impact of the behavioral effects of the arylcyclohexamines, including agitation, violence, and altered sensorium, necessitates consideration of the resulting social issues [360–362]. While not specific to arylcyclohexamines, these issues require the assessment and safeguarding of vulnerable adults – and, indeed, children – due to the potential for significant intimate partner domestic abuse, crime, and incarceration [298, 363].

Children

In addition to the potential for ingestion of arylcyclohexamines in either liquid, tablet, or powder forms, significant accidental poisoning, in particular with PCP, can occur from exposure

Box 1

Criteria for critical care management of acute arylcyclohexamine toxicity

Criteria for admission to intensive care unit	Criteria for discharge from intensive care unit
Agitation or violent behavior requiring sedation and/or intensive monitoring	Settled or settling behavior
Rhabdomyolysis, requiring hemodialysis	Maintenance of adequate urine output and improving renal function
Severe, refractory hypertension	
Severe hyperthermia (temperature >39–40 °C)	Thermoregulation not requiring exogenous cooling
Prolonged coma	Improvement in mental status
Status epilepticus or seizures requiring therapy	Resolution of seizures
Other reason(s) for endotracheal intubation	Successful extubation and maintenance of patent airway
Injuries/trauma secondary to behavioral disturbance requiring ICU level care	

to passive smoke [364]. Signs may be as subtle as listlessness and decreased responsiveness to tactile stimuli, irritability, and poor feeding in the very young [365]. Other neurological signs observed in adult presentations may also manifest in children, with nystagmus, ataxia, increased muscle tone, and opisthotonus all reported [364–366]. Hypertension was also common, found in 30% of children in one study, while seizures, respiratory depression, and apnea were reported more frequently than in adults; agitation and violent behavior were less commonly seen [365, 366].

All pediatric patients with acute arylcyclohexamine toxicity require continuous monitoring to observe for any fluctuation in consciousness or cardiorespiratory status [266]. Infants may require longer observation and admission due to case reports of their delayed recovery [364]. Any child who presents after exposure to arylcyclohexamines should have safeguarding procedures enacted.

Pregnant and Breast-Feeding Patients

Phencyclidine has been shown to cross the placenta and is associated with poor feeding, irritability, and hypertonicity in neonates demonstrating possible withdrawal from PCP [367, 368]. It is also excreted into breast milk,

where it may be present for up to 40 days after last maternal use and in concentrations of up to ten times plasma levels [369, 370].

Studies investigating the impact of intrauterine exposure to PCP have found it to cause symmetrical intrauterine growth retardation [371, 372]. In one study, 42.2% of infants had a birthweight for gestational age below the 25th percentile, and 45.7% had a head circumference below the 25th percentile; while clearly significant, these were less than a comparison group exposed to cocaine, in whom 55.1% and 67.9% of newborns were below the 25th percentile for birthweight and head circumference, respectively [372].

As ketamine is also known to cross the placenta, appropriate post-delivery care should be taken in those newborn infants who are born via Caesarean section under ketamine anesthesia [112]. A recent systematic review and meta-analysis of i.v. ketamine during spinal and general anesthesia for Caesarean section found no significant effects on neonates, though their findings were limited by a paucity of data for both maternal effects and neonatal well-being [373]. There are no human studies investigating the teratogenicity of ketamine or other arylcyclohexamines. Injections of 25 mg/kg ketamine of female dogs in their first trimester did not demonstrate any adverse effects to either the mother or her pups [374]. Another study found that ketamine potentiated

the teratogenic effects of cocaine in mice but that it was not teratogenic on its own [307, 375].

There are no data for MXE to be able to determine whether it crosses the placenta and/or whether it is excreted into breast milk.

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There has been a significant change in the recreational drugs used throughout the world in the last 5–10 years, with increasing availability and use of a wide range of different new psychoactive substances (NPS, sometimes known as “legal highs”) [1, 2]. A popular emerging class of NPS is the synthetic cathinones. In 2013, there were approximately 35,000 drug seizures of NPS reported to the European Union Early Warning System (EU EWS), of which the most common substance category was cathinones (31%). In 2014, the EU EWS was notified of 101 previously unreported NPS (an increase of 25% from 2013), the largest category of these was cathinones ($n = 31$, 30.7%) [3]. Globally, cathinones was the third largest group of NPS to be reported by substance group (15%) in the same year [4]. Initially the cathinones, particularly mephedrone (4-methylmethcathinone), were sold undisguised by their chemical names, but they are also, like many other NPS, sold over the Internet and in “head shops” as “research chemicals,” “bath salts,” or “plant food,” often with warnings “not for human consumption” or “not tested for hazards” [3]. This marketing is an attempt to circumvent existing local, national, or international medicinal and/or drug laws [1].

Cathinone is the β -keto (β k) analogue of amphetamine (1-phenylpropan-2-amine) and is a naturally occurring alkaloid found in the fresh leaves of *Catha edulis* (also known as Khat) [5]. Khat typically grows in East Africa and the Arabian Peninsula and is chewed for its stimulant and psychoactive properties [6]. It has been linked to an increased risk of myocardial infarction, dilated cardiomyopathy, peptic ulcer disease, both acute and chronic liver disease, and oral cancers [7–11]. Synthetic cathinones represent a heterogeneous group of β -keto derivatives of ring-substituted phenylethylamines (amphetamine-related structures as the parent drug). The structure of phenylethylamine is shown in Fig. 1, the cathinones are β -keto derivatives, and most cathinones are a result of various R'-group substitutions to the phenylethylamine backbone as shown in Fig. 2.

Methcathinone was first synthesized in 1928 [12] and was the first synthetic cathinone

Fig. 1 Basic chemical structure of phenylethylamine

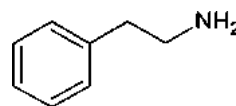
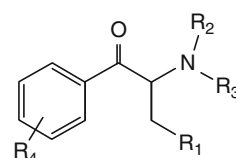


Fig. 2 Basic chemical structure of synthetic cathinones



produced [13]. Methcathinone, also known as ephedrone, was initially used as an antidepressant in the former Russian states in the 1930s and 1940s, but clinical utility of this and other cathinones has been limited, given the issues with abuse and dependence liability [14, 15]. This was first noted as a “street” recreational drug in Leningrad in 1982 and has been implicated in up to 20% of illegal drug trade in Russia in the 1990s [16]. Following this, harms associated with use have been described in other countries – Turkey [17], Israel [18], Eastern Europe [19, 20], and United States [16] – including cases with psychosis, stimulant toxicity, and in some incidences irreversible neurotoxicity (given manganese-containing ingredients associated with its manufacture). To our knowledge, bupropion (marketed under the trade name Zyban[®]) is the only cathinone that is currently licensed in any country and used as a medicinal product; it is licensed in the UK for use as an antidepressant and in smoking cessation [21].

There was then a hiatus in the recreational use of the synthetic cathinones until their appearance as NPS in recreational drug markets in the mid-2000s, and over 50 have been identified thus far [3]. While many synthetic cathinones have been reported as NPS [22], this chapter will focus on 4-methylmethcathinone (mephedrone) and 3,4-methylenedioxypyrovalerone (MDPV) as there is greatest evidence of their recreational use and a more extensive published literature on their pharmacological mechanisms of action and patterns of acute toxicity.

Prevalence and Pattern of Use

Mephedrone

To date, England and Wales are the only countries that collect national data at a population level on the use of mephedrone, through the Crime Survey England and Wales (formerly known as the British Crime Survey) [23]. The use of mephedrone in 2010/11 was reported by 1.1% of adults aged 16–59 and 4.4% of young adults aged between 16 and 24 years (approximately the same prevalence of use as cocaine) [24]; this covered the period during which mephedrone was classified as a Class B, Schedule I drug and a generic definition for the control of cathinone derivatives was accepted by the Home Office (April 2010). There was a subsequent decrease in the proportion of 16- to 59-year-olds reporting last year use of mephedrone to 0.5% in 2012/2013 and 0.6% in 2013/2014 [25]. There was also a decrease in the proportion of 16- to 24-year-olds reporting last year use of mephedrone to 1.6% in 2012/2013 and 1.9% in 2013/2014 [25]. Mephedrone use is positively associated with frequency of nightclub visits, 20 times higher (the largest difference across all types of drugs measured in the Crime Survey of England and Wales) with greater than four visits or more in the past month (4.4%) compared to no visits (0.2%) in the 2012/2013 dataset [26].

Further subpopulation surveys have revealed higher use of mephedrone among students, those who frequent night-time economy venues, and the men who have sex with men (MSM) community [27–29]. In a questionnaire survey of mephedrone use of 1,006 school ($n = 349$) and college/university ($n = 657$) students undertaken in Scotland in February 2010 (prior to the UK classification of mephedrone in April 2010), 205 (20.3%) of those surveyed had used mephedrone on at least one occasion. Additionally, 4.4% reported using mephedrone on a daily basis and were 21 years or younger [27]. A focus group of 154 pupils (aged 14–15) in Northern Ireland were surveyed in 2010. Approximately 40% admitted trying mephedrone at least once and approximately 70% stated that their friends had tried or used mephedrone [29]. Of 308 respondents to surveys

conducted in two “gay-friendly” nightclubs in South London in 2010, 54% reported lifetime use of mephedrone and 52% reported use within the last year [28].

Another subpopulation group in which there have been reports of a higher prevalence of mephedrone use is intravenous drug users – this has particularly been noted in Eastern Europe and the UK Channel Islands. A qualitative analysis in Hungary among 17 voluntary participants (eight male, nine female, age range 18–62 years) in a needle exchange program reported a switch to injecting mephedrone over “old drugs” (heroin and amphetamines) [30].

Although population level surveys are only available from England and Wales, on the basis of subpopulation surveys, it appears that there are significant international differences in the prevalence of mephedrone use. The 2014 Global Drug Survey demonstrated last year use of mephedrone in the UK of 7.9% in the 7,326 participants (19th position out of 20 reported drugs) and of 1.2% in Hungary in 3,239 participants (22nd position out of 26 reported drugs). Mephedrone was not listed in surveyed participant responses from the USA, Australia, New Zealand, and other European and South American countries [31]. Other sources of drug use data, however, may demonstrate NPS use, particularly mephedrone, in these countries. For example, the National Drug Strategy Household Survey in Australia questioned respondents about past 12-month NPS use for the first time in 2013 (mephedrone was listed as an example in this category) – 0.4% (approximately 80,000 people) confirmed use [32]. The last European School Survey Project on Alcohol and Other Drugs (ESPAD) study, which surveys youth around Europe regarding illicit drug use, was conducted in 2011 and did not include cathinone use or synonyms [33]. Finally, the Monitoring the Future Studies, which survey college students and adults (aged 19–55) in the United States, added “bath salts” in 2012. The term “bath salts” is usually colloquially used in the USA to refer to NPS such as cathinones, and in particular MDPV. The annual reported prevalence of use rate for “bath salts” was low at 0.8%, 0.6%, and 1.3% in Grade 8 (7,300), 10 (6,450), and 12 (6,300) students,

respectively. In 2014, the prevalence rates remained comparable at 1.0%, 0.9%, and 0.9% for Grade 8, 10, and 12 students, respectively. The annual prevalence of use for college students was 0.3% in 2012 and 0.2% in 2014 and for young adults (defined as aged 19–28) was 0.5% in 2012 and 0.4% in 2014 [24, 34].

Analytical Detection of Mephedrone in Wastewater Analysis and Other Subpopulation Studies

Wastewater analysis provides a nonintrusive way of measuring drug use within general or subpopulation groups. Analysis of anonymous pooled urine samples from street urinals in nine cities in the UK on one night in April 2014 showed that the most common NPS was 4-methylmethcathinone (five cities); the only other cathinone detected was methylone (London only) [35]. This same research group were involved in collection of pooled urine samples from one urinal outside a nightclub in central London, over 1 weekend for analysis; mephedrone was detected at a median concentration of 2965.1 ng/ml (2444.4–3323.8), as well as metabolites, but no other cathinones [36]. Wastewater analysis in one city in Australia demonstrated a peak in mephedrone use from 2009 to 2010, an 11-fold increase in use was demonstrated within this time frame; however, a reduction of measured concentration by half was observed comparing data from 2010 to 2011 (raw values not expressed) [37]. Wastewater analysis was conducted over two consecutive years (2010 and 2011) at an annual music festival in Australia. Daily composite wastewater samples, representative of the festival, were collected from the on-site wastewater treatment plant (WWTP) in 2010 and compared with data collected at the same time from a nearby urban community. Mephedrone and methylone were the only cathinones detected during this time. Daily mass loads (per 1000 people) of mephedrone halved between the two festival years; in 2010, mephedrone increased from <0.001 mg/day/1000 people on day 1 to 1.9 mg/day/1000 people on day 6. In 2011, mephedrone was detected at a concentration of <0.001 mg/day/1000 people on day 1 compared to 0.9 mg/day/1000 people on day 6 [38]. Composite raw

wastewater samples were collected from WWTPs in 17 cities in Italy (sampled once a year from 2010 to 2013). Mephedrone was detected only in Bologna (12/14 samples were above the limit of quantification; range 1–23.6 ng/L, years detected were unspecified) and Florence (1/14 samples tested positive; 1.6 ng/L, November 2013) which is consistent with a low population prevalence [39]. Khat and mephedrone were the only cathinones screened for in similar wastewater analysis collected from Oslo, Hamar, and Bergen (Norway) in July 2012 and were not detected although limitations around mephedrone stability were highlighted especially with long in-retention sewage times as well as storage techniques [40]. This may be a cause for underestimation of cathinone/mephedrone use in wastewater analysis and has been highlighted elsewhere [41, 42].

Drug samples submitted by users over a 2-year period (2010–2012) to Energy Control, a nongovernmental organization working among recreational drug users in Spain, were analyzed for the presence of cathinone derivatives [43]. Of the 6199 samples analyzed, cathinone derivatives were detected in 228 cases; MDPV was detected in 6.8%, methylone and mephedrone were the most frequently detected (24.9% and 24.5% respectively).

MDPV

Unlike mephedrone, there have been no coordinated national or European population surveys on MDPV use. Data on prevalence of use is, therefore, based on subpopulation surveys many of which focus not just on MDPV but also – particularly in North America – on “bath salt” prevalence as a surrogate for MDPV use. This is possible because there has been greater focus on MDPV use in North America. One study involved an analysis of samples purchased online in California and the general Internet (from USA sites only), between August 11 and December 15, 2011. The majority (32/35, 91%) had one ($n = 15$) or multiple cathinones ($n = 17$) present. Of the fourteen cathinones identified, MDPV was the most common ($n = 19$, 54.3%)

[44]. Additionally, Spiller et al. [45] reported on a retrospective case series of patients with exposures to bath salts from two US poisons centers over January 2010 to February 2011; 19 out of 236 recorded patients had blood and/or urine analyzed using GC/MS; MDPV was detected in blood samples of 13 out of 17 live patients (range 24–241 ng/mL, mean 58 ng/mL) as well as three out of five urine samples (range 34–1386 ng/mL, mean 856 ng/mL). No other synthetic cathinones were detected. The annual “MixMag” Drug Surveys, a UK-based project, reported on MDPV use in UK respondents (the country-specific breakdown of respondents was not provided) in the 2010/11 survey; 4.4% respondents reported that they had ever used MDPV and 3% reported that they had used MDPV in the last year (the total number of respondents was not reported) [46]. Notably, 3,4-methylenedioxypyrovalerone use was not reported in the “MixMag” Global Drugs Surveys from 2012 onwards (which were advertised to respondents worldwide), although 12% of UK respondents (22,000 participants worldwide, the fraction of UK respondents was not specified) in 2013 said they had used drugs promoted as “bath salts,” “legal highs,” or “research chemicals” in the previous 12 months (while these terms often are used to refer to cathinones, and as noted above in particular to MDPV, it is possible that respondents may not specifically be referring to these substances but to other NPS) [47]. In a self-report survey over 3 months among multicenter university students in Southeastern USA, 25 (1.07%) of 2349 respondents reported ever using “bath salts or MDPV” [48].

Analytical Detection of MDPV in Wastewater Analysis and Other Subpopulation Studies

Other analyses providing clues regarding community prevalence of MDPV use have included analysis of wastewater. Urinary metabolite assessment in one city in Australia demonstrated a sevenfold rise in MDPV use from 2009 to 2011 (raw values not expressed) [37]. MDPV has not been detected thus far in consequential wastewater analysis in the UK or the USA [35, 36]. Finnish wastewater

analysis (involving nine WWTPs) spanning the metropolitan area, university cities, and rural towns was conducted over 8 days in August 2012. MDPV was detected in only one town (Savonlinna, in the east), where the concentration was higher than that of the limit of detection during all 8 days of the study (maximum concentration: 5.1 ng/L, mass load of 1.9 mg/1000 people/day). No other cathinones were detected [49]. Other wastewater analysis have, however, confirmed its use in other Finnish cities, outside Savonlinna, within the same year (May 2012) such as Helsinki (2.4 mg/1000 people/day) and the Lappeenranta region (19 mg/1000 people/day) [50].

In Finland and Sweden, MDPV metabolites were discovered in urine samples of opioid-dependent patients undergoing opioid substitution therapy (9 of 34 samples) [51] and 21 (24.1%) of 87 addiction center patients [52] respectively, suggesting the potential that MDPV, like mephedrone, may be commonly used among those who use classical drugs and/or intravenous drug users. Also, a similar possible preference for injecting MDPV use (essentially thought to be amphetamine switching in opioid-dependent patients) was noted in clientele surveys of a large needle exchange program in Hungary [53]. In Finland, 3,4-methylenedioxypyrovalerone has been detected as a culprit agent among those arrested for driving under the influence of drugs (DUID) in 5.7% of 4570 of cases, where alcohol was also not detected [54].

Route of Administration and Dosage

Table 1 summarizes the main forms, routes of use, doses, and duration of effects for mephedrone and MDPV. The main routes of mephedrone and MDPV administration in recreational users are reported to be oral ingestion and nasal insufflation; oral ingestion may be of powder directly, dissolved in drinks or wrapped in cigarette papers (also known as “bombing”). Like mephedrone, there have been reports of intravenous use of MDPV as well as substitution recreational drug use by individuals with known injecting use of

Table 1 Forms of drug and common dosing and observations of use

	Mephedrone	MDPV
Chemical name	4-methylmethcathinone	3,4-methylenedioxypyrovalerone
Systematic chemical name	(<i>RS</i>)-2-methylamino-1-(4-methylphenyl)propan-1-one	(<i>RS</i>)-1-(benzo[d][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl) pentan-1-one
Forms	Powder (most common), powder-filled capsules, tablets.	Powder (most common), powder-filled capsules, tablets, blotters (small paper doses for sublingual/buccal administration), liquids and vegetable material
Physical characteristics	White crystalline in nature but may be light yellow or light brown	Brown or yellow-green amorphous powder
Mode of consumption	Nasal insufflation (most common) Oral ingestion (most common) Per rectum Intravenous Intramuscular Bombing ^a	Nasal insufflation (most common) Oral ingestion (most common) Per rectum Intravenous Sublingual Smoked Intramuscular Bombing ^a Dabbing ^b
Initial dose range per session (mg)	75 – 250 (oral) ^c	5-11 (insufflated) ^c 8 - 15 (oral) 6-12 (rectal)
Peak onset (mins)	15 - 45 ^a	30-60 (oral) 15-30 (insufflated)
Duration of action (hours)	2-3	2-7 (oral) 2 – 3.5 (insufflated)

^awrapped in cigarette wrapper and ingested

^bdipping a moistened finger into the powder

^cSourced from www.erowid.org

heroin/opioids [53, 55]. Given the observed short peak onset to action times, users have reported taking repeated doses per session up to 1 g for mephedrone [56] and 200 mg per session of MDPV [57]. This trend to re-dose in a session has been observed with most routes of drug consumption, as highlighted in Table 1.

Legal Status

Mephedrone and MDPV are not recognized medicinal products and are not used for the synthesis of any other products or active pharmaceutical ingredients. Since 2010, generic legislation in the UK classifies a range of different synthetic cathinones as Class B, Schedule 1 drugs (this generic classification covers both MDPV and

mephedrone and implies legally enforceable penalties including imprisonment associated with supply) [58]. In Europe, following review of both mephedrone in 2010 and MDPV in 2014 under the procedure for risk assessment and control of NPS set up by the European Council Decision 2005/387/JHA, both substances were risk assessed by the European Monitoring Centre for Drugs and Drugs Addiction (EMCDDA) Scientific Committee; the outcome of this risk assessment lead to the Council of the European Union to recommend their control by all European member states [59, 60]. There are legal controls surrounding manufacture, distribution, sales, and use of both mephedrone and MDPV in the USA [61], Canada [62], New Zealand [63], and Australia [64]. Most recently, on the counsel of the World Expert Drug Committee Review, mephedrone and

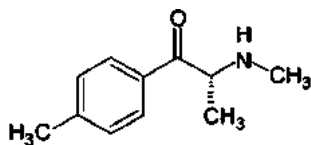


Fig. 3 Chemical structure of mephedrone

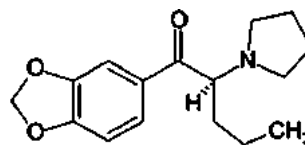


Fig. 4 Chemical structure of MDPV

MDPV have been added to schedule 2 of the United Nations Convention on Psychotropic Substances of 1971 [65, 66].

Biochemistry and Clinical Pharmacology

Mephedrone

Mephedrone was first synthesized in 1929 as a homologue of ephedrine [67]. The systematic chemical (International Union of Pure and Applied Chemistry, IUPAC) name is (*RS*)-2-methylamino-1-(4-methylphenyl)propan-1-one. Mephedrone is a synthetic ring-substituted cathinone closely related to the phenethylamine family, differing only by a keto functional group at the beta carbon as shown in Fig. 3. The molecular formula for mephedrone is $C_{11}H_{15}NO$, and it has a molecular weight of 177.242 g/mol.

The main synthetic route for mephedrone involves α -bromination of 4-methylpropio-phenone. The resulting compound (4-methyl-2-bromopropiophenone) is then reacted with methylamine hydrochloride and triethylamine in an acidic scavenger to produce 4-methyl-methcathinone. The hydrochloric salt form is both stable and water soluble [60].

3,4-Methylenedioxypropylphenylpropan-1-one

The systematic chemical IUPAC name for MDPV is 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one. Its molecular formula is $C_{16}H_{21}NO_3$, equating to a molecular weight of 275.343 g/mol. 3,4-Methylenedioxypropylphenylpropan-1-one is the methylenedioxy derivative of pyrovalerone (Fig. 4). Pyrovalerone is controlled as a Schedule IV drug under the 1971 United Nations Convention (the scheduling relates to the potential a

substance has to be abused and the harms associated with its abuse and therefore the restrictions required on the substance from Schedule I (most restrictive) to Schedule IV (least restrictive)) [68]. The synthesis of MDPV is described in patents from France, Germany, the United Kingdom, and the USA all from the 1960s [69, 70]. Briefly, the precursor 1-(1,3-benzodioxol-5-yl)pentan-1-one is α -brominated to form a 2-bromopentan-1-one intermediate. Reaction of the intermediate with a pyrrolidine ring yields MDPV [71].

Pharmacokinetics

There is one pharmacokinetic study regarding mephedrone use in healthy volunteers [72] but no detailed human pharmacokinetic studies regarding MDPV. Most studies thus far involve in vitro human cells, in vivo animal models, and metabolites analyzed from single human cases. Extrapolation of information from drug user forums as well as plasma concentrations in users, particularly in the case of mephedrone, has informed experimental doses in rat models sufficient to achieve some translational value in humans.

Mephedrone

There are several studies assessing the pharmacokinetic parameters of mephedrone in rats. In Sprague–Dawley rats, the bioavailability of mephedrone (30 and 60 mg/kg) was 10% and protein binding was 21%. Peak concentrations were achieved between 0.5 and 1 h and decreased to undetectable concentrations by 9 h. The plasma concentrations after intravenous administration (10 mg/kg) fitted a two-compartment model

($\alpha = 10.23 \text{ h}^{-1}$, $\beta = 1.86 \text{ h}^{-1}$) [73]. The uptake and elimination of a single dose (5.6 mg/kg subcutaneous [s.c.]) of mephedrone was also determined to be rapid in a further rat model. The peak plasma concentration (C_{max}) observed was 1206 ng/ml with a T_{max} of 0.25 h [74]. Additionally, mephedrone readily enters the brain; a concentration of 4 ng/mg was observed after injection (1 mg/kg) at 2 min and almost totally cleared within an hour (0.4 ng/mg) [75, 76].

The metabolite pattern of mephedrone varies with route of administration. Meyer et al. [77] examined the metabolite pattern after oral administration in Wistar rats. In addition to the parent compound, the metabolites detected in urine were nor-mephedrone, nor-dihydro mephedrone, hydroxytolyl mephedrone, and nor-hydroxytolyl mephedrone. Urine was collected over a 24-h period, and therefore it was not possible to elucidate timing of metabolite formation. Urine samples were analyzed from one human subject (patient) in the same study and a further metabolite was identified, 4-carboxy-dihydro mephedrone (the patient self-reported oral ingestion of both butylone and mephedrone powder); there was no information regarding timing of urine collection in this case. These metabolites have been detected elsewhere in a similar rodent study [73]. Pedersen et al. [78] used cDNA-expressed CYP enzymes and human liver microsomal preparations and found cytochrome CYP2D6 to be the main enzyme responsible for the in vitro metabolism of mephedrone. Experiments involving a range of recombinant CYP isoenzymes resulted in the formation of the metabolites hydroxytolyl- and nor-mephedrone from CYP isoenzymes 1A2, 2B6, 2C8, 2C18, 2C19, and 3A4. However, it appeared that CYP2D6 had a more significant role in the metabolism of mephedrone compared to other enzymes. In particular, inhibition of CYP2D6 with quinidine significantly reduced mephedrone metabolism, with only about 20% of the parent compound having metabolized after 140 min, compared to approximately 60% with no inhibition. This 20% metabolism might have been due

to the action of other NADPH-dependent enzymes, as no metabolism was observed with the control that lacked NADPH. In the human liver microsomes and S9 fraction experiments, only formation of hydroxytolyl mephedrone metabolite was observed, as well as the same pattern of mephedrone metabolism with predominant CYP isoenzyme 2D6. Analyses of blood and a urine sample in four forensic traffic accidents with blood mephedrone concentrations ranging from 1 to 51 $\mu\text{g/kg}$ have yielded two further previously undocumented mephedrone metabolites – dihydro-mephedrone and 4-carboxy-mephedrone [78].

Kavanagh et al. [79] examined the pyrolysis products produced by heating mephedrone under simulated “meth pipe” conditions. Thirteen pyrolysis products were identified; the major ones being *iso*-mephedrone, 4-methylpropionophenone, 4-methylphenylacetone, two pyrazine derivatives (formed by dimerization of mephedrone), *N*-methylated mephedrone (*N,N*,4-trimethylcathinone), two hydroxylated oxidation products, and a di-ketone (there is no information regarding which of these or other metabolites have activity). This highlights the need to study all modes and routes of drug consumption to fully appreciate the pharmacological and/or toxicokinetic profile and impact of the mode of administration on these parameters. There are some discussion narratives on Erowid and other online drug forums documenting the experiences of several individuals with both MDPV and/or mephedrone pyrolysis, but interest appears relatively limited, with only 5–10 users commenting in discussion threads; most of these were deterred as a result of concerns over drug efficacy or safety. Effects were described as “fast” and short-lived, at times as being “harsh” on the throat and lungs [56].

Recently, urine samples were obtained pre-dose and after 4 h from two healthy Caucasian recreational drug users (aged 29 and 36 years) who were given a single oral dose of 200 mg of mephedrone in a controlled administration study [72]. Both were extensive-intermediate CYP2D6 metabolizers. A rapid urine test for main drugs of

abuse was negative before administration. Urine samples were collected before and 4 h after the mephedrone ingestion. The following metabolites characterized for structural elucidation were classified as M1–M10. These included six phase I (M1–M3, M5–M7) and four phase II (M4, M8–M10) mephedrone metabolites. The metabolites previously described in humans or other species were N-demethylmephedrone (M1, C₁₀H₁₃NO), 1-dihyromephedrone (M3, C₁₁H₁₇NO), 1-dihydro-nor-mephedrone (M5, C₁₀H₁₅NO), 49-hydroxymethyl-mephedrone (M6, C₁₁H₁₅NO₂), 49-carboxymephedrone (M7, C₁₁H₁₃NO₃), and 49-carboxymephedrone (M9, C₁₇H₂₁NO₉) [46, 50, 51]. N-demethylmephedrone-3-carboxylic acid (M2, C₁₀H₁₁NO₃), N-succinyl nor-mephedrone (M4, C₁₄H₁₇NO₄), hydroxylmephedrone-3-*O*-glucuronide (M8, C₁₇H₂₃NO₈), and a hydroxylated metabolite of nor-mephedrone (M10, C₁₆H₂₀NO₈) were reported for the first time in this study.

Reported data from user forums suggests that the onset of desired effects of mephedrone varies with route of administration, although there have been no controlled administration studies to corroborate this. Insufflation and intravenous routes are reported to be associated with the onset of effects within a few minutes, compared with 10–45 min when ingested. The duration of action is reported to be between 2 and 4 h, however, can be as short as 30 min with intravenous use. Rectal administration has been reported to have a more rapid termination of effects relative to oral doses, lasting approximately 20 min but absorption is variable. Intranasal and intravenous uses are reported to be associated with a greater compulsion to re-dose to maintain effects [56, 80].

Human blood–brain permeability has been simulated using an in vitro model of conditionally immortalized human brain endothelial cells (TY09) [81]. Permeability coefficient (Pe) ratios indicate the blood–brain barrier permeability of the drug in relation to the extracellular marker lucifer yellow (Pe = 1) with high permeability being a Pe ratio >3 and a very high permeability being a Pe ratio >10. The Pe of mephedrone was

>10 (apical to basolateral transport 14.0 ± 10.4 , basolateral to apical 12.2 ± 6.1) indicating that it has a very high blood–brain barrier permeability [76].

3,4-Methylenedioxypropylvalerone

There have been three studies that have investigated pharmacokinetic parameters of MDPV; two have investigated MDPV metabolism [82, 83] and one has investigated blood–brain barrier permeability [76].

The first study investigating the metabolism of MDPV was an in vitro study. This involved incubation of 1 mL of 1 mg/mL MDPV with 6.5 mL of human liver microsomes and S9 cellular fractions (P450 and transferases) [82]. Eighty percent of the MDPV remained unchanged, which the authors felt may have been related to the dose of MDPV used saturating their model; only a single dose was studied. Approximately 7% of the MDPV was metabolized to catechol pyrovalerone and 10% to methylcatechol pyrovalerone. Neither of these metabolites was found in the second study [83].

Metabolism of MDPV was also investigated using an in vitro human liver microsomal model and in vivo experiments in rats administered MDPV as a single dose of 20 mg/kg via gastric intubation. Urine was collected from the rats over a 24-h period, and additional urine samples from human MDPV users were also analyzed to allow confirmation of metabolites [83]. The metabolites from this study are listed in Table 2. Human enzyme incubations were performed of the ten most important CYP enzymes, assessed by capability to catalyze the formation of the initial metabolite of MDPV, demethylenyl-MDPV, in vitro. The amount of metabolism was: CYP 2C19 (100%), CYP 2D6 (<50%), CYP 1A2 (<50%), and CYP 2A6 (<10%). Phase I metabolites included MDPV-M (demethylenyl-), MDPV-M (demethylenyl-methyl-) MDPV-M (demethylenyl-methyl-oxo-), MDPV-M (oxo-), MDPV-M (demethylenyl-methyl-hydroxy-alkyl-),

Table 2 Pharmacokinetic profile of mephedrone and MDPV

	Mephedrone	MDPV
Absorption	F = 10% Protein binding 21%	N/A
Plasma half-life (h)	0.4 ^a Similar to humans	N/A
Distribution	Two-compartment model $\alpha = 10.23\text{h}^{-1}$ $\beta = 1.86\text{h}^{-1}$	N/A
BBB permeability	High	High – data suggests active transport
Metabolism	<i>Phase I enzymes:</i> CYP 2D6 NAPDH-dependent enzymes <i>Phase II enzymes (conjugation with):</i> Partial excretion glucuronides and sulphates (% not reported)	<i>Phase I enzymes:</i> Uridine 5'diphosphoglucuronosyltransferase (UGT) CYP 2C19 CYP 2D6 CYP 1A2 <i>Phase II enzymes (conjugation with):</i> Predominant excretion as sulphates (~50%) glucuronides (~40%)
Metabolites	<i>Metabolites:</i> ^b nor-mephedrone, nor-dihydro mephedrone hydroxytolyl mephedrone nor-hydroxytolyl mephedrone mephedrone 4-carboxy-dihydro mephedrone dihydro-mephedrone 4-carboxy-mephedrone N-demethylmephedrone-3-carboxylic acid N-succinyl nor-mephedrone hydroxylmephedrone-3-O-glucuronide hydroxylated metabolite of nor-mephedrone	<i>Metabolites:</i> ^c MDPV catechol pyrovalerone methylcatechol pyrovalerone demethylenyl-MDPV demethylenyl-methyl-MDPV demethylenyl-methyl-oxo-MDPV oxo-MDPV demethylenyl-methyl-alkyl-hydroxy-MDPV carboxy-oxo-MDPV demethylenyl-methyl-carboxy-oxo-MDPV demethylenyl-methyl-N,N-bisdealkyl-MDPV demethylenyl-oxo-MDPV demethylenyl-N,N-bis-dealkyl-MDPV demethylenyl-alkyl-hydroxy-MDPV demethylenyl-methyl-phenyl-hydroxy-MDPV
Excretion	Not available	Not available

^bListed as found in Meyer et al. (2010) [77]. The seventh and eighth listed metabolites were derived from DNA-expressed CYP enzymes and human liver microsomal preparations used as well as analysis of urine of persons from forensic traffic cases (Pedersen, Reitzel, Johansen, & Linnet, 2013) [78]. The last four were derived from human case studies (Pozo et al., 2015) [72].

^cThe first three metabolites listed as per Strano-Rossi (2010) [82]. The remaining metabolites listed from human case studies (Meyer, Du, Schuster, & Maurer, 2010) [83].

MDPV-M (demethylenyl-hydroxy-alkyl-), MDPV-M (demethylenyl-hydroxy-phenyl-), and MDPV-M (demethylenyl-oxo-). Besides the unchanged parent compound, the following metabolites were also found in human urine after the intake of an unknown amount of MDPV: demethylenyl-MDPV, demethylenyl-oxo-MDPV, oxo-MDPV, demethylenylhydroxy-alkyl-MDPV, and demethylmethyl-N,N-bisdealkyl-MDPV. These three metabolites were also present in rat urine: demethylenyl-methyl-MDPV, demethylenyl-methyl-oxo-MDPV, and demethylenyl-methylhydroxy-alkyl-MDPV. Phase II metabolites were predominantly excreted as glucuronides and sulfates.

3,4-Methylenedioxypropyvalerone has a high Pe ratio, indicating its likely ability to cross the blood–brain barrier. Subanalyses showed that apical to basolateral transport of MDPV was greater than basolateral to apical transport (Pe ratios for apical to basolateral transport 37.2 ± 11.3 , and basolateral to apical as 12.0 ± 11.2 , $p < 0.05$); this suggests an active transport mechanism of MDPV, possibly through influx carriers. However, the particular transporters implicated in this prototype blood–brain barrier model were not studied [76].

Data from drug user forums suggests that the onset of effects of MDPV when taken orally is 15–30 min (duration 2–7 h) and after nasal insufflation the onset is within 5–20 min of use (duration 2–3.5 h). Most report a come-down effect around 30–60 min orally and close to 15–30 min after insufflation. Onset intravenously is within minutes, and users report a compulsion to re-dose [84].

Pharmacodynamics and Mechanisms of Toxic Effects

A number of recent studies have assessed the binding affinity to monoamine receptors and proposed structure-activity relationships of mephedrone and MDPV. These have increased our understanding of the potential cardiovascular, neurological, and thermoregulatory effects of using these drugs in humans. Convergent lines

of evidence from a heterogenous mix of in vitro and in vivo cell studies as well as animal models suggest that there is modulation around serotonergic, dopaminergic, and noradrenergic transmission and interaction with monoamine transporters to achieve this (as summarized in Table 3).

Simmmler et al. [76] were the first to attempt categorization of cathinones as fitting into three groups based on the variation in their selectivity for transporters of dopamine (DAT), noradrenaline (NET), and serotonin (SERT) and potency to act as monoamine transport inhibitors/substrate releasers shown in Table 4.

Mephedrone

Animal Data

Neurochemistry

Mephedrone stimulates dopamine release and blocks its reuptake through its interaction with the DAT and has displayed affinity to various serotonin receptor subtypes. Early research with in vitro experiments in isolated synaptosomes from rat cortex or striatum demonstrated mephedrone inhibition of serotonin (5-HT) –uptake with an IC_{50} value lower than that of dopamine (DA) uptake ($IC_{50} = 0.31 \pm 0.08$ and $0.97 \pm 0.05 \mu M$, respectively) [50]. Additionally, mephedrone displaced competitively both [3H]paroxetine (used to label SERT) and [3H]WIN35428 (used to label DAT) binding in a concentration-dependent manner (K_i values of $17.55 \pm 0.78 \mu M$ and $1.53 \pm 0.47 \mu M$, respectively), indicating a greater affinity for DAT than for SERT. Through radioligand binding of [3H]ketanserin (used to label 5-HT $_{2A}$ receptors) and [3H]raclopride (used to label dopamine D $_2$ receptors) in rat membranes, it was determined mephedrone had a greater affinity for the 5-HT $_2$ than for the D $_2$ receptors. Interestingly, the affinity of mephedrone for SERT was lower than the IC_{50} value of mephedrone inhibiting 5-HT uptake, indicating that an additional mechanism to the reversible interaction with the 5-HT transporter is possible. There may be competitive inhibition

Table 3 Pharmacodynamic effects of mephedrone and MDPV on catecholamine transporters DAT, NET, SERT

Mephedrone		MDPV
Monoamine uptake inhibiton (IC ₅₀ , nM ± s.e.m.)		
DAT	762 ± 79	4.1 ± 0.5
NET	487 ± 66	26 ± 8
SERT	422 ± 26	3349 ± 305
Monoamine release (EC ₅₀ , nM ± s.e.m.)		
DAT	51 ± 5	2.3 ± 0.8
NET	58 ± 11	13 ± 16
SERT	122 ± 10	Inactive

EC₅₀ and IC₅₀ numbers taken from (Baumann et al., 2013) [70].

Table 4 Basic groups of cathinones as per their monoamine profile and resemblance to profiles of classical stimulant recreational drugs

Group	Example Cathinones
Cocaine-MDMA-Mixed Cathinones (substrates for DAT, SERT and NET)	mephedrone, methylone, ethylone, butylone and naphyrone.
Methamphetamine-like Cathinones (monoamine transporter substrates with DAT selective profiles)	cathinone, methcathinone, flephedrone
Pyrovalerone-cathinones (non-substrate transporter inhibitors)	MDPV, Pyrovalerone

with 5-HT itself [85]. Eshleman et al. [86] have studied the effects of 5-HT subreceptor profiles indicating that it behaves as an antagonist at receptor level and also confirms low potency at h5-HT2A: [¹²⁵I]DOI binding site and low potency to stimulate inositol monophosphate accumulation, a measure of receptor function with IC₅₀ 14.8 ± 1.8 μM. Mephedrone also has low potency to interact with h5-HT2C to achieve

inhibition of 5-HT- stimulated IP-1 formation (IC₅₀ > 440 μM). This confirms that mephedrone is unlikely to share a direct interaction as an h5-HT2A receptor agonist.

Further, Eshleman et al. [86] demonstrated similar receptor profile interactions as above, mephedrone displayed high potency to induce release of preloaded neurotransmitter from monoamine transporters (NET > DAT and SERT) and

thus acts as a transporter substrate. High K_i values for inhibition of binding at hDAT $4.80 \pm 0.75 \mu\text{M}$, hSERT $21.0 \pm 4.8 \mu\text{M}$, and hNET $11.8 \pm 4.0 \mu\text{M}$ compared with IC_{50} values of inhibition of neurotransmitter uptake for hDAT [^3H]DA $0.098 \pm 0.027 \mu\text{M}$, hSERT [^3H]5-HT $0.51 \pm 0.15 \mu\text{M}$, and hNET [^3H]NE $0.0536 \pm 0.0087 \mu\text{M}$, respectively, indicate a higher inhibitory potency at uptake compared to binding and generally induced release of preloaded [^3H]neurotransmitter from hDAT, hSERT, and hNET (highest potency at hNET: EC_{50} hDAT[^3H]DA $1.19 \pm 0.34 \mu\text{M}$, hSERT[^3H]5-HT $11.9 \pm 4.9 \mu\text{M}$, and hNET[^3H]NE $0.41 \pm 0.13 \mu\text{M}$), and thus behaves as a transporter substrate.

Neurocytotoxicity

Studies to date do not demonstrate definitive cytotoxic effects of mephedrone at nerve endings. Female C57BL/6 mice (20–25 g) were given mephedrone under binge-dosing regimens (four injections of 20 or 40 mg/kg with 2-h intervals) attempting to reproduce conditions of similar reported human consumption patterns; mephedrone was not toxic to dopaminergic nerve terminals of the striatum as well as surrogate features of serotonergic damage [87]. However, similar studies investigating the effects of mephedrone on 5-HT nerve terminals are equivocal [88, 89]. In one study, Hadlock et al. [88] demonstrated that repeated mephedrone administrations (4×10 or 25 mg/kg s.c. per injection, 2-h intervals) in male Sprague–Dawley rats (290–400 g, $n = 6$ –10) caused persistent decreases in hippocampal serotonin (5-hydroxytryptamine; 5HT) transporter function and 5HT levels. This was observed 7 days after treatment compared with the saline-treated group (4.0 ± 0.6 , 3.5 ± 0.5 , and $2.1 \pm 0.2^* \text{ pg}/\mu\text{g}$ protein for saline, $4 \times 10 \text{ mg/kg}$, and $4 \times 25 \text{ mg/kg}$, respectively, $p \leq 0.05^*$). In contrast, mephedrone treatment was no different to saline treatment groups when assessing striatal dopamine (DA) transporter function or DA concentrations 7 days post administration (data not shown). Of note, these mice were kept in warmer environmental conditions ($\geq 27^\circ\text{C}$, housed three to four animals per cage). On the

other hand, Baumann et al. [89] did not demonstrate a change in amine concentrations of serotonin, noradrenaline, or dopamine in the striatum and frontal cortex of Sprague–Dawley rats (300–350 g) that underwent repeated administration of mephedrone versus saline, as measured 2 weeks post administration. Rats in this experiment were individually housed and under conditions of controlled temperature ($22 \pm 2^\circ\text{C}$), as well as lower doses of mephedrone were used (3×3 or 10 mg/kg s.c. per injection versus saline, 2-h intervals).

Interestingly, mephedrone's ability to serve as a DAT inhibitor could provide protection against methamphetamine-induced neurotoxicity through competitive inhibition. However, dopaminergic nerve toxicity associated with known doses of methamphetamine (four injections of 2.5 or 5.0 mg/kg at 2 h intervals) was not prevented by preinjection doses of mephedrone (10, 20, or 40 mg/kg) and was significantly enhanced [90]. Mephedrone also enhanced the neurotoxic effects of amphetamine and 3,4-methylenedioxymethamphetamine on DA nerve terminals; hence it interacts with the DAT in a manner unlike that of other typical DAT inhibitors. The status of 5-HT nerve terminals in the hippocampus of female C57BL mice (20–25 g) was assessed through measures of 5-HT, SERT, and tryptophan hydroxylase 2 (TPH2) in an identical experiment [91]. Mephedrone ($4 \times 20 \text{ mg/kg}$ s.c. injections, 2-h interval) did not cause persistent reductions in the concentrations of 5-HT, SERT, or TPH2 either when given alone or in combination with methamphetamine ($4 \times 5 \text{ mg/kg}$). The main effect of drug treatment on 5HT concentrations was significant ($F[3,30] = 5.02$, $p = 0.006$) but neither mephedrone nor methamphetamine alone changed hippocampal 5-HT concentrations. Mice were housed five per cage in a temperature-controlled room (temperature values not specified). Green et al. [92] have hypothesized the paucity of catechol metabolites which produce highly reactive intermediates capable of inciting free reactive oxygen species, such as in MDMA, which may explain the paucity of direct neurotoxicity observed with mephedrone.

Cardiovascular

There are both *in vitro* and *in vivo* studies evaluating the cardiovascular effects of mephedrone and MDPV. Overall these studies show that mephedrone is associated with significant tachycardia, moderate hypertension, with rapid time to peak onset and resolution of hemodynamic parameters. This finding has been confirmed in two separate animal-based studies. Meng et al. [93] performed a three-part study assessing the electrocardiographic, echocardiographic, and hemodynamic effects of mephedrone. Mephedrone (1–30 μ M) had little direct effect on voltage-dependent ion channel activation; maximum mean inhibition on human ether-a-go-go-related gene (HERG) coding K⁺ channels (on stably transfected Chinese hamster ovary cells (CHO)) was $9 \pm 2\%$, human Kv LQT1/mink (on CHO cells) was $0 \pm 2\%$, L-type calcium channels of isolated pig myocytes was $10 \pm 7\%$, and human Nav 1.5 cardiac ion channels (stably transfected in human embryonic kidney-293 (HEK-293) cells) was $4 \pm 3\%$ with a 30 μ M dose.

The effects of *subcutaneous* mephedrone injection ($n = 6$ –7 per group, 3 mg/kg or 15 mg/kg) on heart rate (HR) and mean arterial pressure (MAP) were tested in conscious telemetry-implanted rats, compared to saline controls. For heart rate, the pre-dose value for the saline-treated animals measured 347 ± 9 beats per minute (bpm) and for the 3 and 15 mg/kg mephedrone-treated groups this value measured 309 ± 5 and 324 ± 3 bpm (time = 0 min), respectively. A statistically significant tachycardia was observed in the mephedrone-treated group, peaking at 30% higher at 25 min (3 mg/kg group) and 39% higher than the pre-dose value 45 min after injection (15 mg/kg group). The heart rate of the saline-treated rats began to fall after 10 min and returned to pre-dose levels within about 30–40 min. In contrast, heart rate for the mephedrone-treated group continued to rise peaking at 30% higher than the pre-dose level 25 min following injection of 3 mg/kg and 39% higher than the pre-dose value 45 min after injection of 15 mg/kg. Heart rate remained significantly elevated compared to time-matched saline-treated animals for 105 min

after the 3 mg/kg dose and for 3 h following the 15 mg/kg dose.

Pre-dose values of blood pressure in the saline-treated group were measured as mean arterial, systolic, and diastolic, 107 ± 7 , 128 ± 7 , and 91 ± 7 mmHg, respectively. These same values for the 3 mg/kg mephedrone-treated group measured 106 ± 2 , 126 ± 3 , and 92 ± 2 mmHg, respectively. In the 15 mg/kg treatment group, these values measured 101 ± 3 , 120 ± 5 , and 86 ± 3 mmHg, respectively. All blood pressure measurements for the saline-treated group returned to levels close to pre-dose values within about 30–40 min following injection. In comparison, MAP increased in all treatment groups with a 10–15% peak increase above pre-dose measurements for the 3 mg/kg treatment group and 20–25% peak increase for the 15 mg/kg treatment group, seen within 1–2 h of dosing. These returned to normal within 3–4 h.

Interestingly, reserpine pretreatment (10 mg/kg) to mephedrone-treated rats (subcutaneous injection 15 mg/kg) demonstrated little change to saline-treated control rats (292 ± 7 bpm in the saline-treated group and 299 ± 6 bpm in the mephedrone-treated group, pre-dose MAP 90 ± 1 and 91 ± 3 mmHg in the saline and mephedrone-treated groups, respectively). The echocardiographic findings of anesthetized mephedrone-treated rats (1 mg/kg intravenously) resulted in significant increases in sonographically observed cardiac output (pre-dose 81.3 ± 3.0 ml/min, peak effect 95.0 ± 5.6 ml/min, 10 min post dose 87.6 ± 4.3 ml/min), stroke volume (pre-dose 205 ± 7 μ l, peak effect 223 ± 11 μ l, 10 min post dose 214 ± 9 μ l), ejection fraction (pre-dose $74.3 \pm 2.5\%$, peak effect $86.1 \pm 2.5\%$, 10 min post dose $79.3 \pm 3.2\%$), and impairment of diastolic relaxation (pre-dose 7.25 ± 0.14 mm, peak effect 7.04 ± 0.16 mm, 10 mins post dose 7.19 ± 0.20 mm). These are akin to the echocardiographic findings of rats injected with methamphetamine (given 0.3 mg/kg subcutaneously) (data values not reported).

The principal hemodynamic effects of tachycardia and moderate hypertension were reproduced by Varner et al. [94] when direct

comparisons with methamphetamine were again made. Conscious telemetry-implanted rats (housed individually) received either intravenous mephedrone ($n = 5$ for 0.01–0.1 mg/kg and $n = 7$ for 1–9 mg/kg) or methamphetamine ($n = 7$ for 0.01–9 mg/kg) or 0.9% saline controls. Pretreatment with atenolol (1 mg/kg) blunted the tachycardic response in mephedrone-treated rats (384 ± 10 to 352 ± 8 bpm). Additionally, pretreatment with phentolamine (3 mg/kg) reduced the pressor (114 ± 10 mmHg to 70 ± 5 mmHg) but increased tachycardic (363 ± 3 to 435 ± 24 bpm) responses to mephedrone (3 mg/kg) – presumed to be related to baroreceptor activity. The effect of both beta-adrenergic and alpha-adrenergic activation suggests catecholamine noradrenaline modulation in spite of the blunted effect observed in reserpinized rat. Baumann et al. [89] have explained this physiologically; *in vitro* studies on rat brain synaptosomes support mephedrone as having affinity to noradrenaline transporters (NET) and acting as a NET transporter substrate (release assays conducted using [3H]MPP+ as the radiolabeled substrate for NET; $EC_{50} = 62.7$ nM) resulting in the release of cytoplasmic stores of noradrenaline.

Central Behavior

Mephedrone rapidly increases locomotor activity and stereotypy in a dose-dependent fashion in rat models [89, 90, 95–101]. López-Arnau et al. [102] demonstrated mephedrone (5, 10 and 25 mg/kg) significantly increased spontaneous locomotor activity (measured as occlusions of photobeams in a 10-min period of horizontal activity within a framed box) of mice compared with saline controls (5 mg/kg; $201\ 806 \pm 21\ 894$ – AUC over 360 min vs. $72\ 829 \pm 9524$ for saline controls) lasting approximately 150 min. This hyperlocomotion could be partly reduced with pretreatment with ketanserin (0.5 and 4 mg/kg), a 5-HT₂ receptor antagonist, and haloperidol (0.1 and 0.25 mg/kg), a nonselective dopamine receptor antagonist, measured by about 53% and 65%, respectively, to baseline. Equally, they demonstrated a reliance on endogenous 5-HT given pretreatment with p-chlorophenylalanine (an inhibitor of 5-HT synthesis) decreased

locomotor activity by 53% from baseline controls (raw data not shown). Pretreatment with a selective antagonist of 5-HT_{1B} receptors did not have an effect. This receptor activation has been implicated with methamphetamine use. Additionally, Baumann et al. [89] demonstrated forepaw treading in mice ($F(2, 15) = 22.9$, $p < 0.0001$), a behavior associated with serotonin syndrome, in singly-housed mice enduring a repeat high-dosing regimen of mephedrone (10.0 mg/kg sc, 3 doses). The only reported human cases of serotonin syndrome with mephedrone involved aggregate toxicity with fluoxetine [103].

Mephedrone affects performance in complex motor and memory tasks. It dose-dependently degrades nonhuman primate performance on the rotating turntable and bimanual motor skill tasks, two measures of complex motor skill and procedural learning [101]. Den Hollander et al. [96] treated mice with a binge-like, multiday regimen of mephedrone (30 mg/kg, twice daily for 4 days) and demonstrated impaired recall performance in mice tasked with the Morris water maze. Other examples, of long-term memory degradation in similar multiday exposures (30 mg/kg s.c. once daily for 10 days) results in a failure to discriminate novel from familiar objects 35 days post exposure in adolescent rats [104]. This counteracts the short-term memory and visuospatial learning gains observed in singly-treated rhesus macaques (0.32 mg/kg) [101].

Thermoregulation

The effect of mephedrone effects on body temperature in animal models appear to be dependent on the context. In particular, whether the animals are grouped together versus singly-housed, the drug regimen, and ambient temperatures. Mephedrone (4 or 10 mg/kg) caused a transient decrease (raw data not provided, data are expressed as change in temperature (°C, mean \pm SEM) from the baseline reading taken at the time of injection) in rectal temperature compared with single i.p. injection of saline vehicle (1 mL/kg). Temperatures were measured at 20 min intervals over a 2-h period. The change in temperature with mephedrone peaked at 60 min with approximately -1.5 °C deviation from baseline with mephedrone 10 mg/kg doses.

Individually housed rats then received an i.p. injection of vehicle (1 mL/kg), 0.2 mg/kg prazosin HCl (α_1 -adrenoceptor), 1 mg/kg BRL 44408 maleate (α_2A -adrenoceptor antagonist), 2 mg/kg SCH 23390 HCl (D1 receptor antagonist), or 0.63 mg/kg L-741626 (D2 receptor antagonist), followed 30 min later by vehicle (1 mL/kg) or 10 mg/kg mephedrone HCl ($n = 6-7$ per group). In individually housed vehicle-pretreated rats, 10 mg/kg mephedrone caused a transient significant decrease in rectal temperature. The duration of the mephedrone-induced hypothermia was prolonged in the presence of all drugs with statistical significance compared to mephedrone alone; prazosin (20–60 mins) and SCH 23390 (20–80 mins). In contrast, mephedrone-induced hypothermia was unaffected by pretreatment with either BRL 44408 or L-741626 [72]. On the other hand, repeated high-dose mephedrone treatment (4×50 mg/kg/injection, s.c., 2 h intervals) in a manufactured *warm* environment causes significant and prolonged hyperthermia of up to 40.0 ± 0.1 °C average core body temperature over the 8 h treatment period [88]. Subsequent studies with lower doses of mephedrone (up to 10 mg/kg) have demonstrated mild hyperthermia [47, 48, 76], with core body temperatures rarely exceeding 38.0 °C. Persistent serotonergic deficits have only been reported under these hyperthermic and “binge-dosing” conditions [89].

MDPV

Neurochemistry

There are no formal pharmacodynamic studies evaluating the effects of MDPV in humans.

Based on rodent models, Baumann et al. [95] demonstrated MDPV (NET uptake IC_{50} 26 ± 8 nM, NET release EC_{50} 13 ± 16 nM, DAT uptake IC_{50} 4.1 ± 0.5 nM, DAT release EC_{50} 2.3 ± 0.8 nM) is a catecholamine-selective transporter blocker that displays greater potency than the prototypical transporter blocker cocaine (NET uptake IC_{50} 292 ± 34 nM, NET release EC_{50} 2190 ± 883 nM, DAT uptake IC_{50} 211 ± 19 nM, DAT release EC_{50} 151 ± 35 nM) particular at NET and DAT receptors, promoting in both

mechanisms the maintenance of dopamine and norepinephrine at the synaptic junction. MDPV is a potent uptake blocker at DAT and NET (50 and 10 times more potent than cocaine respectively), with weaker effects at SERT (10 times less potent than cocaine; MDPV SERT uptake IC_{50} 3349 ± 305 nM; SERT release EC_{50} inactive; cocaine SERT uptake IC_{50} 313 ± 17 nM; SERT release EC_{50} inactive).

Neurocytotoxicity

Only one study has assessed the potential for MDPV-related cytotoxicity. Simmler et al. [76] set up a cell membrane integrity assay using HEK-293 cells, which measures the release of adenylate kinase from damaged cells. Cell membrane integrity was maintained at concentrations of 10 μ M and 100 μ M after 4 h of incubation at 37 °C, suggesting that MDPV is not associated with cytotoxicity; however, more work is required to confirm these findings.

Central Behavior

Significant locomotor activity has been reported related to the stimulant MDPV effects [95, 105]. MDPV was 10 times more potent than cocaine in inducing motor hyperactivity tested as stereotypy (repeated interruption of the same photocell beam within 2 s) and forward locomotion (distance traveled in cm), measured for 1 h postinjection after subcutaneous administration of saline, MDPV 0.1–3.0 mg/kg or cocaine 3–17 mg/kg, twice a week while in the activity monitor. Stereotypy was significantly increased by administration of MDPV ($F[4,25] = 26.31$, $P < 0.0001$) and cocaine ($F[3,20] = 7.68$, $P < 0.001$). The threshold dose of MDPV capable of stimulating significant stereotypy is 0.3 mg/kg ($P < 0.05$, Newman–Keuls), while the threshold dose for cocaine was 3 mg/kg ($P < 0.05$, Newman–Keuls) [95]. Interestingly, MDPV produced time- and dose-dependent stimulation of locomotor activity in doses from 0.3 to 30 mg/kg. Stimulant effects of 1 and 3 mg/kg MDPV occurred within 10 min following injection and lasted 190 min. Following the 30 mg/kg dose, stimulant effects occurred after 80 min and lasted 300 min with a biphasic effect; activity depressed

between 10 and 50 min following injection. The ED_{50} values were calculated by estimating the dose producing half of the peak ambulation from the ascending linear portion of the generated dose response curve, MDPV (ED_{50} 1.26 ± 0.08 mg/kg) exceeded cocaine (ED_{50} 7.24 ± 0.14 mg/kg). There was full drug substitution in cocaine-trained rats (ED_{50} MDPV 0.68 mg/kg; ED_{50} cocaine 3.09 mg/kg) and methamphetamine-trained rats (ED_{50} MDPV 0.67 mg/kg; ED_{50} methamphetamine 0.37 mg/kg) [98, 105].

A number of in vivo animal studies have investigated the abuse potential of MDPV using models involving self-administration, intracranial self-stimulation, discrimination, substitution, and taste aversion. In a self-administration study in twenty-four male Wistar rats, MDPV was compared to methamphetamine [47]. The rats went through four sequential phases: lever-press training, drug self-administration acquisition (once daily 1 h self-administration sessions for 10 days, with a drug infusion of 0.05 mg/kg over the 1 h session), fixed-ratio dose response testing, and progressive-ratio dose response testing. Rats readily self-administered MDPV or methamphetamine at a per-infusion dose of 0.05 mg/kg on a fixed-ratio schedule of reinforcement with lever presses consistently favoring the drug-paired lever. Over seven nonfood-restricted sessions, the infusion rate of MDPV ($M = 19$; $SD = 22$; $Max-Min = 115-0$) was consistently higher than that of methamphetamine ($M = 8$; $SD = 7$; $Max-Min = 23-0$), while lever discrimination was similar for both MDPV ($M = 86\%$; $SD = 22\%$; $Max-Min = 100-8\%$) and methamphetamine ($M = 83\%$; $SD = 14\%$; $Max-Min = 100-33\%$).

Furthermore, the abuse potential of MDPV was studied [106]. Sprague-Dawley rats ($n = 48$) were trained to intravenously self-administer drugs every day for 10 days and were divided into four groups which self-administered two hour infusions of MDPV 0.05 , 0.1 , or 0.2 mg/kg or methamphetamine 0.05 mg/kg as a positive control. Self-administration of MDPV was maintained at all three doses. Also, MDPV administration ($F[4,35] = 11.549$, $p < 0.001$) at all tested doses compared to vehicle ($p < 0.05$)

significantly lowered thresholds of intracranial self-stimulation (ICSS) and has been noted elsewhere [107]. These findings may foreshadow compulsive consumption in humans and significant rewarding effects.

Cardiovascular

Pitcher et al. [108] demonstrated dose-dependent increases in heart rate (150%) in *Daphnia magna* (freshwater flea) with equimolar concentrations of synthetic cathinones including MDPV (combined EC_{50} of $1.9 \mu\text{M}$); tachycardic effects were alleviated with both calcium-channel blockers diltiazem and verapamil. Cardiovascular parameters were studied in four rats using telemetry transmitters inserted into the aorta to measure heart rate and blood pressure; subcutaneous doses of MDPV ($0.1-3.0$ mg/kg) were compared to cocaine ($3-17$ mg/kg) and saline control. MDPV administration was associated with tachycardia ($F[4,25] = 32.61$, $p < 0.0001$) and hypertension ($F[4,25] = 3.05$, $p < 0.05$). The peak increase in heart rate associated with MDPV administration was significantly greater with cocaine administration (3.0 mg/kg MDPV vs. 10 mg/kg cocaine, $p < 0.01$) [99] (raw data values not shown).

Thermoregulation

As is the case with mephedrone, the development of hyperthermic effects was not observed under all experimental paradigms. Doses of MDPV ($1-30$ mg/kg) did not increase core temperature in mice compared with saline controls at 20°C ambient temperatures. In contrast, at 28°C , a 10 mg/kg dose of MDPV resulted in a mild temperature rise in mice ($\sim 2^\circ\text{C}$, 10 mg/kg) compared with a similar dose of MDMA ($\sim 6^\circ\text{C}$, 10 mg/kg) [98]. Another study has reproduced a similar result, MDPV effect on temperature was only modestly hyperthermic in male Wistar rats housed in humidity and temperature-controlled environment ($23 \pm 1^\circ\text{C}$); it was higher after MDPV injections of 1.0 mg/kg than after 5.6 mg/kg by the end of the session (180 min postinjection time bin) (raw data values not shown) demonstrating a trend towards hypothermic response at higher ranges. Area-under-the-curve (AUC) measures (summed deviations from the mean of the vehicle

condition) were determined for locomotor activity (represents counts per minute of changes in signal strength from the radiotelemetry transmitter) and body temperature for MDPV and d-methamphetamine. The AUC for body temperature was higher for d-methamphetamine than for MDPV following the 5.6 mg/kg dose but not for the 1.0 mg/kg dose even though the AUC data for activity was significantly higher for MDPV than d-methamphetamine for the 5.6 mg/kg dose but not for the 1.0 mg/kg dose [75]. It would appear that methamphetamine and MDMA elicit greater hyperthermia responses in rats than MDPV alone.

Clinical Presentation

Human Data on Acute Toxicity

Information regarding clinical toxicity of mephedrone is synthesized from reports to drug user forums, calls to regional/national poisons information services, single case reports, and case series. The main limitation of many of these reports or studies is lack of analytical confirmation of substances taken and/or the presence of coingestants (including alcohol) that may be contributing to the clinical symptoms and signs. However, combination of these different data sources, through a process known as data triangulation, builds a more robust picture of the acute toxicity of each individual NPS [109].

Mephedrone

User Reports

Information posted on drug user forums indicates a plethora of positive and negative effects, with cathinones often compared to MDMA, amphetamine, and/or cocaine. Positive effects include feelings of empathy, increased energy, improved libido, alertness, euphoria, and better appreciation of music [110]. In the 2012 MixMag survey [111] which involved 7,700 UK respondents, users of mephedrone, cocaine, and MDMA (number not specified) were asked to rate the frequency with

which they experienced certain negative effects associated with mephedrone use: teeth grinding (52%), depression (41%), extreme sweating (36%), overheating (26%), memory loss (24%), agitation (23%), paranoia (17%), severe headache (12%), numb fingers (12%), hallucinations (11%), severe nausea (11%), chest pain (10%), severe tremors (10%), and aggression (4%).

Poisons Information Service Data

The first published data on enquiries to poisons information services was of 150 calls to the Swedish Poisons Centre relating to cathinones, of which two thirds related to mephedrone. The unwanted clinical features were reported as tachycardia (54%), restlessness (37%), mydriasis (25%), hypertension (14%), and anxiety (14%) [112].

The first enquiry to the UK National Poisons Information Service related to mephedrone use was in May 2009. In 131 calls relating to self-reported use of mephedrone or combined mephedrone/alcohol use, the range of unwanted effects reported have been summarized in Table 5 [113]. The frequency of unwanted effects was agitation/aggression (24%), tachycardia (22%), anxiety (15%), confusion or psychosis (14%), chest pain (13%), palpitations (11%), and nausea (11%). Less frequent effects (<10% of enquiries) included dizziness, abdominal pain, mottling of extremities, skin changes/rash, fever, sweating, headache, insomnia, convulsions, myoclonus, and reduced level of consciousness.

Emergency Department Case Reports and Case Series

There have been numerous case reports involving mephedrone; we have used illustrative examples from the published literature to highlight the reported toxicity associated with the use of mephedrone. The first case report of mephedrone use was in a male who used mephedrone by both oral ingestion and intramuscular injection and

Table 5 Adverse events associated with mephedrone use

Physiological system	Adverse events
Cardiovascular	Palpitations, tachycardia, arrhythmias hypertension, hot flushes, Dilated pupils, blurred vision
Neurological	Headaches, light-headedness, dizziness, tremors, convulsions, loss of concentration, memory loss, fatigue, loss of appetite
Psychiatric	Agitation, aggression, paranoia, hallucinations, insomnia, nightmares, anxiety, dysphoria, (post-use) depression, craving, addiction, dependence
Thermoregulation	Variable
Gastro-intestinal	Sore mouth/throat, abdominal pain, nausea, vomiting.
Musculoskeletal	Bruxism (teeth grinding), painful joints.
Respiratory	Nasal irritation, epistaxis, chest pain, respiratory difficulties.
Skin	Skin rash, sweating. Discoloration of extremities

developed symptoms consistent with acute sympathomimetic toxicity (mephedrone concentration in a serum sample was 0.15 mg/l, no other drugs or alcohol were detected) [114]. This has been confirmed in other case reports [115]. There have been specific cardiovascular events such as myocarditis (drug product tested only) [116] and sudden deaths in young people [117]. The following cases do not provide analytical confirmation of mephedrone use but describe other adverse effects out of keeping with simple sympathomimetic toxicity. *Reversible dilated cardiomyopathy*

is described in a 27-year-old male following inhalation and intravenous injection of mephedrone/MDPV a few hours before presentation [118]. Cardiogenic shock ensued; an echocardiogram showed dilated cardiomyopathy with an ejection fraction (EF) of 15–20% and global hypokinesia; this was treated with low dose norepinephrine intravenous infusion for approximately 6 h. At a 20-week follow-up, a repeat echocardiogram showed the EF had improved to 52% with little hypokinesia. A 33-year-old male presented with *methaemoglobinaemia* and symptomatic cyanosis

(SaO₂ 90%, PO₂ 10.4 kPa, MetHb >25% with FiO₂ 21%) after self-reported use of 1 g of “snow” by nasal insufflation (this was believed to be mephedrone by the authors). He was treated with high flow oxygen, improved and was discharged 8 h postarrival. Methylene blue was not used [119]. A 23-year-old male with severe central chest pain and subcutaneous emphysema with self-reported use of inhaled mephedrone 26 h before presentation; a chest x-ray demonstrated a *pneumomediastinum*, but there was no evidence of pneumothorax or esophageal perforation on CT scanning [120]. He was managed conservatively with medical management. There has been another reported case of subcutaneous emphysema related to mephedrone use [121]. A 25-year-old male presented with worsening severe bilateral loin pain with self-reported mephedrone, methamphetamine, diazepam, and cocaine use over a 3-day drug binge. He was diagnosed with *acute kidney injury* (creatinine 654 μ mol/l (8.58 mg/dl), potassium 4.7 mmol/l, bicarbonate 16 mmol/l, creatinine kinase [CK] 1183 iU/l). Renal ultrasound was normal, although a CT angiogram demonstrated diffuse swelling of both kidneys with no evidence of renal infarction. Despite initial medical management, his renal function continued to worsen and he required two sessions of hemodialysis (at day 5 of admission) and subsequently his renal function recovered [122]. A 25-year-old man was admitted with paracetamol overdose requiring NAC infusion, also reported coingestion of 3–4 g of mephedrone. Sixteen hours postingestion he developed *urinary retention*, the urinary catheter was removed 24 h later [123]. A 19-year-old female from Ireland was admitted with alcohol-induced pancreatitis. She had a background of excessive alcohol intake and recurrent pancreatitis. Upon admission she was placed on supportive care, antibiotics, chlordiazepoxide, and multivitamins (amylase 2577 iU/L). On the second day of her admission she had a witnessed convulsive seizure lasting 4 min. There was no focal neurology post event, however, noted to be hypertensive (systolic blood pressure 160 mmHg) and went on to develop subsequent seizures to be treated with levetiracetam. She admitted to snorting

mephedrone prior to admission. An initial CT suggested acute posterior cerebral edema and an urgent MRI brain showed subcortical hyperintensities consistent with a diagnosis of *posterior reversible encephalopathy syndrome* (PRES). She was treated with an intravenous infusion of 1 g/h magnesium sulfate and intravenous labetalol. Magnetic resonance imaging (MRI) 10 days later showed complete resolution of the radiological features [124]. A 22-year-old male presented with tachycardia, profuse sweating, dilated pupils, resting tremor, generalized hyperreflexia, and inducible clonus and was diagnosed with *serotonin syndrome*. The patient had taken 40 capsules from two bags over a 4-h period – a plastic bag labeled “Plant Food” and a brown paper bag labeled “Red Doves” – along with his regular dose of fluoxetine (40 mg) and olanzapine (10 mg). His signs resolved with general supportive care, intravenous fluids, and oral diazepam [103].

A 6-month case series of twenty patients presenting to emergency departments and acute mental health services in Scotland with self-reported mephedrone use identified main adverse effects of severe agitation (70%), psychosis either visual, auditory or tactile (40%), and suicidal ideation (20%) [125]. Up to one in five persons may suffer an unwanted adverse effects [126], but this has been reported to be as high as 56% in various subpopulation surveys [27].

We have previously reported a case series of 72 patients who presented to a Central London emergency department with acute drug toxicity following self-reported use of mephedrone use between January 2009 and June 2010 [127, 128]. The majority of patients were male (89.9%) (mean age 27.8 ± 8.7 years, range 16–54). The main adverse effects documented included agitation (38.9%), palpitations (25%), vomiting (13.9%), chest pain (12.5%), headache (7.2%), and prehospital seizures (6.9%). Additionally, 13.9% had significant hypertension (defined as a systolic blood pressure ≥ 160 mmHg) and tachycardia (defined as a heart rate ≥ 140 mmHg). There were no cases of hyperpyrexia reported (although it should be noted that these cases were collected during the autumn/

winter when hyperpyrexia is less likely to occur due to the cooler ambient air temperature).

There is a second published UK case series of 89 patients who presented to an emergency department in Scotland [115]. Data was reported in detail on the 57 patients with self-reported lone ($n = 30$) or mephedrone and alcohol ($n = 27$) use. Commonly reported clinical features were anxiety or agitation (40.4%), chest pain (24.6%), paresthesiae (24.6%), palpitations (21.1%), dyspnea (17.5%), confusion (14%), collapse (14%), and nondefined oral symptoms (12.3%). As only a range of heart rate and blood pressure were reported, 64–184 bpm and 88–184 mmHg, so while some patients had potentially clinically significant hypertension and tachycardia, it is not possible to determine the frequency of these.

Analytically Confirmed Case Reports

Nonfatal Intoxications

From the previously described case series in London, blood samples were collected for toxicological analysis for mephedrone and/or other drugs [127]. In seven out of nine patients who underwent toxicological analysis for recreational drugs, mephedrone was detected (the remaining two were late presenters at more than 24 h since use); three had other substances detected, including cocaine ($n = 2$) and butylone/MDPV ($n = 1$). Mephedrone was the only drug in 4 and the highest mephedrone concentration in this group was 0.33 mg/L. The most common clinical feature on presentation was agitation ($n = 4$, 57.1%) followed by palpitations ($n = 2$, 28.6%), chest pain ($n = 2$, 28.6%), self-limiting prehospital seizure ($n = 1$, 14.3%), and headache ($n = 1$, 14.3%). Four (57.1%) patients were discharged home from the emergency department/short stay observation unit, two (28.6%) were admitted to general internal medicine ward, and one (14.3%) to the intensive care unit. Overall, six (85.7%) patients survived to discharge from hospital with no long-term sequelae on discharge. The overall mean length of stay following presentation to hospital of those who survived was 12.0 ± 10.3 (range 3.4–26.3) hours. Those

admitted to short stay observation unit required minimal treatment aimed at symptom control (e.g., antiemetics, intravenous fluids). Three (42.9%) patients required the use of benzodiazepines (oral or intravenous) for the management of agitation. One patient died, and this case is discussed below in greater detail.

Mephedrone-Related Deaths

European member states were asked to report to the EMCDDA regarding number of deaths relating to mephedrone use at the time of the European Risk Assessment of mephedrone in 2010 [60]. The UK and Sweden provided cases directly related to mephedrone use with the UK being the only country to provide cases with analytical confirmation at the time of the report. While there were some case reports in the media in other EU nations including Greece and Romania, these countries did not include mephedrone within analytical libraries, and so it was not possible to determine whether it had been implicated in reported deaths. These cases/case series of fatalities from Sweden and UK are listed below.

The first reported death from mephedrone was that of an 18-year-old girl in Sweden who suffered an out of hospital cardiorespiratory arrest, with cerebral edema and marked hyponatremia (120 mmol/L). It is unclear from the reported details whether the cause of the hyponatremia was investigated further [117].

The National Programme on Substance Abuse Deaths (NPSAD) reviewed drug-related deaths in the United Kingdom, the Channel Islands, Isle of Man, Scottish Crime and Drug Enforcement Agency, and the General Register Office for Northern Ireland and identified 128 alleged mephedrone-associated fatalities. Of these, 90 had postmortem confirmation of mephedrone at the time of the report and inquests had been concluded in 69 cases. The mean age of decedents was 28.8 (SD, 11.3) years (range, 14–64 years). Mephedrone was formally included in the cause of death in 36 cases but was only confirmed in eight cases as the sole drug in antemortem/postmortem analysis. Coingestants in other cases

included alcohol ($n = 26$), stimulants [22], sedative/hypnotics [22], opiates/opioids [13], piperazines [13], and remaining synthetic cathinones [13], antidepressants [8], and antipsychotics [5, 129]. A further literature review was conducted by members of the NPSAD group analyzing mephedrone intoxication and subsequent fatality specifically in 16- to 24-year-olds in the UK between 2009 and 2013 [130]. Thirty cases were identified of which the majority were male ($n = 22$, 73%), all had white ethnicity when known (27/30 cases, 90%), half were employed (12/24 cases, 50%), and most (11/13 cases, 85%) had a history of drug use. Approximately half (14/30 cases, 47%) died in a defined residential address (own home or that of a friend/relative) and one quarter (8/30 cases, 27%) in the hospital. Two thirds ($n = 23$, 63%) were accidental poisonings. Other substances were implicated in 60% of deaths; the most common in descending frequency were alcohol, benzodiazepines, piperazines, cocaine, opiates/opioids, amphetamine, and "ecstasy." Postmortem mephedrone blood concentrations were available in 17/30 cases; mephedrone was the only substance detected postmortem in four cases; however, only two of these cases reported blood concentrations (0.190 and 3.300 mg/L; mean 1.745 mg/L). There were eight cases where mephedrone was felt to be solely implicated as cause of death; however, multiple other substances were identified. Six of these cases had recorded concentrations of mephedrone; mean concentration of drug was 1.372 (range 0.070–2.240) mg/L. Finally, the mean concentration of mephedrone in cases where mephedrone was implicated *with* other substances ($n = 9$) as cause of death was expectedly lower, 0.518 (range 0.002 to < 2.000) mg/L.

The only recorded fatality from the London Emergency Department case series [127] involved a 29-year-old male who collapsed in a night club. On arrival in the emergency department, he had a fluctuating conscious level. A CT head scan showed evidence of significant cerebral edema and impending tonsillar herniation. He had hyponatremia ($[Na^+]$ 125 mmol/L); further biochemical testing suggested water intoxication. Following a seizure he deteriorated

further and a repeat CT scan showed tonsillar herniation and so treatment was withdrawn. Antemortem toxicological screening confirmed the presence of mephedrone at a concentration of less than 0.01 mg/L in serum; analysis of powder found with the patient also confirmed the presence of mephedrone. No other recreational drugs were detected on an extended screen of both the powder and biological samples from the patient.

A fatality related to mephedrone use has been reported in another case report from Sweden. A 36-year-old man was arrested by police with acute behavioral disturbance and with self-inflicted wounds obtained by smashing windows. Shortly after the intravenous administration of midazolam and naloxone by medical personnel he had a cardio-respiratory arrest and resuscitation attempts with advanced life support, adrenaline and atropine were unsuccessful. Toxicological analyses as part of the autopsy revealed tablets seized at home contained mephedrone (96 seized at residence, approximately 140 mg per tablet as the hydrochloride) and trace caffeine; further white powder containing cocaine was also seized. Femoral blood was positive for mephedrone (5.1 mg/L) as well as urine (186 mg/L) and stomach contents (1.04 g/L). The coroner concluded the combination of self-inflicted violence had led to substantial blood loss which may have aggravated the sympathomimetic toxicity and severe agitation which was described as a "fatal excited delirium" [131].

A case report from the USA described of a 22-year-old male found collapsed and unresponsive in his living quarters is described. He was unsuccessfully resuscitated in hospital. Urine screening by gas chromatography coupled with mass spectrometry (GC-MS) was positive for 6-acetylmorphine, codeine, morphine, doxylamine, and mephedrone (198 mg/L). Mephedrone was also detected in postmortem blood (0.5 mg/L). The cause of death was recorded as "accidental multiple drug toxicity." A urine sample from a roommate (who confirmed that both he and the deceased had used mephedrone by nasal insufflation, oral ingestion, and intravenous injection) was positive for mephedrone at a concentration of 28.1 mg/L [132].

Busardò et al. performed a literature review in May 2015 and discerned 18 publications regarding deaths with confirmation of mephedrone in post-mortem biological sample(s) [133]. Fourteen cases were male, two were female, and gender was not reported in two cases. Two of the cases within this review have been discussed above to highlight circumstances surrounding some of the deaths [131, 132]. The average age of the decedents was 27.8 years (range: 17–55). Death was attributed to mephedrone intoxication in nine cases (range of mephedrone concentrations: 1.33–22 mg/L), whereas multiple drug toxicity, involving mephedrone was cited as cause of death in six cases (range: 0.04–1.3 mg/L). Coingestants included heroin, MDMA, methadone, benzodiazepines, cocaine, alcohol, and GHB. Implicated contributing factors to final death included a fatal car accident, underlying cardiac fibrosis and atherosclerotic coronary artery disease and severe blood loss from multiple wounds. The authors postulated that mephedrone may have a narrow therapeutic window given blood concentrations detected were similar to those associated with nonfatal recreational use cases.

In general, many case reports/series of cathinones additional detected substances may cloud attribution of clinical features to one recreational drug/class alone and these same problems have been noted in other fatalities [134, 135]. This should alert the clinician to anticipate the presence of other substances when caring for patients with acute recreational drug toxicity. In some instances, these can act synergistically to heighten the anticipated neurotoxic effects as has been seen in rodent models tested with combined use of methamphetamine and mephedrone [90].

MDPV

User Reports

Positive effects as reported on user forums include positive stimulation (mental and physical), euphoria, increased sociability, productivity and motivation, increased mental clarity and creativity, feelings of empathy, and sexual arousal. Negative effects described include trismus, bruxism, anhedonia, loss of appetite, disturbed sleep patterns,

involuntary body movements, confusion, gastrointestinal disturbance, muscle tension and headache, depressed mood, paranoia and anxiety, psychoses and hallucinations, nystagmus, harsh comedown, a process of fiending (re-dosing repeatedly without planning to do so), and excessive agitation and hyperactivity [136].

Poisons Information Service Data

Two US poison centers reported a retrospective case series of patients with exposures to bath salts over January 2010 to February 2011. There were 236 patients, of which 184 were male (78%). Age range was 16–64 years (mean 29 years, SD 9.4). All cases were intentional recreational use. Clinical effects were primarily neurological and cardiovascular and included agitation (194 cases, 82.2%), combative behavior (134, 56.8%), tachycardia (132, 55.9%), hallucinations (94, 39.8%), paranoia (86, 36.4%), confusion (83, 35.2%), myoclonus (45, 19.1%), hypertension (41, 17.3%), chest pain (40, 16.9%), mydriasis (31, 13.1%), creatinine phosphokinase elevations (22, 9.3%), hypokalemia (10, 4.2%), blurred vision (7, 3%), and catatonia (1, 0.4%). There was one death (discussed below). Therapies were primarily sedation and treatment for persistent myoclonus and included the benzodiazepines diazepam, lorazepam, and/or midazolam (125 cases, 53%); the antipsychotics haloperidol and ziprasidone (47, 20%); propofol (10, 4%); and diphenhydramine (2, 1%). The dispositions of patients were: 116 (49%) discharged from the emergency department, 50 (21%) admitted to a critical care unit, 29 (12%) admitted to psychiatric facility, 28 (12%) were lost to follow-up, and 13 (6%) were managed at a nonhealthcare facility. MDPV was detected in the blood/serum of 13 of 17 patients (range 24–241 ng/mL, mean 58 ng/mL) by GC/MS; four samples had no drug detected, but all of these reported last use of bath salts more than 20 h prior to presentation. Three of five patients had MDPV detected in urine (range 34–1386 ng/mL, mean 856 ng/mL). No other cathinones were detected in the tested cohort; no other drugs screen results were recorded [45].

A retrospective review of self-reported synthetic cathinone use was conducted at a poisons

information center in Paris over a 2-year period (2011–2012). Twenty-one cases were identified. Analytical confirmation was performed in only four cases; MDPV metabolites ($n = 2$), methylone ($n = 1$), and alpha-pyrrolidinovallero-phenone (α PVP) ($n = 1$) [137]. Users were mostly men ($n = 20$), with mean age of 38 years (26–53 years). Interestingly, synthetic cathinones were most commonly administered by intravenous injection ($n = 15$, 71%), particularly among the MSM community attending gay sex parties. Fourteen cases presented with psychiatric disorders: psychotic symptoms (52%), agitation (38%), anxiety (33%), suicidal ideas (24%) or attempt (9.5%), and acute satyriasis (9.5%); hence the main reasons for hospital admission were both psychiatric and addiction disorders (62%). Somatic complications were described in 11 cases and included headache (4.8%), tachycardia (14.3%), confusional states (14.3%), rhabdomyolysis (9.5%), with renal failure or serotonin syndrome (4.8%).

A retrospective review of Carolinas Poison Center records was performed regarding “bath salts” or “plant food” exposure from January 2010 to December 2011. Of the 486 calls, 409 cases reported human exposures of which 277 were male (67.7%) with mean age of 28.8 years (21 months–68 years range). The most common clinical effects reported were tachycardia (218 cases, 53.3%), agitated/irritable (206, 50.4%), hallucination and/or delusions (109, 26.7%), and hypertension (103, 25.2%). Three cases involved MDPV use and this was analytically confirmed; there were two associated deaths [138].

Forensic Data from Traffic Offenses

An alternative source of data includes forensic traffic studies regarding drivers arrested for driving under the influence of drugs (DUID). A study from Denmark in 2011 [139] addressed the detection of novel recreational drugs in a cohort of 1,791 cases. Of these 1,335 cases were tested and police revealed 992 cases (74%) were positive for one or more traffic-relevant drugs above the Danish legal limits. Amphetamine and cocaine were most frequently detected (in 383 (28.3%)

and 335 (25.1%) samples, respectively) as well as various benzodiazepines. Nineteen less common drugs were detected: buprenorphine ($n = 7$), butylone ($n = 2$), cathine ($n = 10$), fentanyl ($n = 5$), lysergic acid diethylamide ($n = 1$), *m*-chlorophenylpiperazine, MDPV ($n = 3$), mephedrone ($n = 3$), 4'-methylamphetamine ($n = 3$), *p*-fluoroamphetamine ($n = 5$), and *p*-methoxy-*N*-methylamphetamine. In another report from Finland [140], data was presented on drivers arrested for DUID in 2010 (it is likely that some individuals were included in both this paper and the paper described above as there is overlap between the study periods). A total of 4532 samples were analyzed and 219 (4.8%) were found to contain MDPV at a median concentration of 0.06 mg/L (maximum concentration 8.4 mg/L). Of the MDPV-positive cases, most were male (89%), and MDPV was co-detected with amphetamine (79%) and benzodiazepines (76%); this combination was seen in 63% of the MDPV-positive cases.

Emergency Department Case Reports and Case Series

The first report on the possible use of MDPV appeared in 2007 [141]. Subsequently, there have been many published cases regarding associated complications of MDPV use. Like mephedrone, these vary from organ-specific complications to complete multisystem failure. We have used illustrative examples from the published literature to highlight the reported toxicity associated with the use of MDPV, the spectrum of complications and subsequent management strategies. A 26-year-old man presented with nasal insufflation of 12 g of bath salts, believed to be MDPV, daily for 7 days. On first presentation he displayed stimulant toxicity (described as agitated, confused, tachycardic, and hypertensive) but these settled with antipsychotics (not specified). Admission CK was 2,700 iU/L which increased to 6,013 iU/L with a creatinine of 194.4 micromol/L (2.2 mg/dL) (timing of this result within the 3-day admission was unspecified). The *acute kidney injury* (AKI) was treated conservatively with intravenous fluids for 24 h and he was discharged home on day 3. He

represented 5 days later post a further binge; creatinine peaked to 406.6 micromol/L (4.6 mg/dL) on day 3 of the second admission. Renal ultrasound showed normal-sized kidneys with no obstruction, and urinalysis was positive for protein only. Intravenous normal saline (0.9% sodium chloride) solution was administered for approximately 72 h. AKI was thought to be most likely due to acute tubular necrosis. Urine and serum drug screen results were negative but actual techniques are not described [142].

A case series described four patients with severe cardiopulmonary and neurologic effects. Two 32-year-old women presented to the emergency department shortly after insufflating bath salts. Both complained of palpitations, chest pressure, and dyspnea. One demonstrated *parkinsonian-type features* including resting tremor and bradykinesia as well as ECG changes. Both had positive urine MDPV at concentrations of 0.1 mcg/mL and 0.52 mcg/mL, respectively. The third patient was a 35-year-old man who presented to the emergency department complaining of a rapid heart rate and shortness of breath after snorting bath salts. His urine was positive for MDPV with a level of less than 0.05 mcg/mL [143]. The remaining case resulted in suicide which is referred to below.

The STRIDA project conducted by the Swedish Poisons Information Centre (SPC) and the Karolinska University Laboratory cooperates in monitoring national trends in acute poisonings with novel psychoactive agents [144]. In the first 9 months of 2012, prospective analysis for MDPV in suspected cases in blood/urine led to detection of 86 positive samples. In 17 of these cases symptoms were severe (Poisoning Severity Score 3). Symptoms/signs ranged from excessive agitation, psychosis, sympathetic stimulation (hyperthermia, hypertension, tachycardia), myocardial infarction, rhabdomyolysis, and renal failure. A few patients required prolonged sedative therapy (several days, no further details given). Lindeman et al. (most likely report on a subset of data highlighted in the case series by Bäckberg et al.) [145] conducted a retrospective study of a nonrandomized subset of patients that presented to a hospital with suspected MDPV outbreak

between April and May 2012 in Västerås, Sweden (population 110,000). Forty-five patients were identified with stimulant toxicity (MDPV was suspected in 82% of cases in 2012) and the number of patients treated in intensive care rose from a total of 2 in 2010–11 to 10 in 2012, and the number of intensive care unit (ICU) days from 2 to 45. Seventeen of the 45 patients underwent liquid chromatography (LC)-MS/MS analysis of which 13 (76%) tested positive for MDPV. Sixty percent of the 95% of patients with suspected/confirmed MDPV use were chronic drug users and Hepatitis C virus positive.

A study was conducted using data supplied to the Pavia Poison Centre (PPC) from Emergency Departments in Italy [146]. All consecutive cases were referred to the PPC (January 2010–October 2011) for suspected/confirmed substances of new recreational drug poisoning and analysis. In 52/192 (27%) new recreational drugs of abuse (NeDA) were declared; 7 per cent of patients were unable to report the substances taken. Ethanol intoxication and body packers were excluded. The most common clinical manifestations were agitation (42%), tachycardia (37%), coma (22%), mydriasis (19%), gastrointestinal discomfort (18%), and hallucinations (14%); two fatal cases were registered. Laboratory investigations were performed in 94% of cases (181/192); 70% of biological samples/products were delivered to PPC. The NeDA identified were: MDMA ($n = 25$), synthetic-cannabinoids ($n = 17$), ketamine ($n = 16$), GHB/GBL ($n = 6$), caffeine ($n = 6$), atropine-scopolamine ($n = 6$), butylone ($n = 2$), MDPV ($n = 1$), harmine/dimethyltryptamine ($n = 1$), methylenedioxymphetamine (MDA) ($n = 1$), and 4-Methylethcathinone (4-MEC) ($n = 1$).

There were 524 nonfatal intoxications (of note, Sweden reported 487 of these cases) associated with MDPV use reported by Member States to the EMCDDA at the time of the European Risk Assessment of MDPV in 2014 [71]. Of these, six Member States have reported a total of 110 analytically confirmed cases: Sweden [98], Italy [3], France [4], Belgium [2], Greece [1], and Ireland [1]. In Belgium, MDPV as well as traces of cocaine and amphetamines was detected in the

urine samples (not quantified) of two patients. They both reported visual and auditory hallucinations, paranoia, and were aggressive. They were treated with antipsychotics and their status returned to normal after 3–4 days. France reported four analytically confirmed cases. In one case, police brought a man to the emergency department with an acute delirium (agitation, hallucinations) as well as rhabdomyolysis, tachycardia, hypotension, and acute renal failure; cannabis and pyrovalerone were detected. In the second case, a patient suffered paranoid psychosis post nasal and oral use of MDPV. The clinical features reported were tachycardia, mydriasis, hypertension, agitation, profuse sweating, tremor, and rhabdomyolysis. MDPV (366 ng/mL) and methylone (4400 ng/mL) were detected. The third case was similar to this. Finally, a 39-year-old male presented to hospital after injecting MDPV and using 4-MEC (route not specified). He had abnormal movements, trismus, profuse sweating, visual disorders, insomnia, anorexia, and vertigo. He also reported dysuria, which lasted 24 h; no further details were reported. Greece reported a case of a 47-year-old male who was intubated after sudden loss of consciousness soon after oral consumption of MDPV. He was admitted to the ICU and treated for subsequent multiorgan failure. MDPV was confirmed in his urine. Ireland reported a case of young man who presented with acute psychosis and subsequently developed hepatic failure following ingestion of butylone and MDPV. Further details are described below, taken from the academic study that was performed in this case. Italy reported three analytically confirmed nonfatal intoxications. A 20-year-old male was admitted to hospital very agitated with tachycardia (heart rate 115 bpm). MDPV was found in urine (14 mg/L) and butylone (concentration not reported). The patient was treated with benzodiazepines and discharged 2 days later. The second case, a 38-years-old male, presented at the emergency department with agitation, mild tachycardia (HR 105 bpm), and visual/auditory hallucinations. MDPV was detected in blood (12 mg/L) and urine (17 mg/L). The final case, a 27-year-old male suffering from agitation, confusion, and anxiety, was taken to hospital by his father. The

patient reported having taken intravenous MDPV for last 3–4 days and benzodiazepines. Analysis of the patient's urine revealed MDPV (55 µg/L), alprazolam (113.79 µg/L), and hydroxylalprazolam (103.59 µg/L).

A retrospective multicenter case series of patients with synthetic cathinone abuse was conducted using the national clinical toxicology database (Toxic) in the USA. Twenty-three cases fit inclusion criteria and had MDPV detected in either blood or urine. Eighty-three percent were male and 74% had used it recreationally. The most common route was nasal insufflation (8 cases, 34.8%), although there were patients who ingested (3, 13%), injected (2, 8.7%), or inhaled MDPV (2, 8.7%) as well. The most common reported clinical effects were tachycardia (74%), agitation (65%), and sympathomimetic syndrome (65%). Nine (39.1%) patients had a heart rate >140 bpm, five (21.7%) had a systolic blood pressure between 161 and 180 mmHg, four had a diastolic blood pressure >100 mmHg, and two (8.6%) had a temperature >38.9 °C. The toxidromes noted included sympathomimetic (15 patients, 65.2%), sedative (3, 8.7%), anticholinergic (1, 4.3%), and unknown (5, 17.4%). Within the first 4 h of presentation, 19 of the patients received benzodiazepine therapy which included lorazepam (13 patients), lorazepam and midazolam [4], midazolam [1], or diazepam [1]. Five patients treated with antipsychotic (haloperidol 4 patients, dose range 2.5–5 mg; 1 patient ziprasidone 20 mg). Five patients were given a paralytic. Vecuronium or rocuronium were both used in two patients, and succinylcholine was given in one patient. One patient who was treated with a paralytic and was not treated with benzodiazepines received propofol and etomidate. None of the patients treated with a paralytic were treated with an antipsychotic. Complications reported included myocardial infarction (3 patients, 13%) and intubation (7, 30.4%); there were no reported seizures or stroke. Cardiac arrhythmia (excluding sinus tachycardia) included bradycardia (2, 8.7%) and supraventricular tachycardia (1, 4.3%). Twenty patients were admitted to Intensive Care (87%). Of those admitted, six had quantitative concentrations of

MDPV – blood concentrations varied from <10 to 89 ng/mL. Urine concentrations varied from 120 ng/mL to 3100 ng/mL. Median hospital stay of 2 days (range 0–20), and ICU length of stay of 1 day (range 1–12). Final disposition was home in 14 patients (60.9%), psychiatric unit (7, 30.4%), jail (1, 4.3%), and death (1, 4.3%) [147].

Further severe cases of multiorgan involvement and recovery as well as specific complications of serotonin syndrome and compartment syndrome have been reported. A 25-year-old man presented with unusual behavior, agitation, and essentially sympathomimetic syndrome (mydriasis, BP 148/66 mmHg, HR 175 beats/min, T 41.3 °C) injecting “bath salts.” He was intubated (Rapid Sequence Intubation drugs: midazolam 2 mg, etomidate 20 mg, and succinylcholine 120 mg) and actively cooled (application of ice packs to the axilla and cooling blankets). Over 2 days he developed multiorgan failure: acute kidney injury (creatinine 901.7 micromol/L, 10.2 mg/dL), fulminant hepatic failure (AST 16,688 U/L, ALT 9,085 U/L), disseminated intravascular coagulation (INR > 9.3, platelets 16,000/microL), and rhabdomyolysis (creatinine kinase 235,377 iU/L). He required continuous renal replacement therapy followed by hemodialysis because of anuric renal failure. He was extubated on hospital day 9, and his mental status normalized by hospital day 13. Length of hospital stay was 18 days. Urine from the day of admission tested positive for MDPV at a concentration of 140 ng/mL with high performance liquid chromatography/tandem mass spectrometry. [148].

A 37-year-old male with a history of a right nephrectomy (secondary to trauma) ingested an unknown quantity of “bath salts” approximately 4 h prior to seeking medical care. He was found with severe agitation and tachycardia (HR 153 beats per minute), tachypnea (RR 50 breaths per minute), and fever (T 39 °C). Initial tests included the following concentrations: sodium 165 mmol/L, chloride 114 mmol/L, CO₂ 18 mmol/L, creatinine 548 µmol/L (new, 6.2 mg/dL), and AST/ALT 863/514 IU/L, CK was 90,168 IU/L. He was intubated and sent to ICU and possibly extubated within 24 h later, although this is not clear. Approximately 12 h later, the

CK increased > 350,000 IU/L and he was started on hemodialysis and subsequently had necrotic muscle from the deep erectors which was resected. A urine drug screen via GC-MS confirmed the presence of caffeine, hydrocodone, MDPV, and propofol. Serum MDPV (via LC-MS/MS) 7 h after first seeking medical care was 120 ng/mL and 89 ng/mL after 10 h. Five months later, the patient remained in renal failure on hemodialysis [149].

A 41-year-old woman met Hunter Criteria for serotonin syndrome after use of bath salts for 2 days preadmission. She was intubated for active cooling. Serotonin syndrome was perhaps induced by in-hospital fentanyl use while unwell, which was ceased at recognition at 24–48 h. The patient had prolonged clinical effects in spite of cyproheptadine use (8 days) with return of clonus when the cyproheptadine was discontinued. After extubation, she admitted to taking bath salts by insufflation but denied coingestants or resumption of her previous alcohol abuse. Her urine MDPV concentration was 3,100 ng/mL (detection limit 100 ng/mL). The comprehensive drug panel result was positive for lorazepam, midazolam, acetaminophen, diphenhydramine, lidocaine, ibuprofen, zolpidem, caffeine, and nicotine. Lorazepam, midazolam, acetaminophen, and diphenhydramine were administered at the referral hospital. No documentation of lidocaine administration is available. No amphetamines, antidepressants, or other serotonergic agents were detected [150].

Lastly, there are many cases of neuropsychiatric complaints/severe agitation as well as suicidal/homicidal ideation [71]. A 19-year-old male presented to an ED in the USA with auditory and visual hallucinations which had begun several hours prior to his presentation and after smoking an Internet-purchased product; he stated that voices were urging him to kill unspecified people and someone was trying to steal his thoughts [151]. The psychosis resolved within 24 h in in-patient psychiatric unit, he was treated with promethazine and risperidone. A urine toxicology screen detected MDPV, caffeine, cotinine (nicotine metabolite), and promethazine. A 23-year-old male with prior psychiatric history was seen in the emergency department for bizarre behavior,

suicidal ideation, and hallucinations; he stated snakes were crawling on him and in his bed. He had insufflated 1 g of bath salts 30–60 min prior to presentation. He appeared diaphoretic with mydriasis with a mild tachycardia (BP 133/68, HR 109 bpm, temperature 36.9 °C, RR 21 with 100% oxygen saturations on room air). A total of 6 mg lorazepam and 2.4 mg of droperidol was given intravenously. He had a history of being prescribed various antipsychotics/benzodiazepines in the past (quetiapine, lithium, aripiprazole, valproic acid, and clonazepam). However, he had negative testing for lithium and valproic acid. His symptoms resolved 5 h post sedation. Serum and urine contained MDPV (186 ng/ml, 136 ng/ml, respectively), flephedrone (346 ng/ml, 257 ng/ml, respectively), and caffeine (387 ng/ml, 367 ng/ml, respectively) [152]. Various drugs have been used to treat similar symptoms including benzodiazepines, ketamine, haloperidol as well as chlorpromazine [152, 153].

MDPV-Related Deaths

There have been multiple reports of MDPV-associated fatalities – we refer the reader to EMCDDA and World Health Organization technical reports for MDPV for a complete discussion of cases with both analytical and nonanalytical confirmation [68, 71]. Below we have discussed representative fatal cases with more detailed discussion of the clinical course and cause(s) of death highlighted.

The first reported death in the literature involved a 40-year-old male who self-reported injection and snorting “bath salts” containing MDPV and suffered from the following complications: agitation, aggression, and PEA cardiac arrest with subsequent multiorgan failure due to hyperthermia (T 40.7 °C). Secondary rhabdomyolysis, coagulopathy, acidosis, and anoxic brain injury ensued. An electronic control device had been discharged prehospital on three occasions to overpower the patient by police on scene. Standard advanced cardiac life support measures were initiated. In spite of vasopressor therapy and intravenous fluid

resuscitation – dopamine (20 microgram/kg/min), phenylephrine (180 microgram/h), norepinephrine was started (4 microgram/min), intravenous normal saline (0.9% sodium chloride) solution (4 L), bicarbonate infusion, hydrocortisone (100 mg IV every 8 h), vasopressin infusion (0.04 units/min), hemofiltration for oliguric renal failure, and blood transfusion for symptomatic disseminated intravascular coagulation – he suffered multiorgan failure (potassium 8.0 mmol/L, creatinine 309 µmol/L (3.5 mg/dL), AST 869 iU/L, ALT 738 iU/L, INR 4.2, and creatinine kinase 14,839 iU/L) and died 42 h after his initial presentation. A number of agents were detected on toxicological analysis of patient sera: ethanol (11 mg/dL), salicylate (7.9 mg/dL), acetaminophen (2.9 mg/L), caffeine, cotinine, lidocaine, trimethoprim, and MDPV (urine 670 ng/mL and serum 82 ng/mL) [154].

At the time of the EMCDDA Risk Assessment of MDPV in 2014 a total of 108 deaths in which MDPV had been detected in postmortem biological samples and/or implicated in the cause of death were reported to the Early Warning System (EWS) between September 2009 and August 2013. The member states included Austria (1), Finland (39), France (1), Hungary (1), Ireland (8), Poland (3), Sweden (21), United Kingdom (31), and Norway (1). In addition, deaths have been reported in the scientific literature that occurred within the European Union (17 deaths although there may be overlap with EWS reports) and elsewhere, including the United States (32), and Japan (1). It is likely that other drugs and/or other medical comorbidities or trauma may have contributed to and/or been responsible for death. In the majority of these cases, MDPV was a coingestant with other controlled or novel psychoactive substances and it is hard to differentiate its contribution. Blood MDPV concentrations recorded in these cases ranged from < 0.1 µg/L to 4, 800 mg/L [71].

In April 2011, a 39-year-old man was found with odd behavior, delusional and wandering with minimal clothing. He self-reported “bath salt” use after police escort to the closest emergency

department. After an initial period of observation he became markedly agitated and tachycardic, transferred to ICU for sedation and intubation. He developed ventricular tachycardia, which was treated with amiodarone and defibrillation. Hyperthermia was noted with a peak temperature of 41.7 °C. Within minutes, the patient became bradycardic at 36 beats per minute and, despite atropine and electrocardiac pacing, proceeded to asystole. Further resuscitation efforts were unsuccessful, and he died approximately 12 h after presenting to the ED. Gross autopsy findings were unremarkable. The bile was positive for salicylates, diphenhydramine, MDPV, promethazine, diazepam, and nordiazepam. The heart blood contained 0.1 mg/L diphenhydramine, 0.2 mg/L promethazine, 0.1 mg/L nordiazepam, and 0.7 mg/L MDPV. The peripheral blood MDPV concentration was 1.0 mg/L. The authors concluded MDPV intoxication as the cause, consistent with MDPV-induced excited delirium state [155].

Equally, as observed in the media and reported in coroner case series, self-harm and at-risk behavior without good prior evidence of comorbid mental health illness has occurred including hangings, gunshots, and self-stabbing [156, 157]. A US case series of four patients had reported on one death involving MDPV use. The decedent, a 21-year-old female, was involved in a high-speed chase with the police. A friend of the decedent advised police that she had expressed suicidal ideations and left in her vehicle. During an attempt to retrieve the patient, she sped up to over 100 mph, struck a second car and then came to a stop on a bridge. The decedent was subsequently located in the river below the bridge. The deceased had a history of substance abuse and had been incarcerated several times. The cause of death was drowning, with multiple blunt force injuries listed as a secondary cause of death; the manner of death was accident. The postmortem heart blood analytical findings were: Methylone (0.06 mg/L) and MDPV (0.47 mg/L) [158]. The single fatality from the US poison Center series (reported earlier)

occurred in a 21-year-old male from a self-inflicted gunshot after an active delusional episode witnessed by family members. Quantitative analysis performed on postmortem samples detected MDPV in blood at 170 ng/mL and in urine at 1400 ng/mL [45].

Some deaths are associated with preexisting medical conditions and in some cases imminent death is noted quickly following severe agitation. Kirshner et al. [159] report on two prehospital deaths associated with MDPV intoxication. A 43-year-old man was found dead by police at the edge of a lake. Collateral history from his girlfriend describes erratic behavior and out of personal concerns she had locked herself in the vehicle during his behavior. It was later uncovered that the patient had injected “hookah cleaner” (glass cleaner) purchased from a head shop. Multiple small abrasions and contusions as well as single vessel coronary disease were noted. Urine was negative for drugs of abuse. Blood ethanol concentration was <10 mg/dL and serum MDPV concentration was 160 ng/mL. The second case involved a 37-year-old man who was naked and screaming prior to paramedic attendance as alerted by neighbors. Soon after, he was found to be in asystole and received advance life support and intubation prehospital. He was declared dead after 55 min. His wife confirmed a history of drug abuse and use again of an MDPV-associated “Crystal Clean Hookah & Pipe Cleaner” obtained from a head shop. Autopsy revealed 3-vessel coronary stenosis and rib fractures consistent with CPR. Urine was negative for drugs of abuse. Blood ethanol concentration was <10 mg/dL. MDPV (340 ng/mL), tramadol, and caffeine were detected in the blood. It is unclear if dysrhythmias contributed. There was one case of precipitated diabetic ketoacidosis in a patient with diabetes mellitus [160]. A 46-year-old male was found dead after several days of smoking and intravenously injecting MDPV. He had previous admissions for diabetic ketoacidosis and a significant drug abuse history including zolpidem, hydrocodone, morphine, hydromorphone, black tar heroin, crack cocaine, and methamphetamine.

In the days prior to death according to a friend, the patient was symptomatic with nausea, malaise, vomiting, and had reported uncontrolled glucose concentrations in spite of repeated insulin injections. He reportedly had refused medical attention. At autopsy, quantitation of MDPV concentrations in blood and urine was 39 and 760 ng/mL, respectively. Metoclopramide concentration in blood was 490 ng/mL and vitreous acetone was 106 mg/dL.

Diagnosis

Diagnosis of Mephedrone or MDPV Use

Confirmation that acute sympathomimetic toxicity is likely to be related to the use of mephedrone or MDPV is usually based on self-reported/reported history of use, since analytical screening is often not available in an appropriate time frame. The pattern of acute toxicity as discussed above is very similar to that seen with other sympathomimetic drugs, and it is not possible to differentiate between them clinically.

Cathinones are not tested for on routine toxicology assays. Specialized testing via laboratories that can perform GC-MS and liquid chromatography tandem mass spectrometry techniques has been developed for the analysis of mephedrone and MDPV and some of its metabolites/precursors [77, 161, 162]. Importantly, the mass spectrometry technique does not distinguish between methylmethcathinone isomers; however, nuclear magnetic resonance spectroscopy (NMR) and other techniques allow the isomers to be differentiated [163–165]. There is ongoing work to enable testing in alternative biological matrixes such as saliva, although currently these are mainly used for forensic and/or research purposes [166]. One study has shown that MDPV can be detected using color spot tests such as with testing kits that use reagents including the Marquis reagent and Liebermann's reagent [167]. Importantly, common immunoassay field tests for methamphetamine give false-positive reactions with some cathinone derivatives [168]. Further, MDPV has been reported to cause false-positive

phencyclidine immunoassay results in urine samples [169], and can confound results.

Treatment

Similar to other sympathomimetic drugs, there are no specific cathinone antidotes. Treatment strategies therefore currently draw upon the clinical evidence base for treating other sympathomimetic drugs such as cocaine, amphetamine, methamphetamine, and/or MDMA. The treatment is essentially supportive with specific care directed towards the treatment of unwanted effects in an attempt to prevent medium- to long-term complications and/or death occurring. For asymptomatic patients or those with only mild clinical effects, observation may be required until symptoms/signs subside over several hours or there is evidence of improvement (whichever is shorter). General measures include monitoring of vital signs for rising pulse rate, temperature, or blood pressure. Where patients have specific complications, hyperpyrexia, serotonin syndrome, agitation/aggression/delirium, and/or cardiovascular toxicity, this may require more specific treatment.

Treatment should be directed towards counteracting excessive dopaminergic, norepinephrine, and serotonergic stimulation. To achieve this benzodiazepines are first line (Grade III recommendation). Second-line agents may involve antipsychotics or adjunct sedatives for specific psychiatric symptoms such as agitation with ongoing combativeness; aforementioned cases have used risperidone, intramuscular ketamine, or haloperidol. However, as with other stimulant drugs phenothiazines and butyrophenones should be used with caution since they may exacerbate hyperthermia, QT/QTc prolongation, and possible torsades de points [170, 171].

While rat models demonstrated successful reduction of heart rate and mean arterial blood pressure values with beta blockers [94], given the risk of possible unopposed alpha blockade leading to worsening hypertension, other antihypertensives are recommended (alpha blockers such as phentolamine, nitroglycerin, verapamil,

Table 6 Life-threatening complications associated with cathinone use

Complications
Hyperpyrexia - more likely with ‘aggregate toxicity’
Severe agitation /delirium
Serotonin syndrome
Electrolyte abnormalities
Multi-organ failure e.g. renal failure, hepatotoxicity, DIC
Arrhythmia
Stroke
Self-harm and violence, trauma

Table 7 Indications for ICU admission

Indications
Coma (GCS ≤ 8) and/or clinical deterioration in conscious state requiring airway control and ventilation
Serotonin syndrome
Status epilepticus
Profound hyponatraemia (< 120 mmol/L)
Evidence of end-organ dysfunction e.g. acute renal failure, acute liver failure, DIC
Hyperpyrexia ($\geq 39^{\circ}\text{C}$)

or hydralazine) (Grade III recommendation). Where acute coronary syndromes are suspected, this may require serial troponin measurements, an echocardiogram, and an adopted management approach as is used in cocaine toxicity [172]. Controversy remains about the most efficacious cooling technique in drug-induced hyperpyrexia [173], nevertheless its presence warrants expedient and immediate cooling to avoid multiorgan failure and disseminated intravascular coagulation and may warrant early paralysis and ventilation. There are a few case reports that support the use of

cypheptadine in amphetamine-related toxicity, and extrapolation of these results may provide benefit in the treatment of drug-induced hyperpyrexia with synthetic cathinones [174, 175]. Ultimately, the aggregate clinical features of cardiovascular toxicity, severe agitation/delirium, and hyperpyrexia/serotonin syndrome may warrant rapid sequence intubation and admission to an Intensive Care Unit. Life-threatening complications as documented in case reports and case series have been summarized in Table 6 as well as indications for ICU admission in Table 7.

Prognosis

There are no prospective long-term studies to date regarding the outcomes of patients with intensive care admissions resulting from isolated synthetic cathinone toxicity. Long-term strategies involve consideration for counseling around recreational drug use and assistance given potential for abuse and dependence. There is one report from the UK of a young professional male who developed dependence following 18 months' use of oral, nasal, and rectal mephedrone [176]. He fulfilled the ICD-10 criteria for dependence syndrome, and after in-patient treatment with olanzapine, his symptoms resolved. There are currently no reports of dependence-related MDPV use. Animal models and information from users suggest that there is increased self-administration and repeat dosing related to both mephedrone and MDPV [106]. While this is not likely to be associated with receptor adaptation and physical dependency, there is the potential for psychological dependency developing, which may require appropriate treatment.

Special Populations

Pediatric

There are scant data regarding the acute health effects of cathinones in neonatal and pediatric populations. There is evidence of use of mephedrone in younger age groups. In the aforementioned school survey of 1006 Scottish school and college/university students of those who self-reported using mephedrone on at least one occasion, 56% had reported that they had suffered at least one adverse effect related to its use. The frequency of adverse events described was bruxism (28.3%), paranoia (24.9%), sore nasal passages (24.4%), hot flushes (23.4%), sore mouth/throat (22.9%), nose bleeds (22.4%), suppressed appetite (21.5%), blurred vision (21.0%), palpitations (20.5%), insomnia (19.5%), hallucinations (18.0%), addiction/dependence (17.6%), nausea/

vomiting (17.1%), burns (17.1%), and blue/cold extremities (14.6%) [27].

A retrospective study used data from the Texas Poison Center Network (TPCN) which involves statewide data collection through six poison centers. Synthetic cathinone exposures reported to the TPCN during January 2010–December 2011 were included. Of the 474 calls entered, 362 (76.4%) were exposures. Fifty-one (14.1%) of the patients were between 13 and 19 years of age, 306 (84.5%) greater than or equal to 20 years of age, and five (1.4%) of unknown age. Of the adolescent subset (those aged 13–19-years-old, 31 males and 20 females), the most frequent adverse clinical effects reported were agitation/irritability (22 patients, 43.1%), tachycardia 19, 37.3%), drowsiness/lethargy (7, 13.7%), hallucinations/delusions (5, 9.8%), fever (5, 9.8%), vomiting (5, 9.8%), and hypertension (4, 7.8%). This frequency of unwanted effects was similar to that since in the adult patients, apart from hypertension which was more frequent in the adult patients (72 adults, 23.5%). Approximately 75% of the adolescents were already at or en route to healthcare facility at the time of the poisons center contact [177].

There may be an increased tendency to develop seizures in adolescent populations. The American Association of Poison Control Centers conducted a retrospective review of data regarding synthetic cathinone exposures in children less than 20 years of age from January 1, 2010, to January 31, 2013. There were 1328 adolescent synthetic cathinone exposures identified; seizures complicated 73 (5.5%) of the cases, with 37 (50.7%) of those cases experiencing a single seizure, 29 (39.7%) multiple seizures, and 7 (9.6%) status epilepticus. Fever and acidosis were associated with single seizures, multiple seizures, and status epilepticus. Coingestants were present in 33 (45%) of these cases, most commonly tetrahydrocannabinol, alcohol, and opioids [178].

There is one published case of a neonate born to a mother abusing MDPV. The mother was found unconscious and subsequently the baby was born preterm at 34 weeks with emergency caesarian. The infant was noted to be small-for-gestational-age and was treated for neonatal

abstinence syndrome with enteral morphine. MDPV was detected in infant blood, urine, and cord blood; however, the mother was also positive for opiate metabolites and THC [179].

Key Summary Points

1. Synthetic cathinones are a heterogeneous group of psychoactive drugs that result from differing amphetamine-related structures.
2. Most likely modulate monoamine transporters resulting in various combinations of SERT, NET or DAT interference and various monoamine concentrations at synapse.
3. Broadly, synthetic cathinones result in sympathomimetic and /or serotonergic toxicity, however, must be considered as unique entities and on a case by case basis.
4. Since acute toxicity can be life-threatening, prompt recognition and management is warranted and in the absence of human studies relies on published data on the management of other stimulant toxicity classes such as methamphetamine, amphetamine, and cocaine.

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Cocaine has been used for thousands of years for its recognized medicinal properties and for its personally gratifying qualities. The first archeological finding of human use of coca leaves dates back to 3000 b.c. among pre-Colombian Andean societies [1]. The leaves were chewed by chasquis (on-foot mail carriers of the Incan empire) to decrease fatigue and enhance endurance as they delivered royal messages by running from town to town.

Chewing the coca leaf was the preferred method of use until Niemann isolated cocaine in 1859. In the late 1800s, Freud advocated the use of cocaine for many ailments, including the treatment of opioid addiction. During this same period, the renowned John Hopkins' surgeon Halsted reported the local anesthetic effects of cocaine. By the end of the nineteenth century, cocaine became widely used in various medicinal pastes and remedies [2]. It was the main active ingredient in the soft drink Coca-Cola until 1903 [1]. As accounts of addiction multiplied, legislation was enacted that curtailed its use although cocaine was still sold over-the-counter in the USA until 1916. Cocaine continues to be a Schedule II drug in the USA with limited use especially in otorhinolaryngological interventions including in the UK and USA [3–5].

Although a resurgence of cocaine use in the USA occurred in the 1970s, use leveled off until 1983, when “crack” appeared, providing a fast and inexpensive method of self-administration. By 1985, the US National Household Survey on

Drug Abuse from the US National Institute on Drug Abuse estimated that 25 to 40 million Americans had used cocaine at some time in their lives (1.5 million of whom were first-time cocaine users) [6]. Cocaine use reached epidemic proportions in the mid-1980s, when it was reported to be the most frequent cause of illicit drug-related visits to emergency departments [7]. In the last 15 years of the twentieth century, the use of the crystallized freebase form of cocaine became widespread, resulting in many cocaine-related hospitalizations and deaths [8]. Results from the National Institute of Drug Abuse indicate that cocaine use has been declining since 1992 to a plateau of 1.8 million regular users in 1998 (5.7 million in 1985) [9, 10]. This trend continued during the first decade of the twenty-first century. In 2013, it was reported that there were 1.5 million current cocaine users, aged 12 or older (0.6% of the population) and an estimate of 601,000 persons who had used cocaine for the first time within the past 12 months in the USA [11]. Also for 2013, an estimated 3.1 million European adults had used cocaine in the previous year (0.9% the population), with higher use in the south and west of Europe. Especially high prevalence of use was reported in the UK and Spain, though a decline in use has been reported since peaking in 2008 [12]. Despite the decline, the incidence of cocaine-related deaths in the USA increased by 14% from 1992 to 1995 [8, 13]. Cocaine continues to be the most commonly illicit drug of abuse involved in drug-related ED visits in the USA per year as reported by the Drug Abuse Warning Network, with 162.1 visits per 100,000 population in 2013 [14]. European data from the European Monitoring Centre for Drugs and Drug Addiction report on cocaine use health emergencies portrays a similarly high burden on emergency services in European countries, especially in the UK and Spain although the lack of systematic data collection limits comparison [15]. The United Nations Office on Drugs and Crime 2015 World Drug Report data reflects that the use of cocaine as a recreational drug is concentrated in North and South America (especially Brazil), Europe, and to a more limited extent Oceania, despite recent declines in demand but that there

is emerging use in areas of Southern and Western Africa, as well as in Asia [16].

Cocaine toxicity involves all of the body's organ systems. Its use brings patients to the hospital with a variety of clinical features. Complications include medical, psychiatric, and surgical emergencies. In 1995 in the USA, the estimated health-care cost of patients with myocardial ischemia alone secondary to cocaine was greater than \$80 million [17]. A retrospective study reported 1.1% incidence of positive urine screens for cocaine among all hospitalized non-newborn patients during a 12-month period. These patients were predominantly young (average age 31.8 years) crack users and required admission to the intensive care unit 20% of the time [9]. An understanding of cocaine's pharmacology and its pathophysiology is beneficial in identifying and treating patients with the highest risks of complications.

Cocaine Chemistry

The natural tropane alkaloid cocaine is extracted from the leaves of the plant *Erythroxylum coca*. Coca paste is obtained by alkaline extraction of the leaves, using ammonia and organic solvents. The active cocaine alkaloids are contained within the organic phase of the extraction medium, which is then treated with hydrochloric acid to create the water-soluble cocaine hydrochloride (HCl) salt. Cocaine hydrochloride (Fig. 1), often referred to as "powder cocaine," is used intranasally and intravenously. This salt cannot be smoked, as it undergoes pyrolysis at the temperatures required for vaporization [18].

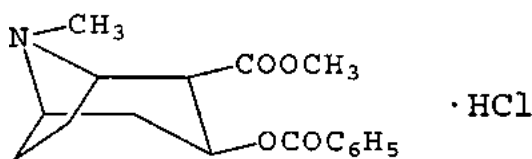


Fig. 1 Chemical structure of the salt cocaine hydrochloride (HCl). When the hydrochloride salt is treated with base, the hydrochloride is removed, leaving cocaine in the alkaloid ("freebase") form

In order to be smoked, cocaine hydrochloride is converted back to its base (non-salt) form, called “crack” or “freebase” cocaine. To convert cocaine hydrochloride to crack, the hydrochloride salt is heated in sodium bicarbonate or ammonia, creating a hard crystallized substance. This crystallized base of cocaine is called “crack” because a popping or cracking sound is often heard when it is smoked. Another process called *freebasing* also gives rise to smokable alkaloidal cocaine. First, the cocaine hydrochloride salt is dissolved in water mixed with an alkaline substance. The base alkaloid is then extracted into ether or another organic solvent, which is separated from the aqueous layer. The final product is obtained by evaporation of the organic phase. This final extraction is hazardous as many of the solvents used are volatile and flammable. Facial and tracheal burn injuries are reported in freebase cocaine users, and fires in clandestine laboratories during the production process have been reported [19]. For the sake of simplicity, in this text all alkaloidal forms of cocaine will be referred to as crack.

Pathophysiology of Cocaine Effects

Pharmacokinetics

Cocaine is absorbed rapidly from all mucous membranes, including the respiratory, gastrointestinal, and genitourinary tracts, giving rise to multiple potential routes of abuse [20]. Its onset of action is almost immediate from the intravenous or inhalational route (0.5–2 min) and is delayed 20–30 min after nasal insufflation [21, 22]. Gastrointestinal absorption is delayed further by a minimum of 90 min. The duration of effect is related closely to the onset of action, with intravenous and inhalational exposure lasting approximately 30 min, nasal insufflation lasting about 1 h, and gastrointestinal use lasting at least 2–3 h (Table 1).

The physiological effects of cocaine are the summation of the effects of the parent compound, its metabolites, and their respective pharmacodynamics. Once absorbed, less than 5% of the parent

Table 1 Toxicokinetic parameters of cocaine

Method of use	Peak onset of symptoms (min)	Duration of effect (hr)
Oral (cocaine HCl)	60–90	>3
Intranasal (cocaine HCl)	30	1–2
Smoking (freebasing, crack)	0.5–1.0	0.25–0.5
Intravenous (cocaine HCl)	0.5–2.0	0.25–0.5

HCl hydrochloride

compound is cleared in the urine [23]. More than 11 metabolites of cocaine have been described, and some deserve mention. Cocaine is metabolized rapidly by a combination of enzymatic and nonenzymatic hydrolysis [24]. Enzymatic hydrolysis by plasma and liver esterases yields ecgonine methyl ester. Ecgonine methyl ester has mild vasodilating properties and has a plasma half-life of approximately 5 h [25–27]. Decreased plasma cholinesterase activity enhances cocaine toxicity in mice [28]. Similarly, patients with relative plasma cholinesterase deficiency seem to be at increased risk of adverse consequences from cocaine toxicity [29].

Another metabolite, benzoylecgonine, is formed mostly via nonenzymatic (chemical) hydrolysis. Although an enzymatic hydrolysis pathway producing benzoylecgonine is known, it probably accounts for only a small percentage of this metabolite [24]. Benzoylecgonine has potent vasoconstrictive properties, although less than the parent compound. It has a plasma half-life of approximately 8 h [26, 28, 30]. One important fact about benzoylecgonine is that this metabolite is tested in most urine immunoassays. It is detected for 48–72 h after infrequent cocaine use or 3 weeks in high-dose chronic cocaine users [31, 32].

Together, ecgonine methyl ester and benzoylecgonine constitute approximately 85% of cocaine’s metabolism [33]. Less than 10% of cocaine is metabolized by *N*-demethylation mediated by CYP3A4 in the liver, forming norcocaine [34, 35]. This metabolite is highly vasoconstrictive

and in animal models produces clinical effects similar to those of the parent compound [26].

Additionally, in the presence of ethanol, cocaine is transesterified by liver esterases to ethylcocaine, which is also known as cocaethylene [36]. Cocaethylene has a longer half-life (2.5–6 h) than cocaine [35]. In humans, coadministration of cocaine and ethanol produces prolonged euphoria [37]. This metabolite has pharmacologically significant central and peripheral effects that are similar to those of cocaine [38–41]. Additionally, animal studies with cocaethylene show a dose-dependent myocardial depression effect and more potent Na⁺ channel blockade than cocaine [40, 42].

Although some data shows that cocaine purity is on the rise in Western Europe [43], average purity is generally below 50% and on the fall in the USA, with indication that increased cocaine purity may be associated with adverse health-care outcomes [44, 45]. Many adulterants are found in cocaine including some with pharmacological activity (phenacetin, lidocaine, tetracaine, diltiazem, caffeine), most of which have minimal toxic effects but may include seizures and nephrotoxicity [46]. Special mention should be made of levamisole, an antihelminthic agent no longer used in human medicine that recently has been reported worldwide as a cocaine adulterant and is found in up to 69% [47] of cocaine in the USA, in Europe [48, 49], and in 54% of samples of cocaine destined to international trafficking in Brazil [50]. Patients presenting with oropharyngeal symptoms, agranulocytosis, leukoencephalopathy, and vasculitis [47, 51–55] are reported after using levamisole-adulterated cocaine.

Mechanism of Action

Cocaine’s effects derive from its sodium channel blockade and its central and peripheral inhibition of monoamine reuptake. Sodium channel blockade is responsible for cocaine’s local anesthetic effects by inhibiting nerve conduction [56]. The effect is also important in the myocardial conduction system, where it produces quinidine-like

Table 2 Mechanism of action and clinical manifestations of cocaine poisoning

Mechanism	Clinical manifestation
Sodium channel blockade	Local anesthesia
	QRS widening on ECG
	Decreased cardiac muscle contractility
	Respiratory depression
Monoamine reuptake inhibition	
Epinephrine	Tachycardia
Norepinephrine	Hypertension
Dopamine	Psychomotor agitation with attendant elevation in temperature. Reward leading to dependence. Movement disorders
Serotonin	Various effects on mood and behavior
Excitatory amino acids	Seizures
Platelet activation and alterations in plasma thrombogenic constituents	Thrombogenesis

ECG electrocardiogram

(sodium channel-blocking), membrane-stabilizing properties that result in QRS widening and decreased contractility [57–59]. In large doses, sodium channel blockade in the medullary centers produces respiratory depression and sudden death (Table 2).

Cocaine’s second mechanism of action (inhibition of monoamine reuptake) increases the concentrations of norepinephrine, dopamine, serotonin, and excitatory neurotransmitters in the synaptic space [58, 60, 61]. This mechanism is responsible for many of the stimulatory effects on the sympathetic nervous system. Some of the centrally mediated effects are euphoria, psychomotor agitation, and respiratory stimulation.

The increase in synaptic and circulating concentrations of catecholamines stimulates adrenergic nerve terminals, resulting in an increase in sympathetic activity [60]. Typically, sympathetic nervous system stimulation manifests as hypertension, tachycardia, diaphoresis, mydriasis, and hyperthermia. Pressor effects are mediated by

norepinephrine of sympathetic neural origin, whereas tachycardia is secondary to epinephrine derived from the adrenal medulla [60].

Other effects of cocaine are secondary to its dopamine reuptake inhibition. Dopamine D₁/D₅ antagonists attenuate the euphoric effects of cocaine [62]. Administration of cocaine directly into motor centers produces an increase in locomotion that is reversed by coadministration of dopamine antagonists [63]. Restlessness, agitation, and seizures can occur from motor center stimulation after cocaine administration. This psychomotor stimulation after cocaine administration is absent in mice lacking the dopamine transporter [64]. Chronic cocaine use also depletes dopamine from reward centers in the brain. This mechanism is thought to be the basis for its reinforcement and addictive properties [65].

The serotonergic effects of cocaine are unclear. Serotonin modulates certain biologic processes, such as mood, personality, temperature regulation, affect, appetite, motor function, sexual activity, sleep induction, hallucinations, and vasospasm. All of these processes may be affected during chronic cocaine abuse and withdrawal [66].

Cocaine increases excitatory amino acid concentrations in the nucleus accumbens by enhancing dopamine stimulation of the *N*-methyl-D-aspartate (NMDA) receptor [60]. In animal models, NMDA antagonists attenuate the effect of cocaine on the nucleus accumbens [67] and prevent cocaine-induced seizures and death [68].

Cocaine has several hematological actions, which may promote thrombogenesis. Tonga and colleagues [69] first noted an increase in rabbit platelet aggregation and thromboxane production *in vitro*. Similar results of platelet activation are reported in *in vitro* human volunteer studies [70, 71] and in an *in vivo* canine model [72]. Cocaine also alters plasma constituents (increases tissue plasminogen activator type I activity, increases von Willebrand factor) that regulate thrombus formation [73, 74]. An additional direct effect of cocaine on the vascular endothelium causes release of endothelin-1, a potent endogenous vasoconstrictor [75]. Lastly, cocaine induces a transient erythrocytosis, further restricting blood flow. This latter effect is well-described in patients

chewing coca leaf during exercise [76–78]. As a result, intravascular thrombosis after cocaine use occurs in a variety of vascular beds [79–84], both in diseased and nondiseased vessels.

Clinical Presentation

Cocaine toxicity may involve multiple organ systems. Although most patients with acute cocaine-associated toxicity may be managed in the emergency department, some require hospitalization due to catastrophic complications. Most complaints are cardiopulmonary (56.2%), neurologic (39.1%), and psychiatric (36.8%), although multiple systems often are involved (57.5%) [85].

The effects of cocaine on the different organ systems are a combination of the overall intrinsic effect of cocaine on vascular tone and thrombogenicity and the specific physiologic response of the involved organ system. Arterial vasoconstriction and spasm and intravascular thrombosis occur in vascular beds throughout the body [79–84, 86–88]. Some of the clinical manifestations of cocaine-induced vasospasm include cerebral infarction, myocardial infarction, blindness, central retinal artery occlusion, mesenteric ischemia, and renal infarction [82, 83, 89–93]. Secondary effects of cocaine that affect multiple organ systems are hypertension and tachycardia, which increase tissue oxygen demand and further impair organ performance.

Hyperthermia

Cocaine use can result in serious toxic effects and death in part because of hyperthermia. Even relatively low doses of cocaine can elevate core temperature and hamper cardiac reserve [94]. High ambient temperature is associated with a significant increase in mortality from cocaine overdose [95].

Cocaine causes hyperthermia in several ways. It increases psychomotor agitation, which results in increased heat production. As a vasoconstrictor of the peripheral vasculature, cocaine impairs heat dissipation. Additionally, because the

thermoregulatory centers in the hypothalamus are dopamine modulated, cocaine has direct effects on temperature control [96]. Several case reports describe fatal hyperthermia without severe agitation or rhabdomyolysis in cocaine users [97, 98]. This model of hyperthermia as a major cause of acute cocaine fatality is well established in cocaine-poisoned dogs [99]. When ambient temperature increased from -5°C to 5°C (23°F to 41°F) in this animal model, the survival rate decreased from 100% to 57% [99]. Of all vital sign abnormalities, hyperthermia seems to correlate most with fatality.

Neurological Manifestations

Cocaine is a popular illicit drug of abuse because of its stimulatory effects on the central nervous system (CNS). Its use also generates a variety of untoward effects on the CNS. These CNS complications occur with all forms of cocaine administration and include cerebrovascular ischemia and infarction, transient ischemic attacks, subarachnoid hemorrhage, intraparenchymal hemorrhage, seizures, cerebrovascular thrombosis, cerebral vasculitis, migraine headache, anterior spinal artery syndrome, and movement disorders (Table 3) [87, 88, 91, 100–108].

Cerebrovascular Accidents

Cocaine-related strokes were first reported in 1977 [101]. Epidemiological studies clearly support cocaine as a risk factor for stroke, although the magnitude of this association is not easily estimated with available studies [122]. Strokes can be either ischemic or hemorrhagic though limited data shows that the form of cocaine used might have an influence on the predominant etiology. The incidence of ischemic and hemorrhagic strokes secondary to crack cocaine is approximately the same [87], whereas 80% of cocaine HCl-induced strokes are hemorrhagic [88].

Patients with cerebrovascular ischemia or infarction may present with focal lateralizing neurologic deficits. Clinical features in these patients are typical of patients with cerebrovascular

Table 3 Cocaine-induced central nervous system complications

CNS complications	Etiology	References
Ischemic strokes	Vasospasm, thrombosis	[87, 88, 91, 101, 103, 105, 109, 110]
Hemorrhagic stroke	Hypertension, vasospasm, thrombosis	[87, 88, 91, 101, 103, 105, 106, 109–112]
Seizures	Reuptake inhibition of excitatory amino acids, CNS hemorrhage, or infarction	[109, 110, 113–118]
Cerebral vasculitis	Direct effects	[100]
Migraine headaches	Dopamine reuptake inhibition, vasospasm	[108]
Movement disorders Agitation Delirium/psychosis	Dopamine reuptake inhibition Diverse mechanisms	[102] [85, 119–121]

accidents, with aphasia, hemiplegia, dysarthria, and/or paresthesiae/sensory loss.

Cocaine-induced cerebral hemorrhage may be intraparenchymal or subarachnoid; however, cocaine-positive patients with intracerebral hemorrhage are more likely to have intraventricular hemorrhage, subcortical localization, seizures, and a poorer prognosis [112, 123]. The incidence of neurovascular complications among cocaine-related hospital admissions is low (0.35–3%) [109, 113]. However, autopsy studies of fatal nontraumatic intracranial hemorrhage reported an incidence of cocaine abuse to be 7–59% [124, 125]. Headache is the most common symptom on presentation. Other presenting signs include meningismus, altered mental status, seizures, and focal neurologic deficits [105].

The mechanisms of cocaine-related ischemic strokes are multiple and overlapping and have been related to focal vascular disease. Proposed causes include vasospasm (either pharmacologically induced or secondary to hypertension), thrombosis, and vasculitis. Cerebral vasoconstriction, documented by magnetic resonance angiography, occurs within 15 min of cocaine

administration in asymptomatic human volunteers [126]. In head computed tomography (CT) scan-proven cerebral infarctions, angiography revealed evidence of vasospasm and thrombosis [91]. Biopsy-proven cerebral vasculitis as a cause of ischemic stroke is also rarely reported [100].

Alternatively, acute systemic hypertension as a result of the sympathomimetic effects of cocaine is the proposed mechanism for cocaine-related hemorrhagic strokes. The sudden increase in blood pressure may precipitate the rupture of a preexisting vascular malformation or aneurysm [87]. Arteriography has shown both of these vascular abnormalities in many cases of cocaine-induced subarachnoid hemorrhage and in some cases of intraparenchymal hemorrhage [105, 109, 111, 113]. Patients suffering from aneurysmal subarachnoid hemorrhage after cocaine use have a higher risk of aneurysmal re-rupture and a higher hospital mortality [127].

Although most strokes occur either immediately or within the first 3 h after cocaine use, Levine and associates [87] reported that 18% of strokes occur after an abstinence period of at least 2 days following a period of heavy crack use. Possible explanations for these delayed events are the prolonged half-life of cocaine's metabolites (benzoylecgonine) and cocaine's intrinsic thrombogenic effect.

Seizures

Although seizures are well associated with cocaine use, they are a relatively uncommon presenting feature of emergency department visits and hospitalizations among patients with cocaine-related complaints (2.8–8.4%) [110, 114, 115]. A systematic review of evidence however did not find an association between cocaine and seizure activity [128]. Most cocaine-induced seizures occur as the only manifestation of cocaine toxicity. They are predominantly single, generalized, and tonic-clonic. Approximately 20% are focal in onset. Seizures that are focal or multiple often are associated with acute intracerebral complications [116]. Although some cocaine-induced seizures occur secondary to a large CNS hemorrhage or

infarction, most are not associated with any lasting neurologic deficits [110, 117].

Most cocaine-induced seizures occur within 90 min of use [117]. Similar to cocaine-induced strokes, this corresponds temporally to peak plasma cocaine concentrations [104, 116, 117]. Delayed seizures may be caused by benzoylecgonine because this metabolite is also a potent CNS vasoconstrictor [129].

Cocaine also lowers the seizure threshold and precipitates seizures in patients with known seizure disorders [118]. Patients with a prior history of epilepsy have a higher frequency of cocaine-induced seizures than patients without a history of seizures [116]. Partial or multiple seizures occur more often in patients with prior history of epilepsy [118]. Additionally, animal studies and human case reports suggest seizures “kindle” after habitual cocaine use [116, 117]. This process increases the sensitivity of the brain following repeated doses.

Neuropsychiatric Features

A wide range of neuropsychiatric features are common complaints in cocaine-associated emergency department episodes [85, 119]. These range from anxiety [120] to psychosis [121], including suicidal intent. Agitation and aggression are hallmarks of severe cocaine toxicity and pose a risk to patient and caregiver safety.

Other Neurological Effects

Cocaine induces a variety of movement disorders, which are presumed to be dopaminergic in origin. These movement disorders include dystonia, choreoathetosis (commonly known as *crack dancing*), akathisia, buccolingual dyskinesia (risus sardonius), and exacerbation of Tourette's syndrome. The high incidence of acute dystonic reactions in cocaine-addicted patients treated with antipsychotic medications suggests a dysfunctional dopamine-mediated basal ganglia effect [102].

In addition to the kindling effect, chronic use of cocaine is associated with an increase in cerebral atrophy [130]. Because reward centers in the brain are under control of dopaminergic tone, depletion

of dopaminergic transmission in these areas after repeated administration of cocaine produces a craving for the drug.

Cardiac Manifestations

Cardiac manifestations of cocaine poisoning are common and have been well recognized for years. Most symptoms relating to acute cocaine use suggest a cardiovascular etiology, with 40% of cocaine-related visits to the hospital having chest pain as the leading single presenting symptom [85]. Other symptoms that occur at presentation and could be related to cardiac events include diaphoresis, palpitations, and dyspnea [85, 119]. Because of cocaine's multiple effects on the coronary vasculature, evaluation of patients for myocardial ischemia or infarction is important with any of these presenting symptoms.

Myocardial infarction as a complication of cocaine abuse was first reported in 1982 [131]. It is now well recognized that myocardial infarction occurs with intranasal, intravenous, and inhalational use of cocaine [132]. Retrospective studies of cocaine-associated chest pain reported an incidence of myocardial infarction ranging from 0% to 31%. Subsequent prospective studies indicated that the frequency of infarction defined by creatine kinase-MB fraction (CK-MB) or troponin criteria more likely approximates 0.7–6% [132–136].

The typical patient with cocaine-induced myocardial infarction is a male, 18–52 years old (median age 33 years old) with a history of regular tobacco smoking and frequent cocaine use. The quality of the chest pain is usually atypical of ischemia, and the location of the pain does not predict myocardial infarction [132].

Two thirds of patients with chest pain experience it within 3 h, and 93% have chest pain within 24 h of cocaine use [90, 132, 137]. A greater delay in the onset of symptoms is experienced rarely but has been documented [138]. Myocardial infarction 3 days after cocaine use was reported by Del Aguila and Rosman [139]. Additionally, Holter monitoring detected ECG changes (ST-T changes, ST-segment elevation) up to 6 weeks after an

inpatient detoxification admission in cocaine-addicted patients (in 8/21 patients vs. 1/42 controls) [138].

Cocaine causes myocardial infarction by several mechanisms. Acutely, cocaine use leads to hypertension, tachycardia, and vasoconstriction, all of which increase myocardial oxygen demand. First, an elevation in heart rate and blood pressure increases myocardial workload. More dramatic elevations in blood pressure may intensify the shearing forces in the major vessels, causing aortic dissection and rupture [140–145]. Dissection of coronary arteries has occurred [146, 147]. Second, cocaine causes local vasoconstriction of the coronary vasculature. In human volunteers, this effect occurs within 15 min of cocaine administration, as is well documented by angiography [87]. This arterial vasoconstriction is markedly worse in coronary artery segments previously narrowed by atherosclerosis [148]. In the presence of cocaine and its increased sympathetic activity, the normal coronary vasodilating response to a diminished oxygen supply is overwhelmed.

The vasoconstrictive effects of cocaine are established to be α -adrenergically mediated. Propranolol, a β -adrenergic antagonist, exacerbates coronary narrowing after cocaine infusion, whereas phentolamine, an α -adrenergic antagonist, reverses this effect [149, 150].

Acute and chronic effects of cocaine are associated with its thrombogenicity and ability to accelerate atherosclerosis. Coronary angiography performed in patients after cocaine-associated myocardial infarction often shows intracoronary thrombus and atherosclerotic lesions at different stages of stenosis in any of the coronaries [137, 151, 152]. Autopsy and coronary catheterization reports of chronic cocaine abusers show advanced atherosclerosis despite a young age [90, 145, 153–156]. Additionally, rabbits fed a 0.5% cholesterol diet and injected with cocaine develop atherosclerotic lesions in the aorta [157]. In humans, chronic cocaine use is said to increase the prevalence of aortic atherosclerotic lesions independent of traditional cardiac risk factors [158]. In contrast, more recent studies in symptomatic patients with low to intermediate risk of acute coronary syndromes (ACS) who underwent

coronary computerized tomography angiography have failed to find an association between cocaine use and advanced atherosclerosis. The presence of coronary lesions as measured by the extent of vessel stenosis ($\geq 25\%$, $\geq 50\%$) [159], extent of calcified and noncalcified coronary plaques [160], and coronary calcium scores [159, 161] were not different among patients who use cocaine and those who do not.

Cocaine use also has global cardiac effects that may produce ischemia. Data from both echocardiography and cardiac catheterization reveal that cocaine use depresses myocardial function. Dilated cardiomyopathy is reported with normal coronary arteries in patients with habitual cocaine use [162, 163]. Ventricular angiography showed myocardial dysfunction as measured by worsening hemodynamic parameters in patients infused with cocaine [164]. Left ventricular systolic dysfunction, secondary to cocaine's myocardial depressant effect, presents as congestive heart failure and cardiomyopathy [151, 163]. These cardiovascular hemodynamic changes alter the genetic expression of contractile proteins in cocaine-treated rats [165]. Inflammatory lymphocytic and eosinophilic infiltrates consistent with myocarditis are found in myocardial tissue from some patients with cocaine-related deaths [166, 167]. These anatomic alterations may provide a substrate for reentrant dysrhythmias and other conduction abnormalities.

Cocaine may produce cardiac dysrhythmias in several ways, including direct effects on the conduction system and release of endogenous catecholamines. In low doses, cocaine may result in bradycardia. Higher doses cause all types of tachydysrhythmias, with sinus tachycardia being the most common. Other rhythm disturbances frequently associated with cocaine use are atrial fibrillation, narrow-complex and wide-complex supraventricular tachycardias, ventricular tachycardia and fibrillation, and torsade de pointes [57, 59, 137, 168–170]. Animal models and case reports of wide-complex supraventricular tachycardias suggest that these dysrhythmias resemble those following poisoning from other sodium channel blockers such as type I antidysrhythmic or tricyclic antidepressants. Slowing of phase 0 of

the action potential in cocaine intoxication is secondary to the direct sodium channel-blocking effects of cocaine [171]. Cocaine-induced Brugada-type ECG findings are reported and are also likely related to the sodium channel action of cocaine [172]. Additionally, ventricular dysrhythmias may develop secondary to cocaine-induced ischemia or infarction. Although QT prolongation is common, torsade de pointes is uncommonly reported [168, 173–175]. Numerous reports document sudden prehospital cardiac arrest secondary to cocaine use, which may be related to cocaine ion-channel blockade or secondary to cocaine-mediated ischemia [145, 152, 167, 176].

A rare but devastating cause of chest pain in cocaine users is aortic dissection. In the International Registry of Acute Aortic Dissection of 3584 patients with aortic dissection, 1.8% had documented recent cocaine use, and these patients were relatively younger (47 years old in cocaine positive patients with type A and type B dissections, 61 and 64 years old for cocaine-negative type A and type B, respectively) [177].

Pulmonary Manifestations

The pulmonary complications of cocaine use arise from its pharmacological effects on pulmonary physiology and from the various methods of administering the drug. Cocaine-induced vasoconstriction and platelet aggregation, pulmonary hemorrhage, and pulmonary thrombus can occur. Hemoptysis is reported to occur in 5.7% of habitual smokers of freebase cocaine [178]. Histopathology of fiber-optic bronchoscopic lavage and autopsy reports of acutely cocaine-intoxicated patients reveal diffuse interstitial and alveolar hemorrhage, bronchial arterial constriction, and ischemic damage [179, 180]. Pulmonary infarction is encountered less often [181], mainly because of the dual blood supply to the lungs from the pulmonary and bronchial arteries.

Since the 1990s, habitual smoking of crack has replaced nasal insufflation of cocaine HCl as the most common method of use in the USA likely because of the faster onset and greater intensity of effects achievable with smoking. Each of these

routes of administration is associated with unique pulmonary complications. Thermal burns of the upper airway, including the tongue, epiglottis, vocal cords, and subglottic area, occur after smoking cocaine [182]; this is from inhalation of either hot cocaine or ether used to prepare the alkaloid form of cocaine. Acute respiratory symptoms (cough, black sputum, chest pain, shortness of breath, asthma) [183] occur with high frequency in temporal association with crack smoking.

Functional disorders of the lungs, gas exchange abnormalities, and reactive airway disease also occur commonly [184]. Subsequent pulmonary artery medial hypertrophy occurs in 20% of individuals who chronically abuse cocaine. This condition occurs in the absence of foreign particle embolization and is independent of the dose, frequency, or route of administration [185].

The condition known as “crack lung” that results from inhalation of cocaine is described as pulmonary infiltrates, fever, and bronchospasm. An immunologic etiology of these effects is supported by the findings of eosinophilia, elevated IgE concentrations, and pruritus, all of which resolve with abstinence of drug use [186–188]. These findings suggest that heavy crack smoking produces respiratory tract injury manifested by acute respiratory symptoms and evidence of chronic airflow obstruction in large airways.

Acute pulmonary edema secondary to cocaine use is also encountered due to both cardiogenic and noncardiogenic causes. Noncardiogenic pulmonary edema (acute respiratory distress syndrome) results from either the direct effect of cocaine or adulterants on the pulmonary alveoli and endothelium by increasing their permeability [189].

Barotrauma occurs in individuals who use a Valsalva-type maneuver for rapid absorption of cocaine. There are numerous case reports of patients presenting to the emergency department with pneumomediastinum, pneumothorax, or pneumopericardium. These abnormalities occur secondary to the mechanics of drug administration rather than directly related to cocaine itself [190–197]. A retrospective study that evaluated

patients presenting with spontaneous pneumomediastinum found that 76% of the cases were associated with illicit inhalational drug use. Of these cases, 53% were secondary to cocaine use. Evaluation of the presenting clinical symptoms revealed that 82% of the patients had a complaint of chest pain or shortness of breath or both. The absence of an abnormal physical finding was uncommon: most patients (88%) had subcutaneous emphysema, Hamman’s crunch, or both [195].

Chronic cocaine smokers develop gas diffusion abnormalities at the alveolar-capillary level [178]. The cause of the diffusion defect is consistent with increased lung epithelial permeability secondary to damage to the alveolar-capillary membrane. This crack-related lung injury, reflected by abnormally rapid ^{99m}Tc -DTPA (diethylenetriamine pentaacetate aerosol) lung clearance, is at least partially reversible after a 3-month period of abstinence from smoking crack [198].

Gastrointestinal Manifestations

Gastric and mesenteric arteries have abundant α -adrenergic receptors [199], which constrict in response to cocaine. The intensity and location of vasoconstriction determine the extent of injury. Acute gastrointestinal ischemia occurs with all routes of cocaine administration. Patients who smuggle cocaine in the gastrointestinal tract in wrapped packets can suffer from local effects (obstruction, perforation), but the most catastrophic outcomes are a consequence of systemic toxicity due to ruptured packets [200, 201].

Pathophysiologically, cocaine’s decrease in mesenteric blood flow results in bowel edema, ulceration, and ultimately necrosis. Perforation of the duodenum, jejunum, ileum, and colon are all well described [82, 202–205]. Large intestinal ischemia from localized vasoconstriction may present as colitis [82, 83].

Kram and colleagues [204] compared patients with cocaine-induced gastroduodenal ulceration and perforations with patients with perforations and ulcerations secondary to peptic

gastroduodenal ulcer disease. These investigators reported the former patients to be younger, to have no prior history of peptic ulcer disease, and to differ in the location of their lesion. In cocaine users, the ulcerations occur in the first portion of the duodenum, the prepyloric region of the stomach, the pyloric canal, or the greater curvature of the stomach. In contrast, in patients with peptic ulcer disease, ulcers primarily develop in the duodenal bulb [206].

Cocaine is also associated with splenic infarction [207] and with abnormal spleen hemodynamics [208]. Cocaine administered intravenously to volunteers caused a 25% reduction in spleen volume and altered hematologic parameters (increase in hemoglobin concentrations, hematocrit values, and red blood cell counts) [209].

Renal Manifestations

The renal effects of cocaine may be related primarily to direct vasoconstriction of the renal vasculature or secondarily to systemic toxicity with resultant hyperthermia, seizures, and rhabdomyolysis. Cocaine-induced acute renal infarction is reported rarely with one case demonstrating renal artery thrombosis and embolization [84, 92]. In this setting, patients may present with flank or upper abdominal pain, nausea, vomiting, microscopic or gross hematuria, and proteinuria. The mechanism may be a combination of spasm of the renal vasculature and thrombogenesis from cocaine's direct effect on platelets and prostaglandins. Kidney biopsy findings demonstrate fibrinoid necrosis involving the interlobular arterioles, similar to those found in scleroderma [210, 211]. It is thought that these changes cause accelerated and/or malignant hypertension inducing acute kidney injury (AKI) ultimately leading to chronic kidney disease. Although rare, other pathological changes found on kidney biopsies are vasculitic in nature. They include Henoch-Schönlein purpura and necrotizing vasculitis with immunoglobulin A, immunoglobulin M, and C3 deposits in the mesangium [212], thrombotic microangiopathy [213], and pregnancy-related AKI mimicking

preeclampsia [214]. There are rare reports of interstitial nephritis-induced AKI [215] and anti-glomerular basement membrane glomerulonephritis [216]. In many patients, kidney function returned to normal while others became dialysis dependent.

Rhabdomyolysis

Cocaine produces both atraumatic and traumatic rhabdomyolysis that may lead to AKI [217, 218]. In large doses, cocaine has a direct toxic effect on skeletal muscle, causing myofibrillar degeneration. Also, muscle ischemia from vasoconstriction may predispose to rhabdomyolysis. Traumatic rhabdomyolysis occurs as cocaine impairs behavioral responses to the environment, causes agitation, and induces seizures.

A prospective case series of patients presenting to the emergency department with complaints related to cocaine use showed a high incidence of cocaine-associated rhabdomyolysis. Of all cocaine users, 24% had rhabdomyolysis, defined by an elevation of creatine kinase (CK) of more than fivefold above the mean (>1000 U/L; >17 μ kat/L). The same study found that only 13% of the patients presenting with rhabdomyolysis experienced any of the classic signs or symptoms (nausea, vomiting, myalgias, muscle swelling and tenderness, weakness) [219]. Other causes of rhabdomyolysis also present without any signs and symptoms, which emphasizes the need for laboratory evaluation when establishing this diagnosis.

A retrospective study of patients with cocaine-associated rhabdomyolysis (defined as CK above 500 U/L or 8.3 μ kat/L) showed that patients at highest risk for complications (acute kidney injury, hypocalcemia, hyperphosphatemia) from rhabdomyolysis were patients presenting with severe signs of cocaine toxicity (altered mental state, hyperthermia, hypotension or hypertension, seizures, leukocytosis or symptomatic arrhythmia), having longer hospital stays than those with milder signs of toxicity (chest pain, anxiety, diaphoresis, dyspnea, tachycardia). Those with acute cocaine toxicity who had admission serum

Table 4 Causes of cocaine-associated acute kidney injury

Clinical presentation	Etiology	References
Acute kidney injury	Rhabdomyolysis	[98, 217–220]
	Vasculitis, scleroderma	[210, 211]
	Thrombotic microangiopathy, malignant hypertension	[212, 213]
	Infarction	[84, 92]
	Interstitial nephritis, glomerular basement membrane glomerulonephritis	[215, 216]

CK concentrations of less than 1500 U/L (25 μ kat/L), a normal serum creatinine concentration, a normal WBC count, and no more than one additional risk factor for rhabdomyolysis (i.e., increased muscular activity, other mind-altering drugs, seizures) did not develop complications and had a shorter hospital stay [220].

In severe cases, laboratory values are consistent with values associated with profound rhabdomyolysis. Serum CK concentrations are reported in the range of 100,000 U/L (>1700 μ kat/L) [219]. Hyperkalemia, hyperphosphatemia, hyperuricemia, metabolic acidosis, and elevations of liver function tests may occur; disseminated intravascular coagulation may develop as a terminal event. In a study of 39 patients with rhabdomyolysis after cocaine use, seven developed disseminated intravascular coagulation, of which six died [98] (Table 4).

Uteroplacental Complications

The complications of cocaine use in pregnancy generally are thought to be secondary to its local vasoconstrictive effects on uterine blood flow [221, 222]. Maternal complications include spontaneous abortion, abruptio placentae, and premature labor [223, 224]. Fetal cocaine exposure results in developmental problems, including small head circumference, low birth weight, neurologic abnormalities, and uterogenital abnormalities [225–231]. The studies on the effects of cocaine on pregnancy and neonates are

controversial because their results are limited and include other confounding factors (study subjects may have less cocaine use, other substance abuse, poor maternal health and prenatal care), in some studies showing little or no effect [232, 233].

Diagnosis

The diagnosis of acute cocaine toxicity is based largely on the patient’s history and physical examination. Testing for cocaine’s metabolites rarely adds valuable information in an acute scenario but may have uses for epidemiology, child abuse and neglect, and evaluation of dual diagnosis in psychiatric patients. Although false-positive or false-negative results for cocaine metabolites in urine are rare [234–236], caution should be made when judging a clinical scenario based on a drug screen usually based on metabolites in urine which may be present for days and not testing for parent cocaine in blood [237]. Testing for parent cocaine in urine in a retrospective study among 61 patients did not identify a difference in vital signs, chief symptoms, nor treatment between patients with cocaine metabolites only versus parent cocaine as well as metabolites in urine [238]. Many patients present with symptoms of mild toxicity and physical examination findings consistent with a sympathomimetic toxic syndrome, which is clinically indistinguishable from other stimulant drug toxicity. Most important clues to deciphering the etiology of the agitated patient are found in the vital signs. Hypertension, tachycardia, and hyperthermia are customary. An elevated body temperature (41.1 °C [>106 °F]) of any etiology is more ominous, however, than an elevated pulse or blood pressure. This information should be obtained early in the management. Because the differential diagnosis for altered mental status with hyperthermia is extensive, other immediate causes, including hypoxia, hypoglycemia, and infection, should be considered and treated promptly.

Unless a patient presents with a severe complication from cocaine, most laboratory tests are not helpful. Electrolyte abnormalities and acid–base

abnormalities are generally secondary to seizures or agitation and hyperthermia and subsequent rhabdomyolysis. Those patients with altered mental status, hyperthermia, seizures, or hypotension or hypertension should be monitored for hypokalemia, hyperkalemia, and hypocalcemia because subsequent dysrhythmias may be a cause of mortality in patients with rhabdomyolysis. Elevated liver enzymes and coagulopathy are ominous findings in the severely hyperthermic patient [239].

Clinical status should guide the use of adjunct diagnostic tools. A chest radiograph is helpful in clarifying the existence of pulmonary pathology or large vessel injury. Extrapulmonary air in the thoracic cavity or a widened mediastinum may be visible.

Similarly, patients with chest pain should have an ECG and cardiac enzyme determination to help exclude cardiac ischemia and infarction. Although these parameters are not perfect tools in diagnosing cocaine-associated myocardial infarction, they are beneficial when definitively abnormal or evolving.

The ECG has a low predictive value for detection of an acute myocardial infarction in patients presenting with cocaine-related chest pain. The sensitivity of the ECG is only 36%, while the specificity is 90% [132].

Non-specific ECG abnormalities in patients with cocaine-associated chest pain are a common manifestation. ECGs of many patients with cocaine-induced myocardial infarctions are normal or nondiagnostic [90, 132, 135]. The typical ECG abnormalities include ST-segment elevations or depressions, T-wave inversions, QRS prolongation and Q waves, and J-point elevation due to early repolarization [132, 134, 135, 240, 241]. J-point elevation on the ECG of patients with cocaine-associated chest pain appeared with a mean frequency of 35%. These elevations in the precordial leads are misinterpreted easily as acute myocardial infarction. In one study, 43% of patients presenting with cocaine-associated chest pain had ST-segment elevations in the precordial leads, meeting ECG criteria for the use of thrombolytic therapy, with none of them meeting biochemical criteria for infarction [134]. The high

frequency of abnormal ECGs in this group of patients was attributed to early repolarization.

This subject is confounded further by the fact that similar ECG abnormalities are often found in asymptomatic chronic cocaine abusers [138, 242]. In cocaine-addicted patients admitted for inpatient detoxification who wore ambulatory ECG monitors, frequent ST-segment elevations were observed; 87% of the episodes for ST-segment elevations were silent. These ECG changes continued to occur in 25% of patients after 2 weeks of drug abstinence. None of the patients had ECG abnormalities after 6 weeks of drug abstinence [138].

In contrast, cardiac troponins are considered the most sensitive and specific biomarkers for diagnosing myocardial infarction in the setting of cocaine use. An early study addressing this issue in 19 consecutive cocaine-related chest pain patients showed that both troponin I and troponin T showed a specificity of 94% (one patient's sample was not adequate for testing), although 74% had elevated CK, 16% had an elevated CK-MB concentration, and only 16% had an ECG described as normal. None of the patients were diagnosed with myocardial infarction based on ECG or clinical criteria [243]. Similar specificities were found in a subsequent study that compared troponin I with CK-MB in patients undergoing serial marker analysis for exclusion of myocardial infarction after cocaine use [244]. Another retrospective study of 111 patients with cocaine-associated chest pain evaluated with CK and CK-MB as well as troponin T did not identify any patients with an elevated troponin T, and one with elevated CK-MB, although none of the patients suffered myocardial infarction in hospital or 30-days later [245]. The value of CK and CK-MB measurements in cocaine-associated chest pain to diagnose cocaine associate-myocardial infarction may be inadequate and confound the diagnosis. These laboratory values may be elevated in patients with cocaine-associated chest pain with subsequent negative troponin I levels [243]. A study among 97 patients with chest pain of which 19 had recently used cocaine, with a similar rate of myocardial infarction in patients with or without recent cocaine use

(12% versus 11%), found a nonsignificant difference in the specificities of CK-MB for myocardial infarction in patients with and without cocaine use (75% vs. 88%). In contrast, the specificities of troponin I were equal (94% vs. 94%) [246]. The timing of troponin testing relative to onset of chest pain after cocaine use and the presentation to the emergency department has not been well studied in the era of ultra sensitive troponin assays, though we believe that based on the experience in cocaine-associated chest pain with an abbreviated protocol with standard troponin assays [247], it would be reasonable to assume that the standard approach for evaluation of ACS in low-risk patients would also be applicable in these patients.

In patients with cocaine-associated chest pain, cardiac imaging studies may be useful in determining whether the chest pain is of cardiac origin. A prospective evaluation by myocardial perfusion imaging with ^{99m}Tc -sestamibi showed that only 5 of 216 (2%) patients presenting with cocaine-associated chest pain had a positive test, with two of five patients having enzymatic evidence for infarction [243]. Single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) was safely and adequately used as a triage tool in 151 patients presenting with myocardial ischemic symptoms secondary to cocaine use and 1213 patients without recent cocaine use. There was no difference in the distribution of SPECT MPI results in patients who presented with symptoms of ACS who used cocaine and those who did not (normal 72%, equivocal 23%, and abnormal 6%). In addition, there was no difference in the mean gated left ventricular ejection fraction in either population [248].

Cardiac catheterization may be able to localize an existing coronary lesion in cocaine-associated myocardial infarction. Of 52 patients with cocaine-associated myocardial infarction who underwent angiography, an initial report found that 67% had significant coronary disease [137]. This high incidence of disease is found mainly because of selection bias, with angiography being performed preferentially in patients who were considered high risk [90, 151]. In a more current study of 90 patients with

cocaine-associated chest pain who underwent angiography, 50% had no significant coronary artery stenosis. Single-, two-, and three-vessel coronary artery disease were present in 32%, 10%, and 5.6% of patients, respectively [249]. In 31 patients who tested positive for myocardial infarction by elevated troponins, coronary artery disease was found in 75%, compared to 35% of those (59 patients) without myocardial infarction [249].

In patients who arrive at the hospital with a cocaine-associated myocardial infarction, the incidence of complications ranges from 19.7% to 28% [90, 137]. These complications consist of congestive heart failure, nonsustained ventricular tachycardia, sustained ventricular tachycardia, supraventricular tachycardia, and bradydysrhythmias. In Weber and coworkers' study to validate a brief observation period for cocaine-associated chest pain, among those patients considered at high risk for ACS (ST-segment elevation or depression >1 mm, elevated troponin concentration, recurrent chest pain, or hemodynamic instability) and not included in the protocol, there was a 23.8% incidence of myocardial infarction (10/42) and a 23.8% incidence of unstable angina (10/42) [247]. Despite this high frequency of occurrence, the mortality during acute hospital stay in one study of 246 patients presenting with chest pain following cocaine use was 0% (95% confidence interval 0–2%) [137]. More importantly, patients who developed complications tended to do so within the first 12 h after emergency department arrival. More than half of the complications already have manifested by arrival [137]. More recent retrospective data from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry of 102,028 patients with myocardial infarction and data collected regarding self-reported cocaine use in the previous 72 h or positive urine test for cocaine showed that the 924 patients with recent cocaine use and myocardial infarction were more likely to have ST-segment elevation myocardial infarction (STEMI) (46.3% vs. 39.7%) and to present with cardiogenic shock at arrival (13% vs. 4.4%), though they did not have an increased hospital mortality (adjusted odds ratio 1.00, 95%

confidence interval 0.69 to 1.44, p value = 0.98) as compared to patients with myocardial infarction not related to cocaine [250].

In the absence of the complications mentioned above, risk stratification of patients who present with cocaine-associated chest pain on the basis of established criteria for ACS (Thrombolysis for Myocardial Infarction scores, ECG changes and troponin concentrations) is safe and may prevent unwarranted hospital admissions. Studies demonstrate the safety of observation of low- to intermediate-risk patients for a 9–12 h period with ECG monitoring and serial troponin I evaluation. The admission rates of patients with high risk for ACS by the criteria defined above have been similar: 11.2–12% [247, 251]. A more recent study found that an abbreviated time of observation of 8 h was safe in this population [245]. On 30-day follow-up, one study reported one cardiac complication in a patient found to have underlying CAD with multiple cardiac risk factors. The second study reported no deaths and four (2%) nonfatal myocardial infarctions in patients who had continued to use cocaine [247, 251].

There is limited diagnostic utility in the use of provocative stress testing before discharge in patients that are less than 40 years of age with a nondiagnostic or normal ECG and normal cardiac markers who are evaluated for ACS [252, 253]. This seems to be the case as well for patients who use cocaine and present with similar symptoms since most of this population are also under 40 years of age and have low risks for ACS. Of 158 patients who underwent cardiac stress testing after presenting with cocaine-associated chest pain and an uneventful 9–12 h observation period, only four were positive. Subsequent cardiac angiography revealed that two of them had multivessel disease, one had nonocclusive disease, and one had no evidence of coronary artery disease [247]. Furthermore, positive stress testing may lead to unnecessary costly and potentially harmful interventions [254]. Stress testing in patients with cocaine-associated chest pain after a period of uneventful observation should not be routinely performed in the emergency department and may be considered, depending on cardiac risk factors and symptomatology.

Studies using coronary CT angiography to assess the extent of ACS are inconclusive. Patients with cocaine-associated chest pain with low to intermediate risk for ACS with normal troponin concentrations had no difference in calcium scores, extent of coronary artery stenosis, and extent of calcified and noncalcified plaques when compared with noncocaine users [160, 255, 256]. In contrast, similar studies found significantly higher coronary calcium scores [161], higher overall number of plaques, and more partially calcified plaques [257] in patients with cocaine use. Other forms of cardiac imaging to visualize injury such as cardiac magnetic resonance imaging (MRI) failed to find myocardial delayed enhancement which is indicative of myocardial fibrosis due to previous myocardial infarction in patients experiencing cocaine-associated chest pain with low to intermediate ACS risk [256].

The long-term outcome of patients who present to the emergency department with cocaine-associated chest pain also seems favorable. There is no difference in the 30-day outcomes among patients who undergo stress testing in the ED compared with those who do not [247]. These patients have a 1-year survival of 98% and an incidence of late myocardial infarction of only 1% [258].

Although the mortality from complications secondary to cocaine-induced myocardial infarction is low, certain patients need close monitoring. We recommend the following criteria for identifying patients who are at greatest risk:

- Complications such as hypotension, dysrhythmias, or congestive heart failure at presentation or during a 12-h observation period
- Persistent chest pain despite standard therapy
- An ECG with features of classic or evolving myocardial infarction
- A positive troponin

When available, helical chest CT or angiography may be performed if an aortic dissection or a pulmonary infarction is suspected. In a prospective multicenter study of 4356 patients for whom D-dimer was ordered to rule-out pulmonary

embolism of which 68 (2%) admitted to recent cocaine use, recent cocaine use was found to be independently predictive of a positive D-dimer (OR = 2.02; 95% CI 1.20–3.38) and significantly associated with false-positive D-dimer results (OR = 2.14; 95% CI 1.26–3.60) [259].

The etiology of global or focal neurologic findings may be elucidated by a head CT scan or magnetic resonance imaging/magnetic resonance angiography. The authors recommend that recent cocaine use should not influence the standard diagnostic approach to new-onset seizures and other etiologies should be excluded. Similarly, in patients presenting with complaints of headache in which a subarachnoid hemorrhage is in question, the standard diagnostic approach is a lumbar puncture if an initial head CT scan is normal.

Treatment

Recommendations for treatment of cocaine toxicity are based on a limited array of scarce high-quality evidence, case series, isolated cases, and expert evidence. A recent systematic literature review for the treatment of cocaine cardiovascular toxicity highlighted the fact that a meta-analysis of effect is not possible due to the limited number and quality of trials, significant diversity in protocols, and subject selection. The data available in this study was analyzed qualitatively, without measures of effect, and reflects conflicting results among practically all treatment modalities [260].

The peripheral complications of cocaine toxicity are likely the result of an increased central excitatory state secondary to an increased sympathetic outflow. Treatment is directed primarily at restoring this central imbalance, which by itself treats many of the peripheral manifestations providing specific treatment to the particular organ complications. Because the major cause of mortality from cocaine toxicity is secondary to the exceedingly severe psychomotor agitation and subsequent hyperthermia, primary attention is given to obtaining control of this agitated state (Grade II-3 recommendation).

Unless there is evidence of a catastrophic CNS or cardiovascular event, most patients with

cocaine toxicity present to the hospital verbal and fully active and without the need for emergent airway management with endotracheal intubation. In an agitated delirious patient, hypoxia and hypoglycemia (likely unrelated to cocaine) may be diagnosed immediately by obtaining bedside pulse oximetry and a rapid reagent glucose.

Hyperthermia should be recognized early and treated immediately due to significantly increased risk of mortality. Body temperatures greater than 41.1 °C (106 °F) place the patient at great risk for end-organ injury. Any temperature greater than 43.3 °C (110 °F) suggests a poor prognosis [239]. Management of hyperthermia consists of rapid immersion in an ice water bath while maintaining control of agitation (Grade II-2 recommendation) [261, 262]. Adequate sedation controls the motor activity and prevents further temperature elevation.

Indications for ICU Admission in Cocaine Poisoning

Chest pain with ischemic changes on ECG, evolving ECG, persistent chest pain despite therapy, myocardial infarction, thrombolysis, symptomatic dysrhythmias

Focal neurological signs, prolonged or focal seizures, coma, subarachnoid hemorrhage, intraparenchymal hemorrhage, delirium

Aortic dissection, rupture, uncontrolled hypertension, hypotension

Hemorrhage, embolism, hypoxia, pneumothorax, pneumomediastinum

Rhabdomyolysis with signs of acute kidney injury, renal infarction

Abruptio placentae, spontaneous abortion with prolonged bleeding

Mesenteric ischemia and infarction, splenic infarction, gastrointestinal perforation

Hyperthermia with altered mental status, metabolic acidosis

Evidence of disseminated intravascular coagulation (complication of hyperthermia)

Although agents such as haloperidol, chlorpromazine, pimozide, and propranolol may normalize some of the vital signs, they do not protect

against the centrally mediated motor activity and lethality in most experimental models [115, 263, 264]. When comparing different therapeutic strategies in cocaine-toxic dogs, survival correlated best with therapies that corrected body temperature [99]. Benzodiazepines decrease mortality by controlling the agitation and lowering the body temperature. Other strategies to control agitation, such as using ketamine [265] or newer antipsychotics, are less studied than benzodiazepines in cocaine-toxic individuals and there are concerns regarding risk of seizure, exacerbation of vital sign abnormalities (i.e., hyperthermia, hypertension, tachycardia) and QT prolongation not present with benzodiazepines [266–268].

Despite an elevated blood pressure, hyperthermic patients ordinarily are volume depleted secondary to the increased insensible fluid losses largely in sweat [269]. Hydration status, electrolytes, and substrates should be replenished. When restrained, the patient should not be covered completely without adequate heat dissipation. Although effective for malignant hyperthermia, dantrolene is not effective for cocaine toxicity [270–272].

Violent activity may be controlled with temporary physical restraint, if necessary, until sedation is achieved chemically. Physical restraint is not recommended in the absence of chemical sedation due to the increased risk of harm to both patient and providers. Continuous motor activity while in restraints may worsen hyperthermia from the increased muscle activity. Wrist and ankle bands instead of blankets should be used for physical restraints because blankets impair heat dissipation and worsen rhabdomyolysis and lactic acidosis.

Benzodiazepines are the pharmacologic agents of choice for sedation of cocaine-induced agitation (Grade II-2 recommendation). These agents control cocaine-induced agitation, hypertension, tachycardia, and hyperthermia in animal models [99, 273, 274]. Similarly, benzodiazepines resolve cardiac performance and symptoms of chest pain in patients with cocaine-associated coronary syndromes (Grade I recommendation) [275]. Additionally, they effectively treat agitation secondary to increased sympathomimetic activity from alcohol or sedative-hypnotic

withdrawal. Benzodiazepines are safe for controlling CNS agitation from other potential causes, such as an infection. We recommend incremental intravenous doses of 5–10 mg of diazepam (or equivalent doses of midazolam) be given to adults until the desired level of sedation is achieved. As the mental status becomes controllable with treatment, the peripheral manifestations of cocaine toxicity also are alleviated (hypertension, tachycardia, hyperthermia, diaphoresis).

An elevated blood pressure that fails to respond to sedation may be controlled with nitroglycerin (starting dose 10 µg/min) or phentolamine (5–20 mg) with titration to a normal blood pressure. These drugs may be given without risk of cerebral hypoperfusion in patients without long-standing hypertension. Cocaine's pharmacokinetics should be kept in mind when using hypotensive drugs as its toxic effects wear off.

Additionally, benzodiazepines control seizures that may occur early at presentation from acute cocaine intoxication or afterward as a manifestation of a CNS or cardiovascular complication. In a canine model of cocaine toxicity, only diazepam and induced hypothermia were able to reduce the incidence of seizures, control tachycardia and hypertension, and improve outcome [99]. Ultimately, barbiturates or propofol may be effective in terminating seizure activity. Because of cardiovascular and respiratory depression caused by these agents, cardiac monitoring and ventilatory support must be provided [276].

If a neuromuscular blocker is used, electroencephalogram monitoring is necessary because central seizure activity may otherwise be overlooked. A nondepolarizing neuromuscular blocker is preferable because of the potential of a depolarizing agent to exacerbate hyperkalemia and rhabdomyolysis. Succinylcholine is also degraded rapidly by plasma cholinesterase, the same enzyme that metabolizes cocaine. Theoretically, use of these agents simultaneously may extend the clinical effects of either or both.

Because most exposures to cocaine are from nasal insufflation or from inhalation, gastrointestinal decontamination generally is not an issue. Ingestion may be lethal because this type of exposure occurs in the setting of smuggling large

amounts of cocaine. Decontamination may require the administration of activated charcoal and, if packets were ingested, whole-bowel irrigation. Any symptomatic patient in whom there is confirmed packet ingestion should undergo a laparotomy to remove the cocaine packets (Grade III recommendations). Internal concealment of drug in patients with suspected cocaine toxicity that is refractory to treatment or with clinical effects lasting longer than expected should be considered, among other differential diagnoses.

Treatment of the cardiac manifestations of cocaine toxicity is directed at reversing the pharmacological effects that cause ischemia or dysrhythmias. As stated earlier, benzodiazepines assist in normalizing blood pressure and heart rate and diminish myocardial oxygen demand. If the physical examination denotes catecholamine excess, benzodiazepines should be the initial treatment modality in patients with cocaine-associated chest pain [277] (Grade I recommendation). Theoretically, aspirin may prevent cocaine's thrombogenic effects. Aspirin has an extensive beneficial record in the treatment of patients with ischemic heart disease. We recommend that 325 mg of aspirin be administered in patients with cocaine-associated ischemic symptoms unless there is also a suspicion of cerebral hemorrhage (Grade III recommendation).

Clinical and angiographic data support the use of nitroglycerin to relieve cocaine-associated chest pain caused by coronary artery vasoconstriction [278, 279]. Cocaine-induced vasoconstriction was abolished in nine patients given sublingual nitroglycerin in a dose sufficient to reduce mean arterial pressure by 10–15% [278]. As in patients with classic ischemic chest pain, nitroglycerin should be the principal treatment for patients with cocaine-associated chest pain as well.

Because cocaine's vasoconstrictive effects are mediated by an α -adrenergic mechanism, the use of β -adrenergic antagonists for the treatment of cocaine-associated cardiac toxicity has resulted in deleterious consequences in human and animal studies [66, 99, 148, 197, 274, 280, 281]. In volunteers given 2 mg/kg of cocaine intranasally or intravenously, the administration of the

β -adrenergic antagonist propranolol caused further coronary artery constriction visualized angiographically [148–150, 278]. Similarly, a prospective cohort using esmolol to treat cocaine toxicity in seven patients resulted in three adverse effects including one hypotensive patient and one requiring intubation [281]. The use of mixed β -adrenergic antagonists, including labetalol, is contraindicated in patients with acute toxicity [280]. Despite this evidence of harmful and potentially lethal effects [282] of β -adrenergic antagonist use in the acutely cocaine-toxic patient presenting with chest pain, there is a resurgence of studies that create controversy regarding their use in this population, as well as the results of a systematic review of the literature [260]. However, these studies have several common limitations that have not changed the authors' conviction of β -adrenergic antagonist use contraindication in acute cocaine toxicity that is manifested by the sympathomimetic toxic syndrome (Grade II-3 recommendation). In all of these studies, data was gathered retrospectively by chart review, cocaine use was determined by urine test rather than by recent cocaine history, the timing and route of β -adrenergic antagonist administration was not exactly determined, administration of β -adrenergic antagonist was at the discretion of the clinician, and the populations in which the β -adrenergic antagonists were administered had more ACS risk factors [283–285]. In weighing the evidence of the risk/benefit of their use in patients with cocaine use and chest pain, the American Heart Association cautions against their routine use [286, 287].

Phentolamine, an α -adrenergic antagonist, reverses cocaine-induced ischemia [150, 288]. Based on limited evidence, we recommend a low starting dose (1 mg) of phentolamine to avoid hypotensive effects, while maintaining anti-ischemic effects (Grade I recommendation) [17]. This dose may be repeated in 5 min and be titrated to control of symptoms and blood pressure. This vasodilating agent with rapid-onset and short-lived pharmacodynamics is preferred because of its simple, dependable control.

Large multicenter clinical trials found calcium channel antagonists not beneficial in the treatment

of myocardial ischemia unrelated to cocaine, whereas in cocaine toxicity, smaller animal and human studies yielded conflicting results [150, 289–297]. In some animal studies, calcium channel antagonists decreased the incidence of seizures and cardiac dysrhythmias and increased survival [150, 289, 290, 295, 297]; others reported opposite results [291–293]. Verapamil reversed cocaine-induced coronary artery vasoconstriction in a human model [296] and is recommended by some authors for the treatment of refractory ischemia [17]. Because of these equivocal results, we recommend that calcium channel antagonists should be used with caution and only when other therapies have failed (Grade III recommendation).

Angiography and angioplasty are advocated by current guidelines in patients with cocaine-associated STEMI [286]. Angiography has been performed safely and successfully in patients with cocaine-associated chest pain [244, 298]. The poor predictive value of the ECG in cocaine-induced acute myocardial infarction and the low incidence of complications after such an event and the potential life-threatening adverse effect of thrombolytic therapy should discourage the routine use of thrombolytic therapy in this setting. In addition, because many patients with cocaine-induced myocardial infarction do not have a thrombus, cardiac catheterization may provide a definitive diagnosis and the ultimate reperfusion strategy when available. If invasive reperfusion facilities are unavailable, and the patient has clear ECG evidence of myocardial infarction without contraindications, thrombolytics may be used. Although the clinical safety of the use of thrombolytic therapy for cocaine-associated myocardial infarction has been documented [250, 299], this treatment modality has significant potential complications [300, 301] and remains a second-line therapy (Grade II-3 recommendation).

Most benign dysrhythmias secondary to cocaine toxicity respond to sedation, fluid administration, and cooling. Supraventricular dysrhythmias and atrial fibrillation that do not respond to this initial treatment may be treated with diltiazem or verapamil. Wide-complex supraventricular tachycardia occurring in an acutely cocaine-intoxicated patient is most likely secondary to cocaine's sodium channel-blocking effects on

the conduction system of the heart. As such, this effect is similar to that of class I antidysrhythmic drugs [168]. Animal and human data report the reversal of the subsequent QRS prolonging effect on the ECG with treatment with hypertonic sodium bicarbonate [59, 302–304]. We recommend a bolus of 1–2 mEq/kg of hypertonic sodium bicarbonate in patients with QRS widening in a pattern characteristic of sodium channel blockade (Grade III recommendation).

Ventricular tachycardia may be treated with lidocaine (Grade III recommendation). The effects of lidocaine on cocaine-poisoned animals are contradictory [304–306]. Concern of administering another class I antidysrhythmic agent with definitive CNS toxicity in cocaine toxicity exists. Evaluation of patients having cocaine-induced myocardial infarction who received lidocaine for various indications showed, however, clear absence of fatality, seizures, or cardiac complications in the emergency department or during subsequent hospitalization [169]. Amiodarone is commonly recommended for management of wide-complex tachycardias. However, the safety and efficacy of amiodarone in cocaine-toxic individuals is unstudied and its use cannot be recommended.

A small number of patients present with manifestations of toxicity that include myocardial dysfunction, wide-complex tachycardia and cardiocirculatory collapse refractory to volume repletion, sodium bicarbonate, and lidocaine. These patients require vasoactive support, preferably with a direct acting pressor, i.e., norepinephrine. Furthermore, in these patients, there may be a role for lipid emulsion therapy. There are limited specific experiences with its use in severe cocaine toxicity [307, 308], although there is more extensive experimental use in local anesthetic toxicity and with other drugs [309]. At this stage we believe that it should be considered a rescue therapy due to the lack of experience and concerns about its safety [310].

Besides the same recommendations concerning supportive care, control of psychomotor agitation, and treatment of hypertension in acute cocaine toxicity described above, there is no reason that further treatment of patients suffering a

stroke after the use of cocaine should not follow similar guidelines as those for individuals not exposed to cocaine. Retrospective data have shown that for subarachnoidal hemorrhage, cocaine use was associated with poor prognosis but not with vasospasm requiring treatment with angioplasty [123]. A small retrospective study showed no differences in safety or outcome with acute ischemic stroke treated with thrombolytic therapy in cocaine-positive and cocaine-negative patients [311].

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Gamma-Hydroxybutyrate and Its Related Analogues Gamma-Butyrolactone and 1,4-Butanediol

76

David M. Wood

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Gamma-hydroxybutyrate (GHB) is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) and is present endogenously in the human brain as a metabolite of GABA in low concentrations. GHB has had a variety of different medicinal uses since it was first introduced as a general anesthetic in 1964 [1]. Although it is not routinely used for this purpose, it is still sometimes used in the management of alcohol withdrawal and the treatment of narcolepsy with cataplexy [2, 3]. In recent decades there has been increasing recreational use of GHB amongst clubbers for its stimulant and prosexual effects, particularly amongst the men who have sex with men community [1, 4–6]. The related precursors and analogues, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), are not found endogenously. However, when they are used, they are metabolically converted to GHB resulting in clinical effects almost identical to GHB. The legal status of these compounds varies around the world, with control of GHB being more widespread. The widespread industrial use of GBL and 1,4-BD (e.g., in cleaning products) results in them often being less subject to legal controls than GHB [4]. This chapter will cover the pharmacology of these compounds, and patterns of acute toxicity, and associated chronic dependence.

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Biochemistry and Clinical Pharmacology

Gamma-hydroxybutyrate has the empirical formula $C_4H_8O_3$ (Fig. 1) and molar mass of 104.10 g/mol. It is often seen as the sodium salt (molar mass, 126.06 g/mol). Its melting point is $-17\text{ }^{\circ}\text{C}$ and boiling point is $178\text{--}180\text{ }^{\circ}\text{C}$. GHB, unlike its analogues, has previously had medical uses. Historically, it was used as a general anesthetic, antidepressant, and in the management of alcohol withdrawal (particularly in Italy) [3]; it is not currently used as an anesthetic or antidepressant. GHB is clinically used in the treatment of narcolepsy with cataplexy, marketed under the trade name, (Xyrem) [2, 7, 8]. Fermentation can result in production of small amounts of GHB, and it can be detected at low concentrations in alcoholic and nonalcoholic drinks and other food substances fermented particularly from grapes (typical reported concentrations are up to 10 mg/L) [9]. Data from animal and human studies showed GHB administration resulted in growth hormone secretion. In the 1970s and 1980s, it was used in the bodybuilding community as it was thought to increase muscle mass, although the actual evidence that it increased lean muscle mass is weak [10–12].

Gamma-butyrolactone has the empirical formula $C_4H_6O_2$ (Fig. 2) and molar mass of 86.09 g/mol. Its melting point is $43.5\text{ }^{\circ}\text{C}$ and boiling point is $204\text{ }^{\circ}\text{C}$. GBL is synthesized industrially through dehydrogenation of 1,4-butanediol; it can also be synthesized by oxidation of tetrahydrofuran. There are no medicinal uses for GBL. However, it has many uses as an industrial solvent and chemical reagent. It is also used as solvent in domestic products such as nail polish and superglue removers and household

cleaning products such as floor strippers. As a result of fermentation, GBL, like GHB, has also been detected in wine and other food substances fermented from grapes (concentrations not reported); there is the potential that this detection is related to the acidic nature of certain beverages favoring a shift in the equilibrium of GHB/GBL towards GBL [9]. Since GBL is a lactone (i.e., a cyclic ester), alkaline conditions result in ester saponification which converts GBL into GHB. The equilibrium for the interconversion of GHB and GBL depends on the pH of the environment.

1,4-butanediol has the empirical formula $C_4H_{10}O_2$ (Fig. 3) and molar mass of 90.12 g/mol. Its melting point is $20.1\text{ }^{\circ}\text{C}$ and boiling point is $235\text{ }^{\circ}\text{C}$. There are several methods of synthesis of 1,4-BD, including (i) reaction of acetylene with formaldehyde to form 1,4-butyndiol, which is hydrogenated to form 1,4-BD; (ii) conversion of propylene oxide to allyl alcohol, which is hydroformylated to form 4-hydroxybutyraldehyde, which is hydrogenated to form 1,4-BD; and (iii) conversion of maleic anhydride to the methyl maleate ester which is then hydrogenated. Biological synthesis pathways using genetically modified organisms have also been reported [13]. There are no medicinal uses for 1,4-BD, but it is used widely in industry as a solvent, in the manufacture of plastics and related products and in the synthesis of GBL.

Pharmacokinetics and Pharmacodynamics

Gamma-hydroxybutyrate and its analogues are rapidly absorbed following oral administration. Although GHB is available as a powder and could be administered by nasal insufflation, there are no reports on the absorption kinetics of this route. In addition, there are no data on the pharmacokinetics following intravenous injection of GHB or GHB analogues.

Eight healthy volunteers received an oral dose of 25 mg/kg GHB resulting in mean \pm standard

Fig. 1 Chemical structure of gamma-hydroxybutyrate (GHB)

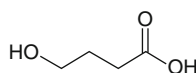


Fig. 2 Chemical structure of gamma-butyrolactone (GBL)

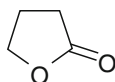
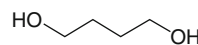


Fig. 3 Chemical structure of 1,4-butanediol (1,4-BD)



error of the mean (SEM) time to peak concentration (T_{max}) of 41.3 ± 2.5 min with peak plasma GHB concentrations of 39.4 ± 25.2 $\mu\text{g/mL}$ [14]. The overall mean (SEM) volume of distribution for GHB in this study was 52.7 ± 15.0 L. In a study of alcohol-dependent patients using GHB, the median T_{max} (30 min) and mean maximum concentration (C_{max}) (54 ± 19 $\mu\text{g/mL}$) were similar following a 25 mg/kg dose to those reported in healthy volunteers. Additionally, repeated dosing every 12 h resulted in no change in median T_{max} (30 min) and mean C_{max} (55 ± 19 $\mu\text{g/mL}$) after 13 doses [15]. In a further study of 32 healthy volunteers, following the oral administration of 20 mg/kg (16 subjects) and 35 mg/kg (16 subjects) GHB, there was no difference in the median time to peak plasma GHB concentration (T_{max}) [20 mg/kg – 35 (range 35–60) minutes and 35 mg/kg – 35 (35–60) minutes] [16]. It should be noted in this study that the first blood samples were collected 35 min postadministration, and it is possible that both the T_{max} and C_{max} may have occurred prior to the first measurement.

In a study of eight human volunteers, the mean \pm standard deviation (SD) time to peak 1,4-BD concentration following a single oral dose of 25 mg/kg 1,4-BD was 26.3 ± 12.0 min with a mean maximum plasma concentration of 3.84 ± 4.57 mg/L [17]. The overall mean (SD) apparent volume of distribution for 1,4-BD was 19.7 ± 18.6 L. Animal studies suggest that GBL is more rapidly and completely absorbed, with a higher maximum concentration and shorter time to maximum concentration than GHB with equimolar doses [18–21]. There are no pharmacokinetic data demonstrating whether this is also the case in humans. However, one study reported more rapid onset of sleep with oral GBL in children than with GHB [22]. Gamma-hydroxybutyrate readily crosses the blood brain barrier [23, 24]. The transfer of GHB into the central nervous system (CNS) is mediated by monocarboxylate transporters (MCTs). A rat model using in vivo microdialysis demonstrated that brain extracellular fluid (ECF) concentration-time profiles closely follow the concentration-time profiles seen in plasma. Following

intravenous administration of GHB, T_{max} for plasma and ECF were 5 and 50 min, respectively, irrespective of dose administered (400 mg/kg, 600 mg/kg, and 800 mg/kg) suggesting no saturation of MCT transport of GHB across the blood–brain barrier across this range of concentrations. It should be noted that these doses are significantly higher than those reported to be associated with coma in humans (>50 mg/kg), and therefore it is unlikely that saturation of blood–brain barrier transfer by MCTs is likely to occur in humans [25].

Following absorption, both GBL and 1,4-BD are metabolized in vivo to GHB; GBL is rapidly metabolized by calcium-dependent serum lactonases, whereas 1,4-BD is metabolized in the liver through two step conversion via hepatic alcohol dehydrogenase to gamma-hydroxybutyraldehyde followed by metabolism onto GHB via hepatic acetaldehyde dehydrogenase [21, 26–29]. This metabolism is rapid following absorption, with GHB being detected in volunteers within 5 min of 1,4-BD ingestion. Those without detectable GHB also had undetectable 1,4-BD concentrations probably reflecting delayed absorption rather than delayed metabolism of 1,4-BD to GHB [17]. In vivo animal studies in rats have shown that both ethanol and fomepizole competitively block the metabolism of 1,4-BD to GHB, through preferential metabolism by (ethanol) or direct inhibition of (fomepizole) alcohol dehydrogenase [29–31]. This is not used routinely in clinical practice to treat acute 1,4-BD toxicity since by the time acute toxicity occurs, a significant proportion, if not all, of the 1,4-BD will have been metabolized into GHB. However, there is the potential that co-use of ethanol with 1,4-BD may delay its metabolism because ethanol is preferentially metabolized and acute toxicity may therefore be delayed.

Following administration of 25 mg/kg of 1,4-BD to volunteers the elimination half-life (t_{1/2}) for 1,4-BD was 39.3 ± 11.0 min and the time to maximal GHB concentration was 39.4 ± 11.2 min after 1,4-BD administration with undetectable 1,4-BD concentrations by 4 h of dosing [17]. This human volunteer study also identified significant inter-individual variation in

the metabolism of 1,4-BD to GHB. Half the volunteers had rapid and extensive conversion of 1,4-BD to GHB and the other half had slower clearance of 1,4-BD, which the authors related to ADH-IB G143A polymorphism and resultant differences in activity of alcohol dehydrogenase. However, it should be noted that text in the paper conflicts with the information in the tables, and it is not clear how the authors defined which subjects were fast or slow metabolizers.

Gamma-hydroxybutyrate is rapidly metabolized via succinic acid semialdehyde to succinic acid, and studies suggest an elimination half-life of between 30 and 50 min [14–16, 27, 32]. The succinic acid produced is subsequently metabolized via the tricarboxylic acid cycle (the “Krebs cycle”). The mean residence time of GHB following oral ingestion (25 mg/kg) is reported to be around 58–73 min in both healthy volunteers and alcohol-dependent patients [14, 15]. This may suggest why users typically redose every 30–60 min when using GHB, due to the short mean residence time of GHB. In addition to the rapidity of GHB metabolism, this metabolism is also very extensive, with minimal amounts excreted unchanged renally. Following an oral dose of 25 mg/kg in both healthy volunteers and alcohol-dependent patients, the recovery of unmetabolized GHB in urine over the subsequent 24 h is only around 0.73–1.2% of the administered dose [14, 15]. Additionally, in a study of eight healthy volunteers given 25 mg/kg GHB, no GHB was detected in any of the samples collected at 24 h postingestion. Of those collected 12 h postingestion, four had GHB detected but all at concentrations below the recommended 10 µg/ml threshold used to differentiate endogenous and exogenous GHB. Therefore, in forensic testing, all of the 12-h samples would have been reported as negative. There was no effect on urinary GHB concentrations in 16 healthy volunteers given 50 mg/kg GHB alone or in combination with 0.6 g/kg ethanol [32, 33]. Similar to other studies, GHB was only detected in samples collection between 0–3 and 3–6 h, although two subjects had urine GHB concentrations below the proposed 10 µg/mL threshold at 3–6 h postingestion. Although there appeared to higher early urine

GHB concentrations following lone administration (in samples collected between 0 and 3 h postadministration), when urine concentrations were standardized to creatinine there was no difference (898 µg GHB/mg creatinine for lone GHB administration compared to 980 µg GHB/mg creatinine for combined GHB/ethanol administration). Interestingly, there appeared to be a racial difference with lower urinary GHB concentrations in Caucasian subjects (7 subjects) compared to non-Caucasian subjects (9 subjects), although it should be noted that the numbers of subjects in each group are low. Following the oral administration of 20 mg/kg and 35 mg/kg GHB to 32 subjects, there was no difference in half-life of GHB of 36 ± 9 and 39 ± 7 min, respectively. However, when the area under the curve (AUC_{0–∞}) for the 35 mg/kg dose was normalized to 20 mg/kg, the geometric mean was significantly greater than that seen for the actual 20 mg/kg dose (20 mg/kg dose 15,747 nmol.min/mL; normalized 35 mg/kg dose 22,922 nmol.min/mL, $p < 0.01$), which suggests a nonlinear dose–response relationship for GHB despite no difference noted in the C_{max} or t_{1/2} between the two doses. GHB is actively reabsorbed from the proximal convoluted tubule of the nephron by both pH-dependent and sodium-dependent monocarboxylate transporters (MCT and SMCT) [34, 35]. There is the potential that inhibition of this reabsorption could increase renal clearance of GHB, therefore reducing its half-life increasing the overall renal elimination of unmetabolized GHB. Animal models in vitro and in vivo have shown that L-Lactate, which is transported by MCTs, can significantly reduce resorption of GHB and increase the renal clearance of GHB [34–38]. When L-lactate (330 mg/kg bolus then 121 mg/kg/h) was administered to rats 5 min after 60 mg/kg intravenous GHB, there was a significant reduction in the AUC and increase in renal clearance of GHB compared to when GHB was administered alone [AUC 131 ± 8.8 -vs- 74.4 ± 9.4 mg.min/mL, $p < 0.05$; renal clearance 0.415 ± 0.06 -vs- 0.910 ± 0.10 mL/min, $p < 0.05$], which resulted in a significantly reduced sleep time [GHB alone 126 ± 15.1 min compared to 87.0 ± 11.1 min, $p < 0.05$] [36]. It should be noted that MCTs are widely distributed

throughout the body, including at the blood–brain barrier [39]; there is the possibility that some of the reduction in sleep time seen was due to reduced CNS transfer of GHB rather than increased renal clearance of GHB. However, there is the potential for future studies to look at development of more specific renal MCT and or SMCT blockers to increase renal clearance of GHB as potential therapeutic agents to shorten the duration of coma in patients with acute GHB toxicity.

Gamma-aminobutyric acid is converted to succinic semialdehyde which can be converted to GHB. This conversion can be reversed to GABA by GHB dehydrogenase [23]. Gamma-hydroxybutyrate has a number of actions within the brain on different neurotransmitters, receptors, and pathways. Unlike other sedatives (e.g., benzodiazepines and barbiturates), GHB has no action on GABA-A receptors [40]. These actions include: (i) partial agonist actions at the GABA-B receptor (in part due to GHB itself and in part due to conversion to GABA); (ii) “GABA-like” activation of chloride channels; (iii) inhibition of pre-synaptic voltage-gated calcium channels (reduced neurotransmitter release); and (iv) increased opening of inward rectifying potassium channels (reduced postsynaptic excitability). These actions result in inhibition of dopamine release and glutamatergic transmission and increases in serotonin [24, 41, 42].

Chronic administration of GHB leads to cross-tolerance to baclofen (GABA-B receptor activity) but not flunitrazepam (GABA-A receptor activity) [43]. Gamma-hydroxybutyrate acts at GABA-B receptors to inhibit dopamine release, which can lead to upregulation of dopamine receptors with chronic use [44]. Animal studies show that GHB enhances dopamine concentration in the substantia nigra and the mesolimbic system both by reducing nerve firing and stimulating intracellular production [45]. During withdrawal, augmented dopamine release within these areas contributes to the psychotic symptoms seen. Chronic use of GHB (similar to that seen with chronic use of alcohol, benzodiazepines, and baclofen) is associated with down-regulation of the inhibitory GABA receptor [46–50]. This leads to

an increase in release of excitatory neurotransmitters and release of inhibition of excitatory pathways, such as dopaminergic neurotransmission pathways.

In an in vivo rat microdialysis model studying GHB concentrations in brain extracellular fluid, sleep time increased with increasing concentrations of GHB administered ($200\text{ mg/kg} - 90.4 \pm 14\text{ min}$ compared to $800\text{ mg/kg} - 171 \pm 12\text{ min}$) [25]. In a further rat model, increasing doses of GHB (200 mg/kg , 600 mg/kg , and $1,500\text{ mg/kg}$) were shown to have a dose-dependent effect on reducing respiratory rate with a matched increase in tidal volumes; this effect on both respiratory rate and tidal volumes was more prolonged in duration with higher doses of GHB administered [38]. In this model, administration of a GABA-B inhibitor (SCH50911) blocked the GHB mediated effects on respiratory rate and tidal volume, whereas the GABA-A inhibitor bicuculline had no effect. The effects of the GABA-B inhibitor were also dose-dependent, with a “threshold” to improve all respiratory pharmacodynamics parameters of 10 mg/kg . Administration of L-Lactate as an MCT inhibitor demonstrated that L-Lactate on its own had no effect on respiratory rate or tidal volume, but in the presence of GHB ($1,500\text{ mg/kg}$) L-lactate partially reversed some of the respiratory effects seen with GHB. Additionally, there was an additive effect when combined with SCH50911 (5 mg/kg), with improvement in all respiratory pharmacodynamics parameters. As previously described, the administration of L-Lactate was associated with an increased renal clearance. Therefore, it is likely that the respiratory effects of GHB are mediated through the GABA-B receptor and that the effect of L-Lactate is through increased renal clearance and associated reduced serum GHB concentrations rather than any effect directly on respiratory pharmacodynamics.

Doses in humans of 10 mg/kg , $20\text{--}30\text{ mg/kg}$, and $>50\text{ mg/kg}$ are reported to be associated with anxiolytic, hypnotic, and potentially acute severe unwanted effects such as coma, respectively. In context, many recreational users report using “a capful,” and the dose per cap varies between 500 mg to 5 g . In a human volunteer study of

32 healthy males given either 25 mg/kg or 35 mg/kg oral GHB, there was no significant effect of either dose of GHB on blood pressure (systolic or diastolic) or heart rate, although there was no report of the effect on respiratory rate or effort [16]. Volunteers reported that GHB was associated with sedation, stimulation, and dizziness lasting 2 h and that the sedation and dizziness was greater with the higher dose (no effect on stimulant effects was seen with increased dose). There was no reported acute pharmacological tolerance to GHB seen in this study, and higher plasma concentrations generally appeared to be associated with greater subjective effects. Interestingly, maximal sedative effects were seen with peak plasma concentrations (between 35 and 60 min after administration), whereas maximal stimulation and dizziness was seen around 60 min after administration (a time when GHB concentrations were already falling).

In a study of 1,4-BD in eight healthy volunteers, blood pressure transiently increased 15 min following administration, whereas oxygen saturations (respiratory rate and tidal volume values were not reported) decreased compared to placebo by 45 min following administration and remained reduced for around 100 min [17]. In terms of subjective effects, subjects were less awake/alert ($p = 0.013$), less able to concentrate ($p = 0.045$), and more light-headed/dizzy ($p = 0.01$) compared to placebo. Effects were maximal within 60–90 min postdosing and last for up to 4 h.

Prevalence of Use

Data on the prevalence of use of GHB and its related analogues GBL and 1,4-BD are not routinely collected at a population level. The United Nations Office on Drug and Crime 2015 World Drug Report did not report on the prevalence of use of GHB [51]. The 2015 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) European Drug Report noted that only Norway provided information on the prevalence of use of GHB, with a last year prevalence of use rate in 15–64-year-olds of 0.1% [52]. The British Crime Survey has included GHB in its annual survey of 16–59-year-olds in England

and Wales since the 2009 survey (this has subsequently been renamed the Crime Survey England and Wales). The most recent data on the use of GHB and GBL was from 2011/2012, where 0.1% of those aged 16–59 years self-reported GBL/GHB use in the last year (an increase from 0.0% in the 2010/2011 survey). Although not reported in the 2011/2012 survey, in the 2010/2011 survey there was greater use in younger people (last year use 0.1% in those aged 16–24 years old compared to 0.0% in those aged 24–59 years old) [53, 54].

Since there is limited data available at a population level, most of the information on the prevalence of use of GHB and its related analogues comes from subpopulation level surveys, particularly school children and those who frequent nightclubs and other night-time economy venues. One of the difficulties in interpreting the prevalence of use of GHB and its related analogues relates to how survey participants have been asked about their use; in some they are asked about GHB, some ask about GHB and GBL separately and some combined GHB/GBL use. Therefore, it is not possible to easily determine the relative use of GHB compared to GBL. It should be noted that the majority of surveys do not ask about the use of the related analogue, 1,4-butanediol, and therefore there is little information available on its prevalence of use.

The European School Survey Project on Alcohol and other Drugs (ESPAD) is a longitudinal study surveying school students aged 15–16 years old every 4 years since 1995 to monitor trends in alcohol, smoking, and recreational drug use [55]. Approximately 103,000 European students were surveyed across 36 countries in the 2011 ESPAD survey [56]. Overall lifetime prevalence of use of any illicit drug was 18%, with a higher lifetime prevalence in boys (21%) compared to girls (15%); this was an increase from a lifetime prevalence rate of illicit drug use of 11% in the initial 1995 survey [56, 57]. In 2011, cannabis was the most prevalent illicit drug, with lifetime prevalence rates of 19% for boys and 14% for girls. In comparison, the average lifetime prevalence of use of GHB in the 2011 ESPAD survey was 1% and ranged from 0% to 3% across the 36 countries

involved. Although there was no overall difference in lifetime prevalence of GHB use between boys and girls, where there were gender differences in individual countries and typically rates amongst boys were higher than girls apart from Denmark (boys 0%, girls 1%) and Liechtenstein (boys 1%, girls 3%) where there was a reported higher lifetime prevalence in girls.

The Monitoring the Future project based in the USA surveys approximately 50,000 8th (13–14 year olds), 10th (15–16 year olds), and 12th (17–18 year olds) grade students every year, since the first survey of 12th graders was undertaken in 1975 [58]. While this longitudinal study includes questions on other recreational drugs, it does not include questions about the use of GHB or related analogues.

The Independent Drug Monitoring Unit in the UK, which conducts on-line surveys of drug users reported the relevance of GHB use between 1999 and 2002; although this data is rather historical now, there was a year-on-year increase in the reported lifetime prevalence of use of GHB from 2.8% in 1999 to 3.9% in 2002 [59].

The MixMag drug surveys undertook annual surveys of clubbers, initially through the MixMag dance magazine, and then more latterly through the MixMag Internet site. The initial surveys of 3,873 clubbers between 1999 and 2003 demonstrated lifetime use prevalence rates of GHB varying from 12.8% in 1999 to 17.5% in 2003, and last month use rates varying from 3.4% in 1999 to 3.1% in 2003 [60, 61]. These surveys did not include data on use of the related analogue GBL. The last MixMag drug survey, undertaken in 2010/2011, reported on the use of both GHB and GBL; lifetime prevalence of use of GHB amongst those surveyed was 14.8% and of GBL was 5.6%; last month use of GHB and GBL were 2.5% and 2.4%, respectively [62]. Since then, the MixMag Drug Survey has been expanded to become the Global Drug Survey, which includes different methods of recruitment for participants and also recruits from an increasing number of countries around the world. The 2012/13, 2013/14, and 2014/15 Global Drugs Surveys have not specifically included GHB or GBL in their annual reports; therefore, the latest data is available from

2011/12 only [63]. Since this change in the survey methodology, in the 2011/12 survey there appeared to be an increase in the prevalence of use of GBL compared to GHB in UK respondents (lifetime use 7.7% compared to 3.8%; last year use 1.6% compared to 1.5%). Similar to other studies, there appeared to be higher rates of use amongst those who self-classified themselves as “frequent clubbers,” with last year rates of use of 2.5% for GBL and 2% for GHB. In addition, this survey also specifically reported last year use amongst US respondents, although prevalence of use appeared to be lower than in the UK (US respondents: GBL 1% and GHB <0.5%).

There have been a number of in situ surveys undertaken amongst clubbers in a variety of different settings, which suggest a high prevalence of use of GHB and GBL amongst the “gay” (men who have sex with men) clubbing scene. In a survey of 408 individuals in bars in Amsterdam, the Netherlands, overall lifetime prevalence of GHB/GBL use was 10%, although there was a higher prevalence of use in those surveyed in “gay” (men who have sex with men) bars (17.5%) compared to those surveyed in “more mainstream” bars (<5%) [6]. A survey of 308 clubbers in “gay friendly” dance clubs in South East London in 2010 reported a higher lifetime prevalence of use of GHB in comparison to GBL, although more recent use of GBL was higher than GHB: (i) lifetime GHB 34%, GBL 27%; (ii) last year GHB 22%, GBL 24%; (iii) last month GHB 14%, GBL 19%; (iv) already used/planning use on the night of the survey GHB 7%, GBL 14% [64]. In a subsequent in situ survey of 315 clubbers in the same South East London nightclubs 1 year later in the summer of 2011, use of either GHB and/or GBL on the night of the survey was the second most common drug (24% of participants) after mephedrone (41% of participants) [5]. GHB/GBL was also the second most favorite drug (12% of participants) in this survey, again behind mephedrone (20% of participants).

There is a similar pattern of higher reported use of GHB and GBL amongst men who have sex with men attending sexual health clinics [65]. In a

self-completed questionnaire survey of 729 males attending two London sexual health clinics, there was a significantly greater use of both GHB and GBL amongst the 254 men who have sex with men (MSM) survey participants compared to the 475 non-MSM participants: (i) lifetime GHB use 22.7% compared to 5.7%; (ii) last month GHB use 2.4% compared to 0.2%; (iii) lifetime GBL use 16.1% compared to 2.7%; and last month GBL use 3.1% compared to 0.2%. Interestingly, similar to the in situ nightclub surveys, although lifetime use of GHB was greater than GBL, more recent use demonstrated a potential switch towards GBL use.

Clinical Presentations and Life Threatening Complications

Acute Toxicity

In addition to the discussion of acute toxicity related to the use of GHB below, there is the potential for elevated GHB concentrations as a result of a rare autosomal recessive condition known as succinic semialdehyde dehydrogenase deficiency which was first described in 1981. This condition has been documented in 350–400 families worldwide, most of which are consanguineous. The clinical features of this condition are the result of GHB accumulation due to inhibited GHB metabolism. Reports describe a range of clinical features including hypotonia, hyporeflexia, seizures, and ataxia.

There have been numerous reports of acute toxicity associated with the use of GHB, GBL, and 1,4-BD [4, 66–69]. The majority of these reports were initially related to GHB as this was the most commonly used drug, although more recently there have been increasing reports of acute toxicity related to the use of GBL. This not only mirrors the changes in the self-reported prevalence of use of GBL compared to GHB seen in the UK following the control of GHB, but also data from analysis of liquid samples seized at nightclubs [4, 66, 69]. Despite these changes, the pattern of acute toxicity is similar for GHB and

both related analogues as the toxicity is related to the GHB to which the analogues are metabolized. The only thing to note is that since 1,4-BD is metabolized to GHB predominately by alcohol dehydrogenase, in the presence of alcohol the onset of acute toxicity may be delayed as the alcohol will be metabolized preferentially over 1,4-BD [29–31].

There are a number of reasons why the true frequency of acute harm related to the use of GHB and its analogues is not known. Firstly, we do not have a true background rate of GHB and analogue use to compare the reported rates of acute toxicity. Secondly, not all patients who develop acute unwanted effects related to the use of GHB and its analogues will present to healthcare facilities for assistance. Some individuals who become drowsy will be looked after by “friends” until they get better. Finally, the recording of acute GHB or analogue toxicity by healthcare professionals may not always occur. For example, if there is no history of use or the healthcare practitioner is not aware of the clinical toxidrome associated with toxicity from GHB or its analogues, then the presentation may be attributed to ethanol or another depressant drug. Routine toxicological screening is not undertaken in the majority of emergency departments, as the results are generally not available in a time-frame to alter that individual patient’s management. In addition, where screening is undertaken, often this does not include GHB and its analogues. Therefore, the diagnosis of acute GHB or analogue toxicity is based upon the recognition of the clinical toxidrome associated with the overdose of GHB or its analogues.

In a survey of 76 GHB users (defined as use within the last 6 months) in Sydney and Melbourne, Australia, 53% reported that they had at least one overdose related to the use of GHB (the study authors defined an overdose as “having lost consciousness, and unable to be woken up”) and 63% had seen another individual overdose on GHB [10]. Thirty three percent of those who had overdosed had done so on more than three times; individuals who had previously overdosed on GHB thought they more likely to overdose

again in the future compared to those who had never overdosed (33% compared to 6%, $p < 0.05$). Those individuals who had overdosed on GHB had used for longer (median years of GHB use: 2 compared to 1 year, $p < 0.001$), used more times (median number of times ever used: 35 compared to 7, $p < 0.001$), and used more frequently (median number of days in last 6 months: 7 compared to 3, $p < 0.01$). In addition, there was an increased frequency of overdose amongst more frequent users; of those who had used >15 times, 75% had overdosed at least once. The most common reasons study participants gave for their last overdose were too much GHB taken (37%) and GHB stronger than usual (21%); whereas few participants identified too frequent dosing (8%), use with alcohol (8%), or lack of knowledge (0%) as contributing factors. Interestingly, when considering why others overdosed on GHB, too frequent dosing (15%), use with alcohol (17%), and lack of knowledge (22%) were more commonly reported. Setting of use appeared likely to impact on whether an individual gets medical attention or is taken to hospital – dance party/club 50%, public place 33%, and private house 19%; this is important in terms of education for individuals around GHB overdoses. The most recent 2015 Global Drugs Survey, formerly known as the MixMag survey, asked over 1,000 GHB users (exact number was not reported) about previous issues related to the use of “G” (GHB or GBL) [70, 71]. Of those who participated, “1 in 5” reported that they had passed out on “G” in the last year. In the European Drug Emergencies Network (Euro-DEN) project, of the 5,529 presentations to the 16 cities in 10 European countries between 1st October 2013 and 31st September 2014, 711 (13%) involved the use of GHB and/or GBL [72]. Overall, GHB/GBL was the fourth most common drug associated with an emergency department presentation after heroin, cocaine, and cannabis. There was significant geographical variation in the presentations where GHB/GBL had been used, with nearly 92% of cases being in the London, UK; Oslo, Norway; and Barcelona, Spain centers.

There are certain behaviors that have been associated with a higher-risk of hospitalization associated with the use of GHB. In a survey of 131 individuals, 26 reported the need for hospital treatment on at least one occasion for GHB-related toxicity/adverse effects [73]. The study authors had ten predefined high-risk behaviors, and participants were asked to determine whether any of these contributed to the need for hospital treatment. Of these ten predefined behaviors, four were associated with significantly increased risk of hospital treatment: (i) using GHB with ethanol – done by 58%, odds ratio (OR) of requiring hospital treatment 5.2 (95% CI 1.7–16.1); (ii) driving under the influence of GHB – done by 29%, OR of requiring hospital treatment 3.2 (1.3–7.8); (iii) use of GHB to treat withdrawal symptoms – done by 17%, OR of requiring hospital treatment 2.9 (1.1–7.9); (iv) co-use with ketamine – done by 23%, OR of requiring hospital treatment 2.7 (1.1–6.7). Certain high-risk behaviors were associated with certain population groups: (i) sex under influence of GHB was associated with being male, aged >30 years old or gay/bisexual/transgender; (ii) use of a GHB analogue or precursor was associated with being male; (iii) driving under influence was associated with being male; and (iv) use of GHB on their own was associated with being a non-LGBT individual.

The clinical features of acute GHB and analogue toxicity have been well described in five large case series totally 585 patients from London, UK (158 patients); Zurich, Switzerland (65 patients); San Francisco, USA (88 patients); Barcelona, Spain (104 patients); and Melbourne, Australia (170 patients) [4, 69, 74–76]. Overall, the commonest clinical feature seen in all of these case series was neurological depression; other commonly seen clinical features included bradycardia, hypotension, and mild hypothermia.

There was variability in the concurrent use of other recreational drugs in these case series, with 28–78% reporting use of other recreational drugs [4, 69, 74–76]. The most commonly reported co-used substances were stimulants [London – methylenedioxymethamphetamine (MDMA)

21% and cocaine 34% of presentations; San Francisco – Amphetamine 17% and MDMA 14%; Zurich – MDMA 18%, Cocaine 15% and Amphetamine 8%; Barcelona – Amphetamine derivatives 43% and cocaine 25%; Melbourne – MDMA 37% and methamphetamine 24%]. Not only it is possible that some of the clinical features reported to be associated with acute toxicity related to the use of GHB or its analogues may be “masked” by these stimulant substances, but they could impact on severity of acute toxicity (discussed in more detail in the management section below). An example would be the expected bradycardia from acute GHB toxicity may not be present in an individual who has co-used a stimulant recreational drug. In addition, it is possible that the acute GHB toxicity may be accentuated by concurrently used sedative substances. The co-use of ethanol was higher than would be expected (between 22% and 73% of presentations there was reported co-use of ethanol with the lowest co-use in the Australian case series and the highest co-use in Spanish case series), particularly as many individuals report that they are aware of the risks of co-use of sedatives with GHB or an analogue. In addition, there was a lower reported use of other sedatives (benzodiazepines 3%, opioids 1–2%, and “sedatives” 2–8%). Previous reports have suggested that co-use of ethanol concurrently with GHB is more likely to be associated with the presence of severe GHB-related complications [69, 73, 77]. In the Swiss case series, co-use of ethanol with GHB/GBL was associated with a significant increased risk of agitation/aggression (9 out of 31 (29%) patients) compared to those with sole GHB/GBL use (2 out of 34 (6%) patients, $p < 0.02$) and a nonsignificantly increased risk of vomiting (combined GHB/GBL-Ethanol use: 12 out of 31 (38%) patients; sole GHB/GBL use: 8 out of 34 (24%) patients, $p < 0.07$) [69]. However, in this case series the co-use of ethanol with GHB/GBL was not associated with any worsening of the level of consciousness or the duration of coma compared to lone GHB/GBL use. In the placebo-controlled double-blind study of GHB and ethanol taken alone or in combination discussed in more detail previously in the

pharmacology section, there was a higher rate of adverse effects in the GHB-ethanol co-ingestion arm compared to either the lone ethanol or lone GHB arm [33]. The increased risk of adverse effects included: Vomiting – 6 cases in the combined GHB-Ethanol arm, 1 case in lone GHB arm, and 1 case in lone ethanol arm; Hypotension – both episodes of significant systolic hypotension (SBP 71–73 mmHg) occurred in the combined GHB-Ethanol arm; Hypoxia – all three treatment arms lead to reduced oxygen saturations (hypoxia) compared to placebo for the 4-h duration of observation, although the reduction ($-2.12 \pm 0.34\%$) seen in the combined GHB-Ethanol arm was significantly greater than the lone GHB arm ($p = 0.0027$) and lone ethanol arm ($p = 0.013$). Although there was no statistical difference in the pharmacokinetic profile of GHB when taken either alone or in combination with ethanol, there was a nonsignificant increase in both the C_{max} (16% increase) and half-life (29% increase) which could possibly explain the increased adverse effects in the combined GHB-Ethanol group.

The most common clinical feature was a reduced level of consciousness – all patients in the Spanish cohort had coma (Glasgow Coma Score (GCS) ≤ 8) on the scene of use [74]. Although the time of transfer from the scene of acute toxicity to the Emergency Department (ED) was not reported, 50% had recovered to a GCS > 8 by the time of arrival in the ED. The overall rate of “nonresponsive coma,” typically defined as a GCS of 3/15, in the large case series ranged from 16% to 34% [4, 69, 74–76]. Despite this proportion of individuals with a “nonresponsive coma,” overall only 3–17% required endotracheal intubation for management of their airway.

Overall, in the previous published case series of acute toxicity the reported rates of intubation were 2–12% [69, 74, 76]. In the Australian case series, of those patients with a “low GCS” (not specifically defined) on arrival at the Emergency Department, 87% were not intubated. Overall in this case series 87 (51%) had an “airway intervention” – this included an oropharyngeal airway (51 patients), nasopharyngeal airway (23 patients),

and/or endotracheal intubation (13 patients) [76]. It is not possible to determine what proportion of those who were intubated failed the use of an airway adjunct prior to intubation from the information reported. It should be noted that – unlike patients presenting with a GCS ≤ 8 for other medical reasons, who are commonly intubated – of the 33 patients with a GCS of 3/15, only 33% were intubated and the remaining 67% were managed conservatively without the need for intubation [74, 75]. Additionally, given the rapid recovery from acute GHB or related analogue toxicity, patients may regain consciousness rapidly; in the Australian case series the median time from admission to the Emergency Department and recovery of GCS to 14 or 15 was 112 min [76]. This rapid recovery of neurological depression can mean that those who have been intubated in the Emergency Department often wake rapidly and can be extubated prior to transfer to a Level 2/3 bed; in the US case series, 2 (18%) of the patients intubated for a reduced level of consciousness woke up sufficiently to be extubated and discharged direct from the Emergency Department [75]. In the Australia case series, where 13 (8%) patients were intubated (1 prehospital and 12 in the Emergency Department), 9 (69%) were successfully extubated in the Emergency Department and discharged directly home [76].

In a case series of 21 individuals with suspected acute GHB toxicity at rave parties that were screened for the presence of GHB, 6 had no GHB detected although they had blood alcohol concentrations between 2.5 and 3.2 mg/L [78]. The median time that individuals had a GCS of ≤ 8 was 90 min (30–105 min) and the median time from GCS ≤ 8 to a GCS ≥ 12 was 30 min (range 10–50). Once a patient had a GCS of >9 , their GCS did not drop below 8 again. The median GHB concentration when patients had their last GCS ≤ 8 was 183 $\mu\text{g/L}$ (100–321). However, by the time the patient had woken up the median concentration had fallen to only 150 $\mu\text{g/L}$ (78–256), suggesting that patients woke up while still having significantly high GHB concentrations. Serial serum GHB concentrations were measured in 15 patients who presented with

acute GHB toxicity to an Emergency Department in San Francisco, the initial serum GHB concentration in the whole study population [median 180 mg/L, range 45–295 mg/L] was comparable to that in the 11 who developed a GCS of 3 [median 193 mg/L, range 124–242] [79]. Peak GHB concentrations did not correlate with time to awakening, and when patients had recovered to a GCS of 15, serum GHB concentrations were declining from initial peak concentrations on arrival but were still in the range 75–150 mg/L (range 0.5–2.5 h after initial concentration).

The range of patients who had vomiting in these series was between 16% and 31% [4, 69, 74–76]. The effect of co-use of ethanol with GHB was reported to nonsignificantly increase the risk of vomiting (39% in those with co-used ethanol compared to 24% in those who had not co-used ethanol) [69]. Typically, vomiting in the context of a reduced level of consciousness, in particular those with a Glasgow coma scale (GCS) of ≤ 8 , is thought to increase the risk of aspiration due to the lack of protective airway reflexes. Of the 28 patients with vomiting in the Australian case series, 20 had vomiting with reduced GCS (defined as ≤ 13), only 2 were intubated [76]. In a US case series of 88 patients, vomiting typically occurred either during the emergence from the coma and/or during periods of fluctuating levels of consciousness during recovery from the acute overdose [75]. Of the 22 patients who had vomiting, there were no documented episodes of pulmonary aspiration, despite 85% of these individuals having an initially GCS of ≤ 8 .

The reporting of cardiovascular toxicity in the case series can be difficult to interpret due to the high proportion of patients who have co-used other substances, particularly stimulants, which may have their own acute cardiovascular toxicity. Bradycardia was reported in between 20% and 38% across the published series, although the definition of bradycardia varied between case series between <55 and <60 beats per minute (bpm). There was a significant correlation between level of consciousness and bradycardia [69]. Patients with bradycardia (defined as heart rate ≤ 55 bpm) had a median initial GCS score of 4 compared to a median GCS of 9.5 in those

without bradycardia [75]. Hypotension has also been reported in a number of patients, although generally this was associated with the co-use alcohol and/or other recreational drugs and/or the presence of other cardiovascular or neurological toxicity [74, 75]. For example in the US case series, all 10 patients with hypotension had taken alcohol and/or at least one other recreational drug and six had concurrent bradycardia [75]. Similarly, in the Spanish case series, all seven patients with hypotension had a GCS ≤ 7 on arrival to the Emergency Department, all had taken alcohol and/or at least one other recreational drug and four patients were also bradycardic [74].

Seizures were documented to have occurred in 2–10% of the five large case series [4, 69, 74–76]. Although not formally reported in the case series, it was commented that often the “seizures” occurred in the prehospital setting and/or were unwitnessed by medical professionals; in the Swiss case series where 5 (8%) patients had seizures, only 1 was witnessed by hospital staff within the Emergency Department [69]. It is known that GHB and its analogues can cause myoclonic jerks, with 3% and 4% of patients in the Spanish and Australia case series reported to have myoclonus, respectively [74, 76]. Therefore, it is not possible to determine what proportion of the “seizures” were in fact misinterpreted “myoclonic jerks.”

Chronic Dependency and Withdrawal

The prevalence of GHB and related analogue dependency and associated physical withdrawal on cessation of use is currently not clearly understood. This lack of understanding was highlighted in the 2008 European Monitoring Centre for Drugs and Drug Addiction “emerging trend case report” on GHB and its precursor GBL, where the EMCDDA noted that there was no pan-European system for reporting or collating data on the frequency of GHB or related analogue dependency [80].

As discussed earlier, GHB has been used in the management of alcohol dependency, which provides some data on the misuse of GHB in this

setting and the potential for GHB dependency developing. In an Italian multicenter study, 179 patients with alcohol dependency were recruited from 19 centers and treated in an open label study with 50 mg/kg GHB three times per day for 24 weeks [81]. Of the 109 participants who completed the study, 11 (10.1%) showed “craving” for the GHB and voluntarily increased their doses, in some cases to six to seven times the recommended treatment dose, to obtain the desired anxiolytic and hypnotic effects. Gallimberti and colleagues reviewed their use of GHB (up to 300 mg/kg/day in divided daily doses) in the management of Italians with dependence from psychoactive substances (138 alcohol dependent, 23 opiate dependent, and 34 polydrug dependent individuals) to determine the abuse potential of GHB in these settings [3]. Of the 195 patients recruited into these two studies, 29 (14.9%) were thought to show “GHB abuse.” The authors characterized these into three distinct groups: Group 1 7 patients who self-increased the dose of GHB up to twofold recommended dose as they felt the prescribed dose was too low; Group 2 12 patients who increased the dose of GHB in a similar fashion, but this was associated at times with episodes of acute intoxication; Group 3 10 individuals who appeared to have GHB dependency with similar behaviors as seen in those patients with alcohol and/or drug dependency (constant engagement with searching for the euphoric, empathogenic, hypnotic, anxiolytic, and/or antidepressant effects of GHB), with individuals reporting that “life without GHB was unacceptable.” Overall, this equated to GHB dependency prevalence of approximately 5%.

More recent studies have suggested that individuals with previous heroin or cocaine dependency may be at greater risk of developing GHB dependency when it is used for the management of alcohol dependency [82]. Craving for and abuse of GHB was studied in an open label study of 50 mg/kg GHB three times a day for 3 months given to four groups of patients: Group 1 – lone alcohol dependency (14 patients); Group 2 – alcohol dependency with previous heroin dependency (abstinent for >12 months) (10 patients); Group 3 – alcohol dependency with previous cocaine

dependency (abstinent for >12 months) (13 patients); or Group 4 – alcohol dependency on a current methadone replacement treatment program (10 patients). There was no reported craving or abuse in the group 4 patients, and while 2 (14.3%) of patients in Group 1 had cravings for GHB, there was no reported abuse. However, in those patients with previous cocaine dependency (Group 3) although reported rates for craving were not significantly different from those without previous cocaine dependence (38.5% compared to 14.3%, $p = 0.1$), there were significantly high rates of abuse (38.5% compared to 0%, $p = 0.01$). Those patients with previous heroin dependency had significantly higher rates of craving (90.0%, $p < 0.001$) and abuse (60.0%, $p < 0.001$) compared to those without. It has been postulated that chronic heroin and/or cocaine use can lead to down-regulation of dopamine D1 and D2 receptors and that these changes can persist for prolonged periods after cessation of use of the drug [82–85]. In addition, chronic cocaine use can lead to reduction in GABA-B receptor activity in the meso-cortico-limbic areas, reducing dopamine release and potentially predisposing individuals to craving and abuse for GHB since this acts through GABA-B receptors [82, 86, 87]. There are no published data on whether those individuals who are previous or current users of stimulant or other recreational drugs have a higher prevalence of GHB and related analogue dependency.

The first case of GHB-related dependency was reported in the medical literature in 1994 [88]. A 30-year-old female patient had been consuming 25 g of sodium oxybate (which is GHB) per day in five divided doses for approximately 2 years; she reported that use was associated with “feelings of relaxation, increased libido and striking euphoria.” Three months prior to presentation, she had abruptly reduced her daily intake to 10 g per day (2 g five times per day) with “anxiety” that lasted for approximately 1 week. On six occasions following the reduction to 10 g she attempted to stop use completely; on each occasion, within 12 h of her last dose, she developed tremor and anxiety. Following review in a drug treatment facility she was told to cease GHB use but was not provided

with any pharmacological intervention to manage the withdrawal symptoms; she subsequently was reviewed following a period of abstinence and reported that she had had insomnia, tremor, and anxiety for 12 days following cessation of use.

The same drug treatment facility reported a case series of eight individuals with GHB use related issues in 1997, five of these eight individuals had symptoms suggestive of GHB-dependency and withdrawal on cessation of use [89]. One of these had been previously published and is discussed in detail above [88]. The other individuals were one female and three males aged between 31 and 40 years old using GHB to ameliorate effects of other stimulant recreational drugs (1 individual), euphoria (1), hypnotic effects (2), or anabolic effects (3). All had histories of using increasing amounts of GHB per day secondary to developing tolerance and decreasing effects. Symptoms on cessation of use included insomnia, muscle cramps, anxiety, and tremor; only one individual required pharmacological treatment with a single dose (30 mg orally) of phenobarbital to manage these withdrawal effects.

Since then, there have been numerous published case reports and series of dependency developing following the chronic use of GHB and its analogues [46, 94–102]. It is not possible to determine whether there is a difference in the risk of dependency developing between the different GHB-related analogues, and it is likely that the difference seen in the reported cases of dependency (initially predominately GHB, with increasing numbers related to GBL), reflect the changes described earlier in the change in the use and availability of GHB and GBL over time. Similarly, the limited number of 1,4-BD related cases mirrors the significantly lower self-reported prevalence of use of this compared to both GHB and GBL.

Dependency to GHB and/or its analogues typically occurs in individuals who have been using for several months or years and usually multiple times throughout the day and night. Typically, individuals will have started as “weekend” recreational users associated with clubbing, parties, and sexual liaisons. Over time, their use increases

usually with doses between infrequent events to help with sleep and/or adverse effects of stimulant recreational drugs before they become daily users of GHB or its analogues [1, 93, 101]. The estimated daily doses of GHB or related analogues being used varies between individuals but typical reported ranges are 18–100 g and 10–60 g for GHB and GBL respectively [101]. Based on the literature and our own clinical experience, the majority of patients have been using for a minimum time period of 2–3 months and are using at least three to four times per day [1, 46, 92, 94]. In the case series of 38 GHB/GBL-related withdrawal cases, the authors concluded that thrice daily dosing was the minimum frequency associated with physical dependency and withdrawal and the mean duration of use prior to dependency was 1.3 years [101]. However, the majority of those who have dependency are using considerably more frequently, typically every 1–2 h throughout the day, and may be waking at night to redose due to prevent onset of withdrawal symptoms. In addition to escalation of frequency of use, typically individuals may have a history of escalating doses used [46]. This can be potentially risky since unlike alcohol, benzodiazepines, and opioids, individuals do not develop the same tolerance to GHB as with these other drugs, and so they are still at the same risk of acute overdose and associated toxicity.

Although, as noted, dependency typically develops after prolonged regular use, there are examples of dependency developing after shorter periods of high-frequency use. A female who presented to an Emergency Department with symptoms suggestive of GHB withdrawal; she had started using GHB 8 days previously as a “sleep aid and intoxicant” and the dosing rapidly escalated to “3 ounces” of GHB every 2–3 h “round the clock” [103]. This phenomenon has been described for alcohol, benzodiazepines, and opioids where high-dose and/or high-frequency use over a short period of time can be associated with the rapid development of dependency and withdrawal upon cessation of use.

The clinical features of GHB and its analogue withdrawal are similar to those seen with ethanol

and/or benzodiazepine withdrawal and acute stimulant recreational drug/novel psychoactive substance toxicity. Therefore, without a clear history of regular dependent use of GHB or related analogue, which can be difficult to obtain at the time of presentation if the patient has florid withdrawal symptoms, it is often difficult to make a definitive diagnosis of GHB withdrawal at presentation. From a clinical perspective, as discussed under the management section below, this often does not alter management as currently the mainstay of treatment is benzodiazepines, which often is the initial treatment for all of these clinical scenarios.

The onset of withdrawal often is very rapid following the cessation of use, and individuals may develop symptoms of withdrawal within a few hours of last use and they can rapidly deteriorate becoming severe within a short period of time. In a case series of eight individuals presenting with GHB withdrawal, the onset of symptoms occurred within less than an hour to 6 h after last dose [46]. In a series of 38 cases of unplanned GHB/GBL related acute withdrawal, most presented within 24 h of their last dose [101]. Some have suggested that there is a difference in time to onset of withdrawal between the different analogues (GHB 7.5 h, 1,4-BD 6 h, GBL 72 h). However, the number of cases in the GBL and 1,4-BD groups were much less than the GHB group and additionally, these cases were from the published literature only [93]. In our experience, and based on the pharmacology of these compounds, there is no reason to suspect that there should be any difference between them in terms of time to onset of withdrawal. In addition, it is recognized that individuals may develop withdrawal when recovering from an acute GHB/GBL overdose as their GHB concentrations fall. This is different from alcohol and benzodiazepine withdrawal where there is often a longer time-lag of many hours between cessation of use and onset of severe withdrawal symptoms [46]. It is also important to be aware that some individuals may present through other routes than in unplanned acute withdrawal or to drug treatment services seeking planned withdrawal. There has been a

Table 1 Typical clinical effects by organ system seen in acute GHB or related analogue withdrawal

Organ system	Symptoms
Cardiovascular	Tachycardia
	Hypertension
Gastrointestinal	Nausea and vomiting
	Diarrhea
Neuropsychiatric	Anxiety
	Agitation and aggression
	Hallucinations (auditory, visual, or tactile)
	Insomnia
	Delusions
	Paranoia
	Tremor
	Seizures; cravings
Other	Confusion; muscle twitches
	Diaphoresis; rhinorrhoea

reported case of a 32-year-old male admitted following a road traffic accident and associated pelvic fractures under an orthopedic team where the issue of GHB-dependency was not detected on admission, and the patient subsequently started to develop features of withdrawal on the second day of his hospital admission [104].

The common clinical features of GHB and related analogue withdrawal are summarized in Table 1 [1, 46, 90–107]; there is a predominance of neuropsychiatric effects during withdrawal, particularly agitation and aggression, delirium, florid hallucinations, and delusions. It has been suggested that the severity of neuropsychiatric effects seen in GHB and related analogue withdrawal is similar to that seen with acute baclofen withdrawal. Some authors have reported that the neuropsychiatric effect can have a longer duration than the physical symptoms and may persist for up to 14 days after the physical symptoms have settled [105].

A previous review of 31 patients who presenting to our clinical toxicology service with acute GHB-related withdrawal confirmed the predominance of neuropsychiatric symptoms [107]. The most common neuropsychiatric symptom was anxiety (in 61% of presentations); other symptoms included agitation (48%), tremor

(39%), hallucinations (36%), paranoia (19%), confusion (16%), amnesia and delusions (both 13%), and sexual disinhibition and insomnia (both 10%). This is similar to a case series of 38 unplanned GHB/GBL withdrawal, where the frequency of clinical features were: tremor (74%), tachycardia (66%), anxiety (61%), hallucinations (55%), delusions/paranoia (37%), delirium (53%), insomnia (53%), diaphoresis (32%), hypertension (29%), and nausea/vomiting (18%) [101]. In a further case series of 57 patients identified from 27 published articles (36 GHB-related withdrawals, three 1,4-BD and 18 GBL), there frequency of symptoms experienced was broadly similar across the three different analogues [93].

Based on a case series of seven patients, the time course of effects of acute GHB withdrawal has been outlined [46]. This can be described as three phases: early (1–24 h), “progressive” (1–6 days), and then episodic during recovery (7–14 days). Predominant early effects include: severe-anxiety, restlessness, and insomnia; moderate – nausea and vomiting; mild – tremor, tachycardia, hypertension, and diaphoresis. Predominant “progressive” effects include: severe – anxiety, restlessness, insomnia, confusion, delirium, and hallucinations; moderate – tremor, tachycardia, hypertension, and diaphoresis; mild – nausea and vomiting. During the recovery phase, the effects typically are reducing, with none graded as “severe”; moderate symptoms include anxiety, restlessness, insomnia, confusion, and hallucinations and mild symptoms include diaphoresis, tachycardia, and hypertension. Overall the mean duration of withdrawal has been reported to be 8–9 days (range 3–15 days), which is longer than that reported for acute alcohol withdrawal (typically 3–7 days) [93, 101].

Not only does the pattern of clinical features vary between patients, it has been reported to be variable within individual patients who present with recurrent episodes of dependency and/or withdrawal [98]. A 29-year-old female with a history of 4 years of GHB use, which escalated from recreational use to daily use between 48 and 96 g per day, presented with four episodes of

withdrawal over a 2-year period. Some clinical features were present on all or three of the four withdrawal episodes (anxiety, tremor, insomnia, nausea and vomiting, vivid dreams, and fatigue), whereas other clinical features were only present on one or two of her withdrawal episodes (hypervigilance, tachycardia, paranoid delusions, irritability and somatic, visual or auditory hallucinations). The frequency/occurrence of clinical features did not appear to be related to the dose of GHB being used prior to the episode of withdrawal. Additionally, it is generally accepted that an individual who has had previous episodes of GHB or related analogue dependency and associated withdrawal on cessation of use typically develops recurrent dependency within a much shorter time-frame than the time taken to develop their initial dependency.

In terms of severe effects associated with GHB or related analogue dependency and withdrawal, there is a single case report of Wernicke-Kosakoff Syndrome in a 23-year-old female with a history of using GHB for last 18 months [108]. In addition, she had alcohol excess since age 15, which stopped when she started using GHB. Similar to other cases, her dose frequency of GHB use increased due to developing tolerance, and self-initiated periods of abstinence failed due to severe insomnia, paranoia, tremors, and restlessness; she would often self-medicate with alcohol to help herself sleep and prevent the withdrawal symptoms occurring. She was reviewed in hospital the day following a car accident (having been seen and discharged from an ED on the day of the car accident) and she was paranoid, hallucinating (visual and auditory), tremulous, confusion/disorientated, incoherent, and had "crossed eyes." She was managed with thiamine, benzodiazepines, and chlorpromazine. The next day she was reviewed by a neurologist and noted to be drowsy, dysarthric, have a poor memory, nystagmus with ocular cranial nerve palsies, and was ataxic. A diagnosis of Wernicke-Korsakoff Syndrome related to GHB use was made. One month following her withdrawal, the neurological signs had resolved and there was no evidence of cognitive impairment. It

should be noted that while this was attributed to her GHB dependency, it is more likely to be related to her ongoing ethanol use and poor nutritional intake (when using, she would often go without food for several days and prior to this particular admission, she had not eaten for over a week).

To date there has only been one reported death associated with the management of GHB or related analogue dependency and withdrawal, although the circumstances surrounding the death and the relationship to the GHB withdrawal management are unclear [46]. A 24-year-old male presented with a 12-month history of GHB use, with dose frequency escalating to every 30 min to prevent the onset of GHB withdrawal hallucinations. On presentation, he complained of nausea, vomiting, diarrhea, feeling "weak and swollen," diplopia with blurred vision, shortness of breath, urinary frequency, and blackouts for the last 2 months. He was managed with lorazepam for agitation, although he developed tachycardia, visual hallucinations, agitation/combativeness, and tremors. His initial admission was complicated by a right lower lobe pneumonia required ventilatory support during which time he was sedated with propofol. Following extubation he remained confused and was hallucinating requiring physical restraint with benzodiazepines and antipsychotic (not specified) medication. He appeared to be improving on day 12 postadmission, so his lorazepam dose was tapered. However, on the evening of the following day he had an "episode of spontaneous, generalized, spastic muscular contractions with an upward gaze" which was followed by "cardiac arrest." Autopsy demonstrated pulmonary oedema, cardiomegaly, left ventricular hypertrophy, and coronary artery disease. The cause of death was reported as "a complication of GHB withdrawal resulting from chronic substance abuse." It is not possible to determine the significance of the initial presentation of GHB dependency in the events that happened a number of days after presentation, and it is unlikely that this death was directly, if at all, related to the GHB dependency and withdrawal.

Indications for Admission to ICU

Acute toxicity	Prolonged reduced level of consciousness not improving after 2–3 h of onset
	Vomiting and risk of aspiration requiring endotracheal intubation for airway protection
	Toxicity related to the co-use of other drugs requiring monitoring and/or treatment in a high dependency (HDU, Level 2 bed) or Intensive Care Unit (ICU, Level 3 bed) environment
	Cardiovascular instability requiring treatment in an HDU or ICU environment
Withdrawal cases	Patients with agitation/aggression not manageable in a Level 1 bedded area
	Requirement for intravenous benzodiazepine treatment if not available in a general ward area (i.e., requires a Level 2 or Level 3 bed for administration)
	Requirement for IV barbiturates and/or other sedative treatment where intubation and ventilation is indicated

Diagnosis

It is possible to measure GHB concentrations in a variety of different biological matrices [1]. Urine is generally considered the biological matrix of choice for analysis, due to the longer time in which GHB can be detected [32]. Analyzing for GHB in biological samples using a variety of different analytical techniques is challenge for a number of reasons. Firstly, since GHB is produced endogenously as a breakdown product of GABA, the detection of GHB in the blood, urine, and/or another biological matrix does not confirm use. Therefore, there is the need to use a “threshold concentration” to differentiate between the detection of endogenous production of GHB from that following use. Broadly speaking, a concentration of 10 µg/mL has been accepted in antemortem urine as indicating use, as endogenous concentrations are typically around 1 µg/mL [109–115]. Since GHB concentrations in blood are lower

than those in urine, a concentration of between 1 and 5 mg/L has been suggested as indicating an exogenous GHB source when interpreting blood analyses [116, 117]. In addition, concentrations of GHB in both blood and urine specimens can increase with both increased time between collection and analysis and if samples are stored at room temperature prior to analysis [118–123]. This is thought to be less of an issue with urine, since endogenous concentrations above the 10 µg/mL cut-off have not been reported [110, 119, 120]. However, concentrations in blood greater than 100 µg/mL have been detected in postmortem samples definitively not related to GHB or related analogue use. The reasons for this extensive ex vivo production is not understood, but in some part may relate to bacterial metabolism [121, 122]. Therefore, it is important that samples collected for GHB or related analogue detection are appropriately stored and rapidly analyzed to prevent the possibility of a false-positive result. Secondly, GHB is metabolized to carbon dioxide through the Krebs cycle, meaning approximately only 1% of GHB is eliminated in urine [14, 15, 124]. In addition, with this extensive metabolism, there is no metabolite of GHB or its analogues that can be detected in biological samples for longer than the parent molecule. Typically, this means that GHB or related analogues can only be detected in biological samples for around 12 h following use, so samples need to be collected as soon as possible following use to prevent a false-negative result [14].

There are a range of different analytical techniques available to detect both GHB and its related analogues. These include colorimetric and enzymatic assays, gas chromatography with flame ionization detection (GC-FID) or mass spectrometer (GC-MS), liquid chromatography quadrupole mass spectrometer (LC-MS/MS), gas chromatography isotope-ratio mass spectrometry (GC-IRMS) [14, 111, 113, 125–134]. There are some caveats with these different analytical methods. Firstly, there are differences in the limits of detection (LOD). For example, colorimetric and enzymatic based methods have an LOD of 100 µg/mL and 50 µg/mL, respectively,

whereas GC-FID, GC-MS LC-MS/MS have LODs of 0.01–5 µg/mL. This means that some analytic methods may “miss” samples with concentrations above those associated with endogenous GHB but below their LOD, giving a false-negative result. Secondly, some analysis may be direct detection of GHB, GBL, and 1,4-BD themselves (e.g., LC-MS) or for GHB through derivatization (e.g., GC-FID, GC-C-IRMS), whereas other techniques require the conversion of GHB (and 1,4-BD) to GBL prior to analysis (e.g., GC-FID). Analysis through conversion to GBL precludes determination of exactly which analogue was used. Finally, it should be noted that these analytical techniques may not be available in every acute hospital setting and/or may not be available at all times (i.e., outside working hours), meaning that the analytical results may not be available in a time-frame that would alter an individual patients’ management.

Therefore, the diagnosis of both acute GHB or related analogue toxicity and chronic dependency and withdrawal is largely based on history, symptoms, and/or signs, rather than analytical confirmation. A survey of professionals with training related to GHB intoxication, and professionals without training, compared their ability to determine which of a number of statements related to acute GHB intoxication indicated significant risk of potential failure in vital physical function [135]. The most highly rated amongst all 105 respondents were cardiac arrest, coma, hypoxia, generalized convulsions, slow respiratory rate, and slow heart rate. Additionally, there was no significant difference between those with and without training, suggesting that non-specialists were able to detect patients at significant risk.

Management of Acute Toxicity

The majority of patients with acute GHB toxicity start to recover with improvement in their level of consciousness within 2–3 h of onset, and therefore the management as discussed further below is largely supportive.

In vitro activated charcoal GHB adsorption studies demonstrate up to 84% adsorption of a dose of 800 mg GHB with an in vivo equivalent dose of 100 g activated charcoal (the standard 50 g dose of activated charcoal was associated with approximately 70% adsorption) [136]. However, since the onset of acute toxicity is rapid and the majority of individuals present with a reduced level of consciousness, in clinical practice there is unlikely to be any benefit to activated charcoal administration or any other form of gastric decontamination.

Although not reported in most case series, the majority of patients recover sufficiently quickly in the Emergency Department to be discharged directly from the ED. For example, in the UK case series of 158 GHB/GBL patients, only 12 (8%) were admitted to hospital [4]. In the Spanish case series, the mean time to regain complete consciousness was 66 ± 55 (range 1–360) minutes [74]. In a cohort of 66 individuals with acute GHB toxicity, mean time to recovery of consciousness was 146 ± 93 (range 16–389) minutes in 55 nonintubated patients compared to 274 ± 94 (161–439) minutes in the 11 intubated patients. The authors acknowledged that this increased time to recovery in the intubated patients may reflect the use of sedatives during intubation [75]. In addition, the time to recovery related to initial presenting GCS on arrival in the ED was: GCS 3–5 177 ± 109 (31–389) minutes; GCS 6–8 134 ± 75 (16–268); GCS 9–13 116 ± 81 (16–260) minutes. In the 158 patients in the London series, the median length of hospital stay was 2.8 (IQR 1.9–4.0) hours, and those presenting with a low GCS (defined as ≤ 8) had a significantly longer hospital stay (median length of stay 3.8 (2.4–7.5) hours) [4]. The co-use of alcohol with GHB was not shown to increase the duration of coma compared to those with GHB/GBL use alone [69]. However, co-use of GHB/GBL with stimulant recreational drugs (e.g., cocaine, MDMA, amphetamine) was associated with more severe (GCS of 3 in 65% of those with co-used stimulants compared to 20% in lone use, $p < 0.001$) and prolonged (time to recovery 155 ± 60 min compared to 94 ± 54 min, $p < 0.02$) coma. The rate of ICU admission

from the ED for acute GHB/GBL toxicity is 4–7% [4, 76]. As expected, admission to ICU was associated with an increased length of stay of (median 18 (IQR 10.1–39.2) hours) compared to those directly discharged from the ED (2.4 (IQR 1.7–3.0) hours) [4]. Additionally, the length of stay following attendance at the ED has been shown to be related to: (i) degree of reduced level of consciousness on presentation to the ED: those with low GCS (defined as 3–8) had a median length of stay of 219 (interquartile range [IQR] 188) minutes compared to 174 (IQR 125) minutes in those with a high GCS (defined as 9–15), $p < 0.001$; and (ii) whether the patient was intubated: those with intubated had a median length of stay of 460 (IQR 506) minutes compared to 192 (IQR 132) minutes in those not intubated, $p < 0.001$ [76]. In addition, those individuals who had a low GCS (defined as 3–8) and were intubated had a significantly longer length of stay compared to those with a low GCS who were not intubated (intubated 392 (IQR 417) minutes compared to nonintubated 209 (IQR 161) minutes, $p = 0.001$).

Based on the information discussed in the acute toxicity section above, the management of acute GHB or analogue toxicity is largely supportive care. Given the short duration of the reduced level of consciousness, the need for intubation is debatable and often the recommendation for endotracheal intubation for airway protection and/or ventilatory support is related to other indications rather than just the reduced level of consciousness. It should not be assumed that those patients with a reduced level of consciousness have significant respiratory depression and associated respiratory acidosis as to dictate endotracheal intubation for respiratory management. While all nine patients in the US study with a pH less than 7.30 had a reduced level of consciousness (six had a GCS of 3 and three had a GCS of 6), of those 21 with a pH ≥ 7.31 , nine had a GCS of 3, and 12 had a GCS of between 4 and 14 [75]. Therefore, the decision to intubate should not solely be made on the basis of level of consciousness. In patients where there is vomiting associated with a reduced level of consciousness, then endotracheal intubation

may be appropriate to prevent aspiration. However, in nonintubated patients with acute toxicity with GHB and its analogues, vomiting in those with the greatest degree of neurological compromise was not associated with pulmonary aspiration, suggesting that “prophylactic” intubation in case of vomiting is not indicated [75]. Evidence from our own clinical practice, and that reported in the other large case series, indicates that routine intubation of patients with acute GHB or analogue toxicity is not indicated unless there is vomiting in patients with a reduced level of consciousness, recurrent seizures, or another clinical indication for intubation (Grade IIb/III recommendation).

There is currently no specific antidote to reverse the acute effects of GHB or its analogues. Previously it has been suggested that naloxone and/or flumazenil may be beneficial in the management of patients with acute GHB or analogue toxicity. In one case series of 104 patients, 14% were empirically administered naloxone and/or flumazenil with no response in the level of consciousness [74]. We believe that the only role for naloxone in the management of these cases is where diagnosis of GHB or analogue toxicity is not certain and to exclude opioid toxicity as a potential cause for the clinical features. However, in patients where acute GHB or analogue toxicity is clinically the most likely diagnosis, there is no pathophysiological or pharmacological basis for the routine use of naloxone, as the mechanisms of action of GHB and its analogues are different to that of opioids. Similarly there is no pharmacological basis for the administration of flumazenil, since this acts specifically on benzodiazepine receptors and therefore should not have an action to reverse GHB or analogue toxicity. Previously there have been suggestions that physostigmine, an inhibitor of acetylcholinesterase, could be beneficial in the treatment of acute sedative overdoses such as GHB. A structured literature review found that there was insufficient evidence to support the use of physostigmine due to limited published evidence and/or methodological flaws and confounding factors in the published case series [137]. In addition, there has been interest in the use of specific GABA-B

antagonists (e.g., SCH50911) in animal models to prevent and/or treat the respiratory depression seen following GHB administration [38], although this has not progressed into human clinical trials to date.

In terms of prevention of acute toxicity related to the use of GHB and its related analogues, the Global Drug Survey produced in 2014 a “Highway Code” for more safely using GHB and related analogues [138]. In the production of this, the authors surveyed over 850 “G” users with a number of suggested harm reduction methods and asked them how important they rated this (out of 10) in terms of reducing harm associated with use and the frequency that they utilized these methods to prevent harm from GHB/GBL. The most common harm-reduction method was using premeasured doses of GHB/GBL, thought to be of high importance (scored 9.1 out of 10) and done by 85% of users regularly. Other methods included avoiding alcohol (9.1, 70%), timing doses (8.8, 32%), setting limit on amount used (8.3, 56%), avoiding stimulants (7.2, 40%), and writing G on wrist so if they collapse responders can know what they have used (6.9, 2%). Some of these harm-reduction methods may be useful in discussing with patients prior to discharge to prevent overdose and associated acute toxicity in the future, particularly given the high self-acknowledged risk of future overdoses in individuals who have had a previous overdose.

Management of GHB and Related Analogue Dependency and Withdrawal

When an individual has been identified as potentially dependent on GHB or a related analogue, and therefore at risk of withdrawal on cessation of use, the management depends on the situation in which the patient has been identified. In those who have been identified within a hospital environment, these can be broadly divided into the following categories:

1. Not wanting to cease use at this time and able to continue to source GHB or related analogue

2. Wanting to stop use, not acutely withdrawing and able to continue to source GHB or related analogue
3. Wanting to stop use, not acutely withdrawing but unable to continue to source GHB or related analogue
4. Require admission for another medical reason
5. In acute withdrawal with or without delirium at the time of review

Individuals in Group 1 can be provided with information on local drug and alcohol treatment services and/or specialist drug treatment services for the MSM community and advised to engage with services when they feel that they wish to stop using. Those in Group 2 do not require admission for inpatient detoxification and again can be provided with information on appropriate local services. We recommend that both groups should be advised not to stop using prior to engagement with services so that their cessation of use can be medically supervised and appropriate pharmacological treatment provided as required. It is often possible on discussion with individuals in Group 3 that they can actually source GHB or related analogue until they can engage with an appropriate service for ongoing management. If this is truly not possible, they may require admission for observation and management of withdrawal. Individuals in Groups 4 and 5 require admission to hospital with appropriate pharmacological management for withdrawal.

A case-based vignette study of addiction specialists was undertaken in The Netherlands to try and more robustly identify biological, social, and psychological characteristics that help determine whether a patient should be offered inpatient or outpatient detoxification [139]. Twenty-one addiction specialists contributed 20 case vignettes of a range of severity of GHB detoxifications that they had previously managed. These case vignettes were then reviewed by a focus group (11 other psychiatrists and addiction specialists), rating them on a scale of -5 to $+5$, where -5 indicated with certainty that outpatient detox appropriate, $+5$ indicated with certainty that inpatient detox was required, and 0 if they were unable to determine whether inpatient or outpatient

treatment should be offered. Additionally, they provided three reasons to support their decision for each case vignette. Based on these scores, the focus group then determined their consensus opinion as to whether inpatient or outpatient treatment was appropriate; of submitted case vignettes, 11 were rated by $\geq 60\%$ as either ≤ 3 (outpatient) or ≥ 3 (inpatient) management, 1 vignette was rated by 10 as inpatient and 1 did not comment (consensus decision was inpatient) and in eight vignettes they were unable to determine whether treatment should be inpatient or outpatient based. A further panel of 5 qualified addiction medicine specialists then reviewed responses provided around each vignette where there was consensus of $\geq 60\%$ to determine biological, psychological, and social criteria for determining whether treatment should be inpatient or outpatient based (Table 2). Additionally, the authors commented that while these criteria can be useful in assisting the setting of detoxification, it is also important to consider the patient's wishes when making the final decision.

Having made the decision to admit a patient for GHB or related analogue withdrawal, then the next considerations are (i) when to dose and (ii) what drug(s) should be used in the management of withdrawal. Unlike individuals presenting with alcohol or opioid dependency, where standardized validated scoring systems such as Clinical Institute Withdrawal Assessment for Alcohol revised tool (CIWA-Ar) and the Opioid Withdrawal Score can be used to determine when drug treatment is required, there is currently no recognized or validated scoring system for GHB or related analogue withdrawal. While some of the features of GHB or analogue withdrawal will be detected using the CIWA-Ar tool, this scoring system is only used clinically every 2 h, whereas GHB withdrawal patients can deteriorate more rapidly between these fixed scoring intervals. In addition, previous experience has shown that scoring all of the neuropsychiatric effects is not sufficient to dose patients appropriately [102, 140, 141]. In 8 patients undergoing detoxification (4 inpatient, 4 outpatient), CIWA-Ar scores were calculated during the first 24 h of withdrawal management and CIWA-Ar triggered

Table 2 Decision-making criteria for inpatient vs. outpatient detoxification treatment [139]

	Outpatient detoxification	Inpatient detoxification
Biological criteria	GHB abuse ≤ 32 g/day ≥ 2 h frequency Limited/no night use No history of severe withdrawal symptoms Limited psychoactive substance co-use	Pregnancy Severe somatic disease (e.g., hepatic, renal, or cardiovascular impairment) Epilepsy
Psychological	Psychiatric disorders mild or in stable form	Psychiatric disorders such as psychosis, bipolar disorders, severe anxiety, depression, ADHD on treatment
Social	Socially integrated Stable supporting system Residence	Social disintegration Drugs abuse in system Rambling

benzodiazepine dosing was compared to symptom triggered dosing. In the inpatient treatment group, all had episodes where the CIWA-Ar was less than 10 (no benzodiazepine dosing) but the patient required benzodiazepines based on clinical manifestations (33–100% of times where CIWA-Ar was < 10). Additionally, the opioid withdrawal scale (OWS) has been used to determine the frequency of symptoms in this scale in 15 patients with acute GHB or related analogue withdrawal [142]. While some features were present in 14 or 15 of the patients (fatigue, agitation, craving, tremors, sweating), others were less frequently present (anxiety, sleepiness, muscle twitches, pupil dilatation, running nose, looks depressed, abdominal pain, vomiting) and some were not present at all (yawning, “goose flesh,” watering of eyes, general restlessness, nausea, seizures, dullness/slowness). This suggests that currently

patients should be treated using a “symptom-triggered dosing regimen” rather than attempting to utilize a scoring system such as CIWA-Ar or OWS to determine when dosing should be administered.

The optimal management regimen for GHB, GBL, and 1,4BD withdrawal is still unclear. Some of the potential drug treatments tried and recommended are summarized below. Currently, the majority of patients are managed with benzodiazepines, either alone or in combination with other drugs. There is increasing evidence on the use of novel treatment modalities, particularly baclofen and pharmaceutical grade GHB. It is likely that over the next 5–10 years a standardized treatment regimen will become more widely available, although the legal status of certain treatments in different countries may limit the widespread use of these drugs.

Physical Restraints

Some authors have reported the use of physical restraints in managing patients with acute delirium and other neuropsychiatric effects seen in acute GHB or related analogue withdrawal [46, 94, 96, 100, 143]. However, we would not recommend their routine use due to the potential for trauma and serious physical injury to a patient in the setting of severe delirium, agitation, and/or aggression.

Benzodiazepines

To date, a substantial portion of the published literature and the first published treatment regimen has focused on the use of benzodiazepines in acute GHB and related analogue withdrawal [1, 93, 101, 102]. Benzodiazepines are used in a variety of other withdrawal scenarios (e.g., alcohol, benzodiazepines), largely due to their activity at the GABA-A receptor. Theoretically, regular use of GHB or a related analogue could lead to tonic inhibition of the glutamergic excitatory neurotransmitter system which in turn leads to upregulation of this system. During withdrawal as the inhibitory GHB is removed, it is likely that the hyper-excitability is mediated through

the *N*-methyl-D-aspartate-glutamate receptor complex, which may be insensitive to benzodiazepines. However, it is possible that benzodiazepines may have an inhibitory effect through their GABA-A activity. In addition, as discussed in the pharmacology section, GHB acts predominately through the GABA-B receptor, and therefore this in part may explain why benzodiazepines alone may be insufficient in most cases of GHB and related analogue withdrawal. In our experience, almost 50% of those patients presenting to hospitals with acute unplanned withdrawal will require additional treatments beyond just benzodiazepines and possibly admission to an Intensive Care Unit for ongoing management. Often these individuals have delirium at the time of presentation [102].

Some reports have used of different benzodiazepines (Diazepam, Clonazepam, Temazepam, Lorazepam, Chlordiazepoxide) and administration by different routes, but there are no data to suggest that any one benzodiazepine is superior to others [1, 46, 94, 96, 97, 100, 102, 103, 143]. We recommend that they be administered by the most appropriate route depending on the severity of the withdrawal and the ease of administration.

In the review of published cases of acute GHB, GBL, or 1,4-BD withdrawal, of the 57 patients identified 90% were treated with benzodiazepines and 20% received no additional treatment [93]. Similarly, in a further 38 cases of acute GHB/GBL withdrawal 91% of patients were treated with a tapering course of benzodiazepines, although in 82% this was in combination with one or more other drug treatment [101]. The overall diazepam equivalent doses of benzodiazepines required to “manage” the acute withdrawal ranged from 20 to 2,655 mg. Based on the review of these cases, the authors postulated a potential algorithm for managing acute GHB or GBL withdrawal, which was dependent on the frequency of use, total daily dose of GHB or GBL used, and the presence or absence of delirium on presentation to the healthcare facility:

- Less than 3 doses per day, <30 g GHB per day, or <15 g GBL per day then consider outpatient

treatment with 20–40 mg diazepam initially reducing over 7 days with daily physical assessments

- More than 3 doses per day, >30 g GHB, or >15 g GBL per day with no delirium on presentation then manage initially with 80–150 mg diazepam reducing over 7 days
- More than 3 doses per day, >30 g GHB, or >15 g GBL per day with delirium on presentation, treat with high-dose diazepam (150–200 mg per 24 h) and if benzodiazepine resistant after the first 24 h, add pentobarbital in an ICU setting

Interestingly, while these authors made recommendations about the ongoing management and reducing of benzodiazepine doses in the less-severe groups, there was no real recommendation on ongoing management after the first 24 h for the most severe group (heavy use with delirium present). After the initial period of assessment with benzodiazepines based on symptoms/signs of acute withdrawal, we recommend the use of a reducing regimen based on the requirements in the first 24 h; in our experience we use a regimen based on tapering with Chlordiazepoxide after the first 24 h along the same lines as that used for alcohol withdrawal. These patients may need an extended tapering course, since as noted previously the withdrawal from GHB and its analogues tends to be more prolonged compared to ethanol [102].

GHB and GBL

There has been interest in the Netherlands and Switzerland in the use of GHB and GBL in the management of withdrawal [142, 144–146]. As summarized below, while there is some evidence for the use of pharmaceutical grade GHB, one major limitation to its use in these situations in many countries is the existing controls around how it is stored, prescribed, and/or administered which will make it practically difficult to administer within most healthcare environments. In addition, the use of illicit GBL (or GHB) from street-level drug dealers is more complicated not only by its legal status but also by the

variability in the concentration of the sourced drugs.

The use of tapering doses of pharmaceutical grade GHB has been shown to be beneficial in the management of GHB withdrawal [142, 145, 146]. Twenty three patients with GHB-dependence (average duration of GHB use 1.6 years, dosing 2–4.2 g per dose every 45–90 min) were recruited to be managed with a tapering dose of GHB [142]. The initial dose of pharmaceutical grade GHB (specifically produced at a concentration of 150 mg GHB/mL) administered was approximately 60–70% of their usual dose. This was then increased or decreased by 0.45–1.2 g of GHB every 3 h based on symptoms of withdrawal or over-sedation until an “acceptable dose” was determined. From the second day, the dose of GHB administered was tapered by 0.3–0.45 g per medication dose each day. During the withdrawal period, individuals completed a Subjective Withdrawal Scale (a 35 point scale with a maximum score of 140) and using a tapering dose of GHB the SWS decreased from an initial mean of 26 (range 6.4–109.9) to 5.9 (range 0–26) on day. There were no episodes of psychosis or delirium with this treatment regimen, and all patients were managed within an addiction treatment facility. It should be noted that 16 patients experienced uncomfortable withdrawal symptoms between the 3 h doses, particularly on the first 3 days of treatment, suggesting the interval between dosing was too long. In addition, 16 patients required additional treatment with diazepam and 8 patients required treatment with temazepam for severe insomnia, suggesting that the dose of GHB administered was not sufficient to manage all of the withdrawal symptoms. As a result of these initial reports of using pharmaceutical grade GHB, there has been more widespread use of this grade of GHB in the management of GHB withdrawal in The Netherlands. In a review of 229 patients treated using this protocol, 86% of patients successfully underwent detoxification. Of the remaining patients, 8% self-aborted treatment and 6% were discharged for ongoing use of street GHB in addition to the pharmaceutical grade GHB [146]. More recently,

there have been reports of using pharmaceutical grade GHB in the management of patients with benzodiazepine-resistant GHB withdrawal [145]. Three patients (28-year-old female, 33-year-old male, 42-year-old male) with GHB-dependency all failed initial treatment with benzodiazepines and were commenced on pharmaceutical grade GHB with rapid resolution of the GHB withdrawal symptoms and stabilization of the patient. Based on the clinical experiences reported to date using pharmaceutical grade GHB, the authors suggested a modified treatment regimen using a licensed prescribable pharmaceutical grade product (Xyrem, sodium oxybate) which has a GHB concentration of 500 mg/mL (compared to the 150 mg/mL produced for the initial studies of tapering doses of GHB in the management of GHB-dependency).

There is only one case report on the use of street GBL in GBL-dependency, and no published data on the use of pharmaceutical grade GHB in patients with GBL-dependency. A 36-year-old female who had been treated on several occasions for GBL-related withdrawal with benzodiazepines, less than optimal control of her with severe behavioral disturbances, was hospitalized with a further episode of GBL withdrawal [144]. During this admission, she was noted to be attempting to self-administer GBL and was assisted in the self-administration of 2–4 mL every 5 min over a period of 30 min. Over this time, her behavioral disturbances settled, she became oriented and her cognitive function and mental capacity were restored. Unfortunately, she then left the hospital, making it not possible to determine whether continuation of the self-administered GBL could have successfully managed her withdrawal.

Baclofen

Baclofen is a GABA-B receptor agonist and since GHB acts at the GABA-B receptor, pharmacologically baclofen would be expected to have a potential role in the management of GHB and related analogue withdrawal. In animal models, cross-tolerance to baclofen has been seen in both rats and baboons chronically administered GHB [20, 43]. It is likely that baclofen, similar to methadone

in opioid withdrawal, is acting as a substitution agent rather than managing the withdrawal itself.

There are currently limited clinical data on the use of baclofen in the management of acute GHB and related analogue withdrawal [102, 107, 147, 148]. A 61-year-old female with chronic dependency on GHB (initially prescribed for insomnia, but increased doses/frequency to treat anxiety and worsening insomnia) was admitted to an ICU from a psychiatric detoxification facility following seizures during acute GHB-related withdrawal [147]. She was initially treated with GHB every 4 h (prehospital she was taking GHB every 3 h) with additional benzodiazepines but had increasing seizures and was started on 5 mg baclofen every 8 h. Her seizures ceased, and they were able to wean her GHB dosing as her baclofen dosing was increased to 10 mg every 8 h.

Following this case report, there was a case series of individuals with GBL-dependency treated with both diazepam and baclofen in an outpatient detoxification service [148]. In this case series of 19 patients, 17 were treated with baclofen (10 mg three times a day) in addition to symptom triggered diazepam on day 1 of outpatient treatment. There were no specific unwanted effects associated with the baclofen. Several patients reported that the baclofen helped to “reduce craving for GBL,” and four continued baclofen for “several weeks” afterwards, which assisted with sleep, concentration, and anxiety control. Fifteen patients remained “nondependent” at the last contact with the drug treatment service (up to 2 months following completion of the withdrawal treatment). Of the ten patients who were contacted by telephone at 2 months, eight reported that they were abstinent from GBL use and two reported that they had “dabbling” GBL use. Based on these few published cases and our previous experience, our current local policy for managing GHB/GBL withdrawal is symptom triggered benzodiazepine administration with baclofen (10 mg three times a day) on day 1, followed by a reducing course of benzodiazepines for 5–7 days; the baclofen is continued during the reducing course of benzodiazepines and then weaned over the last 24–48 h of treatment [102, 107]. There has also been interest

in “preloading” with baclofen in the 24–72 h prior to starting detoxification, in an attempt to stabilize an individual’s use of GHB or related analogue and potentially to improve the overall detoxification management. However, in our experience some individuals report that baclofen can make them feel too drowsy and/or develop other unwanted effects such as ataxia and unsteadiness. Although there is a pharmacological basis for the use of baclofen in the management of GHB withdrawal and anecdotal experiential evidence that it is beneficial, there are no proven data to support its use and/or to look at utilizing this in preference to benzodiazepines. We are involved in a randomized placebo controlled trial looking at the feasibility of using baclofen during both preloading and treatment of GHB and related analogue withdrawal in both inpatient and outpatient setting.

Treatment with baclofen, along with other drugs, has typically been during the acute withdrawal phase, with drugs being tapered or ceased after a short period of time. However, the first reported case of baclofen use in GHB withdrawal was followed by 10 weeks of baclofen at 10 mg three times a day. During this time the individual was reported to be abstinent from GHB [147]. There is increasing interest in the potential for using a more prolonged course of baclofen to prevent relapse of GHB use following initial detoxification [149, 150]. Fourteen patients with a history of GHB dependency were recruited to undergo detoxification with GHB followed by a maintenance course of GHB for 12 weeks following stabilization of dose [149]. Patients were initially treated with 5 mg baclofen three times a day, along with a maximum of 20 mg diazepam a day, and the baclofen dose was increased by 15 mg every 3 days until a maintenance dose of baclofen was achieved in the second week of treatment. This was continued for a further 12 weeks before tapering over a further 2 weeks. During the maintenance period, abstinence from GHB use and impact on cravings were assessed. It should be noted that three patients were excluded from the trial due to severe psychiatric symptoms [2] or drop-out [1], suggestive that this initial baclofen-only based treatment regimen would only be suitable for those who do not develop severe

withdrawal symptoms (i.e., less useful in the intensive care setting). Five individuals remained abstinent throughout the study (one additional patient was abstinent for 7 weeks and then dropped out of the study), while four used on one or more occasion during the study and one relapsed to regular GHB use after 5 weeks of treatment. Overall, prolonged use of baclofen appeared to reduce cravings for GHB, with only one patient reporting that there was no change in their craving for GHB. The most common unwanted effects were dry mouth (seven patients, reported as present frequently), sweating/tremors/fatigue (five patients, reported as present sometimes), and drowsiness/sedation (four patients, reported as present sometimes); three patients reported no unwanted effects with the baclofen treatment. Based on the experience in this small case series, there is currently an open label study of baclofen for relapse prevention in the management of GHB dependency underway [150]. In this study, 40 patients are being recruited to receive baclofen (45–60 mg per day) following detoxification, and its impact on relapse to GHB use within 6 months of recruitment (primary outcome measure), craving for GHB, psychiatric symptoms, and quality of life, will be compared with a treatment as usual cohort (40 patients) and historical controls (274 patients).

The unwanted effects of baclofen are predominantly neuropsychiatric (for example, sedation, drowsiness, confusion, euphoria or depression, visual disturbances, ataxia, tremor, nystagmus, hallucinations, nightmares, dizziness, insomnia); other unwanted effects include gastrointestinal upset, hypotension, dysuria and urinary frequency, abnormal liver function tests, and hyperhidrosis. These unwanted effects are more common at the start of treatment and particularly if the dose is escalated too quickly; they are typically transient and can be treated by appropriate dose-reduction. There has been a report of severe acute toxicity related to co-use of GHB in an individual being treated with baclofen for GHB detoxification [151]. The 21-year-old female patient completed her fourth GHB detoxification program and was commenced on baclofen for relapse prevention. She was found unconscious

with bradypnoea and episodes of respiratory apnoea and a bottle of GHB in her pocket. Following supportive care, she recovered and subsequently reported that she had relapsed into regular GHB use, which had been without problems until she co-used 80 mg of baclofen concurrently. It is therefore important that if considering outpatient unsupervised use of baclofen, either during acute withdrawal or as part of relapse prevention, that patients are appropriately counseled about the potential risks of severe acute toxicity if baclofen is co-used with GHB or a related analogue.

Other Drugs

A range of other drugs have been reported to be used in patients either alone or in combination with benzodiazepines. These include antipsychotics (haloperidol, trifluoperazine, risperidone, trazadone, quetiapine), barbiturates (pentobarbital), and other sedatives (clonidine, propofol, diphenhydramine, chloral hydrate) [1, 46, 91, 93, 95, 96, 101, 105, 152]. In the series of 38 cases of acute GHB/GBL withdrawal, the frequency of other used pharmacological treatments was: antipsychotics – 43%; anticonvulsants (valproate, carbamazepine, gabapentin) – 21%; barbiturates – 18%; chloral hydrate – 8%; trazadone – 8%; baclofen – 5%; clonidine 5%; beta-blockers – 5%; propofol – 3%; and bromocriptine – 3% [101]. There was a similar frequency of other drugs used in the 57 cases of acute GHB or related analogue identified in the literature review: antipsychotics – 63%; anticonvulsants – 23%; barbiturates – 18%; chloral hydrate – 8%; trazadone – 5%; baclofen – 10%; clonidine – 13%; beta-blockers – 8%; propofol – 8%; bromocriptine – 3%; fentanyl – 3%; and physostigmine – 3% [93]. Despite the frequent use of antipsychotics in these cases, there is concern with using antipsychotics in the setting of acute GHB or related analogue withdrawal as they can potentially both lower the seizure threshold and lead to prolongation of QT/QTc with associated increased risk of arrhythmias. The increased risk of seizures when using antipsychotics has been reported in the setting of acute alcohol withdrawal [153]. In addition, there is a

report of an individual who allegedly developed “neuroleptic malignant syndrome” while being treated with haloperidol, loxapine, and benzodiazepines for GBL withdrawal [154].

In terms of barbiturates, there is a pharmacological basis for using pentobarbital over other barbiturates. Unlike most other barbiturates, Pentobarbital is able to directly open GABA-A related chloride channels and voltage-gated chloride channels [123]. Therefore, there is the potential that pentobarbital may be more beneficial in patients with severe withdrawal unresponsive to benzodiazepines. There has been a case series of four individuals with severe GBL withdrawal, where pentobarbital was used [143]. Two patients received pentobarbital after treatment failure with 6 h of high-dose lorazepam and the other two received it at the onset of treatment. All had rapid (reported as within 2–6 h) improvement in their symptoms after pentobarbital [1–2 mg/kg every 30–60 min]. Subsequent weaning of the pentobarbital resulted in a recurrence of the withdrawal symptoms. All four patients were managed without the need for intubation and mechanical ventilation as there was no associated respiratory depression and there was no hypotension seen with some other sedatives.

Criteria for ICU Admission	
Acute toxicity	Prolonged reduced level of consciousness not improving after 2–3 h of onset
	Vomiting and risk of aspiration requiring endotracheal intubation for airway protection
	Prolonged and/or recurrent seizures
	Acute toxicity from co-ingestants that requires admission to ICU
Withdrawal cases	Patients with agitation/aggression not manageable in a general ward area
	Requirement for intravenous benzodiazepine treatment if not available in a general ward area
	Requirement for IV barbiturates and/or other sedative treatment where intubation and ventilation is indicated

Special Populations

In addition to the risk of acute toxicity due to accidental or intentional ingestion of GHB or its analogues, there was previously an issue of acute 1,4-butanediol toxicity in children due to the inappropriate use of the solvent in the production of toy bead products (known as Aqua Dots in North America and as Bindeez Beads in Europe and Australia) [155–157]. In 2008, there were reports from Emergency Departments in the UK, Australia, and North America of young children presenting with significantly reduced levels of consciousness and in some instances nonresponsive coma, with rapid recovery and no long-term neurological sequelae. Although the clinical picture was in keeping with acute GHB or analogue toxicity, there appeared to be no obvious source of exposure. This clinical suspicion of acute GHB-like toxicity was confirmed when GHB was detected on toxicological testing. Through further questioning of the child, parents, and/or siblings, the common feature between these cases was that the affected child had been playing with a toy bead product prior to becoming affected. The product labeling did not mention that the beads contained GHB or any of its related analogues. However, they reportedly contained an alternative solvent known as 1,5-pentenediol (1,5-PD). Toxicological analysis of the both Aqua Dots and Bindeez Beads demonstrated that they did not contain 1,5-PD but instead contained 1,4-BD. It has been reported that the manufacturers in China intentionally changed from using 1,5-PD in the production to 1,4-BD. It is not clear whether they were aware of the potential toxicity of the alternative solvent used. The reasons for this change in solvent are unclear. It is possible that this occurred due to the cheaper cost of 1,4-BD compared to 1,5-PD or that the production processes are easier if 1,4-BD is used. Following the discovery that these products contained a GHB analogue, there was an international recall of this product to prevent further cases of accidental 1,4-BD.

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The hallucinogenic indolealkylamines (IAAs) are analogues of 5-hydroxytryptamine (5-HT or serotonin), a monoamine neurotransmitter known to influence human mood and behaviors. IAAs include many natural substances and are listed in Table 1. Indolealkylamines have been used in ritual for centuries. Ceremonial use of hallucinogenic mushrooms by native populations was documented in the 1500s after the Spanish conquest of Mexico [1]. Evidence suggests that bufotenine (5-hydroxydimethyltryptamine) is not psychoactive in vivo due to its poor penetration of the blood–brain barrier [2–4]. *N,N*-Dimethyltryptamine (DMT) is a naturally occurring tryptamine found in mammalian brain. In South America, it is used in snuff for religious ceremonies [5]. Methylated indolealkylamines, derived from 5-HT via methylation [6–9], are endogenous in humans including 5-MeO-DMT found in the pineal gland and retina.

Indolealkylamines have also been isolated or synthesized for use in the treatment of migraine headaches including ergotamine and triptan drugs (sumatriptan, naratriptan, and almotriptan). Because of their similarity of structure, the synthetic hallucinogens lysergic acid diethylamide (LSD), dipropyltryptamine, α -methyltryptamine (AMT), diethyltryptamine (DET), 6-hydroxydimethyltryptamine, α -ethyltryptamine (ET), and 4-acetoxy-*N,N*-dimethyltryptamine (*o*-acetylpsilocin) are considered to belong to this group. LSD is an ergot derivative and an especially potent hallucinogen that has had an enormous cultural impact since its discovery by the Swiss chemist Hofmann in

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Table 1 Indolealkylamine Sources

Chemical group	Name	Source
Tryptamines	Psilocin	<i>Psilocybe</i> mushrooms
	Psilocybin	African shrub <i>Tabernanthe iboga</i>
	Ibogaine	Sonoran Desert toad <i>Bufo alvarius</i>
	Bufotenine	Sonoran Desert toad <i>Bufo alvarius</i> and
	5-methoxy- <i>N,N</i> -dimethyltryptamine (5-MeO-DMT)	Numerous plant preparations including <i>Virola</i> snuffs
β-carbolines	Harmine	South American plants <i>Peganum harmala</i> and <i>Banisteriopsis caapi</i>
	Harmaline	Drought-tolerant perennial plant, <i>Peganum harmala</i> and ayahuasca; hallucinogenic brew made from the South American jungle vine, <i>Banisteriopsis caapi</i>
Ergolines	Lysergic acid amide	American tropical morning glory species <i>Ipomoea violacea</i> and
	Isolysergic acid amide	<i>Rivea corymbosa</i>

1938 [10]. Additionally, it has provided insight into the chemical and molecular bases of human psychosis.

Indolealkylamines of fungal origin such as psilocin, ibotenic acid, and muscimol have been proposed for use in psychiatry and psychotherapy inciting controversy. Some recent findings suggest these compounds can improve perception and mental skills. The states of altered consciousness elicited using psychedelic drugs in religious settings increase susceptibility to suggested messages and can be accompanied by negative emotions such as fear, terror, anxiety, shame, or sense of guilt. Induced psychotic episodes may result in psychopathology including confusional syndrome and schizophrenia [11–17].

Psilocybin/psilocin is presently used to model schizophrenia and study psychosis [18–27].

Hallucinogenic compounds from fungi of the genera *Psilocybe* and *Amanita* have been used recreationally since the early 1960s [28, 29]. Psilocin and psilocybin, the psychoactive principles of *Psilocybe* mushrooms, were isolated and identified by Hofmann in 1958 [30]. Ibotenic acid and muscimol seemed the most active hallucinogens from fly agaric [31–33]. Chronic exposure to these substances is associated with mental health disorders as well as cardiovascular and neurodegenerative complications.

Given adverse effects, including fear, anxiety, paranoia, personality change, and psychosis, most claims of therapeutic benefit from psilocybin or

psilocin in psychotherapy are on tenuous footing at best. Benefit has been observed, however, in the treatment of obsessive-compulsive disorder [34–38]. A therapeutic benefit in treating cluster headaches has also been reported [39]. In order to limit abuse of indolealkylamine hallucinogens, many of them have been added to the US Drug Enforcement Administration's (DEA) list of controlled substances. ET, AMT, bufotenine, DET, DMT, ibogaine, LSD, psilocybin, and psilocin are all DEA Schedule I, defined as substances with no currently accepted medical use and a high potential for abuse. Lysergic acid and lysergic acid amide (LSD precursors) are Schedule III, defined as having low to moderate potential for physical or psychological dependence.

Severe toxicity from indolealkylamine hallucinogens is uncommon, although abuse of these agents is prevalent. The exact prevalence of use is impossible to determine because of the inherent inaccuracies of self-reporting, the substitution of one substance for another by dealers, and the lack of laboratory confirmation in most cases. In one survey of 1500 American college students, 15% admitted to mushroom abuse and 5% admitted to misuse of LSD [40]. The 2014 American Association of Poison Control Center's National Poisoning Data System (NPDS) report documents 520 single exposures and one death from LSD and 335 single exposures to hallucinogenic mushrooms containing psilocybin and psilocin and no deaths [41].

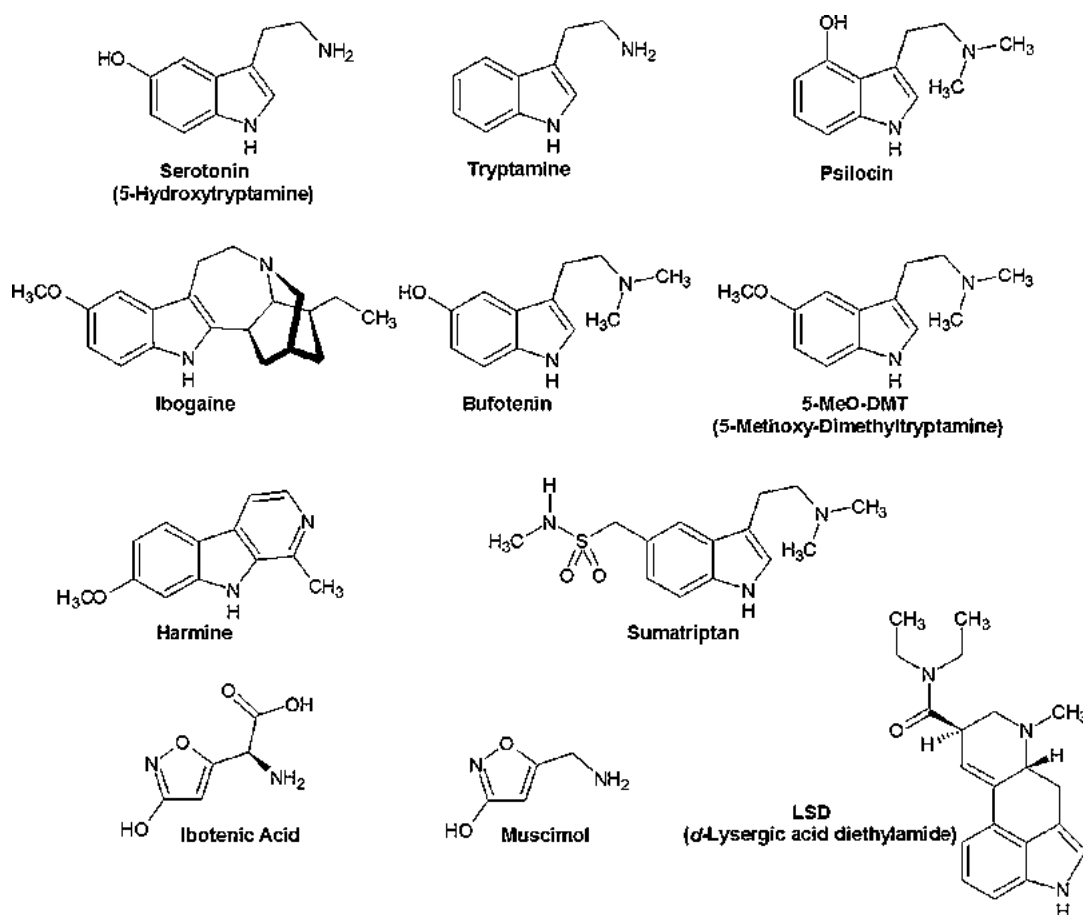


Fig. 1 Chemical structures of common hallucinogenic agents. The tryptamines are structurally similar to serotonin

Death from poisoning by these substances is rare and often related to secondary events, such as trauma while intoxicated. Many toxic sequelae of poisoning with the indole hallucinogens are potentially life threatening, however, and could result in the necessity of intensive care unit admission.

Biochemistry and Clinical Pharmacology

The three main chemical groups of hallucinogens of clinical importance are the indolealkylamines (the subject of this chapter), phenylethylamines, and atypicals (arylcyclohexylamines).

Representative chemical structures of indolealkylamines are illustrated in Fig. 1. There is substantial chemical similarity between the indolealkylamine hallucinogens and the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]). Although there is variety in structure among hallucinogens, which may account for differences in their clinical presentation overall, agonism at select cerebral serotonin receptors seems to be a necessary common denominator for their ability to produce hallucinations [42–44]. The commonly encountered indolealkylamines are psilocin (dimethyl-4-hydroxytryptamine); psilocybin, harmine, and ibogaine (all dimethyl-4-phosphoryltryptamine); 5-methoxydimethyltryptamine; LSD; lysergic

acid amide; isolysergic acid amide; dimethyltryptamine; dipropyltryptamine; α -methyltryptamine; diethyltryptamine; and 6-hydroxymethyltryptamine. In addition, IAAs have been developed for use in migraine therapy [45–47]. Ergotamine acts mainly via 5-HT_{1B/1D} receptors. The side effects are mediated via dopamine and 5-HT_{1A} receptors. Newer triptans are much more selective for 5-HT_{1B} and 5-HT_{1D} receptors with high affinity [48].

Tryptamine (see Fig. 1) serves as the basic structural unit for serotonin and the indolealkylamine hallucinogens. The IAAs are made up of an indole moiety and a basic nitrogen atom connected by an alkyl chain of at least two carbons in length [48]. Dialkyltryptamines, such as dimethyltryptamine, diethyltryptamine, and 5-methoxydimethyltryptamine, are not psychoactive if given orally, presumably due to rapid hepatic metabolism, and generally are smoked or, in native cultures, inhaled as snuff [49]. Exceptions to this lack of oral activity are psilocin and psilocybin. The latter is converted by hydrolysis in vivo to the former, which is the active species [50, 51]. Affinity of indolealkylamines for 5-HT₂ receptors seems to be influenced by the lipophilicity and electron-withdrawing properties of the four-position substituents [52]. The mechanism of hallucinogenesis seems to be sensitive to ring substitution. With the exception of 5-methoxy, 4-methoxy, or 4-phosphoryloxy (psilocybin) substituents, no other ring-substituted compounds have been found to be psychoactive in humans [49].

Structural features on the aliphatic side chains also influence activity. An α -methyl group confers the ability to resist degradation by monoamine oxidase and to be orally bioavailable.

α -Methyltryptamine is not degraded by monoamine oxidase, preventing the metabolism that so rapidly occurs with other non- α -methylated tryptamine derivatives. The α -methylated compounds, such as α -methyltryptamine, have an increased duration of action [53]. Stereochemical considerations also are important. With α -methyltryptamine and 5-methoxy- α -methyltryptamine, the (+) enantiomer is the most active [54, 55].

Radioligand competition studies in rats revealed the following structure-activity

relationships for IAAs at serotonin receptors: All IAAs show greatest potency for the 5-HT_{2A} receptor; most show 2–10 times lower affinity at 5-HT_{2B} receptors; moieties lacking indole ring substitutions at the 4- or 5-position showed lower affinity for all 5-HT receptors; 4-hydroxylated derivatives had 25–380-fold selectivity for the 5-HT_{2A} versus 5-HT_{1A} receptor; 5-substituted derivatives were equally potent at both 5-HT_{1A} and 5-HT_{2A} receptors; 6-substituted derivatives showed > micromolar affinities for all 5-HT receptors studied; the *N,N*-dialkyl substituent was a secondary determinant of affinity, i.e., substituents larger than *N,N*-diisopropyl markedly reduced affinity at 5-HT_{2A} and 5-HT_{1A} receptors; and hallucinogenic 4-hydroxy-indolealkylamines, like the psychotomimetic phenylisopropylamines, are potent and selective ligands at 5-HT_{1A} receptors [56].

LSD is extensively metabolized in animals [48]. At least 4 urinary metabolites have been identified in humans [57]. The metabolism of psilocybin and psilocin is not well characterized at this time. Psilocybin is a secondary metabolite of mushrooms of the following genera: *Agrocybe*, *Conocybe*, *Copelandia*, *Galerina*, *Gymnopilus*, *Hypholoma*, *Inocybe*, *Panaeolina*, *Panaeolus*, *Pholiotina*, *Pluteus*, and *Psilocybe*. Most mushrooms are cultivated – *Psilocybe cubensis* is the mushroom of choice for abusers, is easy to culture, and fruits readily in vitro. Oral psilocybin is quickly hydrolyzed in the gastrointestinal tract. Phosphorylation in the stomach or via alkaline phosphatase in the small intestine produces psilocin, the active form of the drug, which unlike psilocybin is easily absorbed from the GI tract. There is glucuronidation of psilocin metabolites in the liver and intestinal tissue [58]. Ibogaine is a Schedule I substance which undergoes *O*-demethylation by CYP2D6 as a dominant pathway to an active metabolite, noribogaine. As a result, ibogaine has potential for significant drug–drug interactions in co-ingestion with CYP2D6 inhibitors such as the serotonin-selective reuptake inhibitors paroxetine or fluoxetine or the antiarrhythmic drug quinidine [48].

The tryptamines, including DMT, bufotenine, and 5-MeO-DMT, are primarily excreted via

oxidative deamination involving monoamine oxidase A (MAO-A) [59–63]. Oral DMT undergoes extensive first-pass metabolism via the monoamine oxidase (MAO) system necessitating co-ingestion of an MAO inhibitor-containing plant (e.g., *Banisteriopsis caapi*, in ayahuasca brews) in order to achieve a psychedelic response [64]. Alternatively, smoking a plant mixture extract can bypass hepatic first-pass metabolism to allow the parent compound to gain access to the CNS [65].

5-methoxy-*N,N*-dimethyltryptamine is mainly deactivated via deamination by MAO-A. A secondary metabolic pathway involves *O*-demethylation by CYP2D6 to the active metabolite, bufotenine [66, 67], which binds to the 5-HT_{2A} receptor with an affinity ten times that of the parent compound [68, 69]. However, its psychedelic potency has been questioned due to its poor lipid solubility and penetrance of the blood–brain barrier (BBB) [70–72]. 5-MeO-DMT showed nonlinear pharmacokinetics in mice suggesting saturable hepatic metabolism [73]. Bufotenine is Schedule I, while 5-MeO-DMT is not.

MAO inhibitors lengthen the elimination of 5-MeO-DMT and increase production of bufotenine. Defective allelic isoforms of CYP2D6 were associated with decreased production of bufotenine [74]. The main pathway of bufotenine metabolism is also deamination via MAO so an MAO inhibitor also inhibits its elimination. Thus, the C_{\max} and AUC of bufotenine are increased 2.6- and sixfold, respectively, in mice after harmaline pretreatment [74].

Little is known about the metabolism of many of the β -carbolines. Metabolism of the β -carbolines by *N*-methyltransferase can produce highly neurotoxic metabolites [75, 76]. Harmaline is metabolized by CYP2D6, which is known to be subject to genetic polymorphisms [77]. Prolonged exposure to harmaline can result following ingestion in patients who are poor metabolizers [78].

5-MeO-DMT, harmaline, and bufotenine are all serotonergic agonists and may in combination produce a serotonin syndrome. 5-MeO-DMT is also a serotonin reuptake inhibitor [69]. Additionally, harmaline, as an MAOI, inhibits 5-HT

metabolism as well as that of 5-MeO-DMT. The result is increased and prolonged exposure to the latter as well as shunting metabolism to *O*-demethylation increasing production of the psychoactive metabolite, bufotenine [48]. In this light, it is not surprising that co-ingestion of 5-MeO-DMT and harmaline is associated with fatalities [79, 80]. Harmine has two primary oxidative pathways of metabolism, *O*-demethylation, and 6-hydroxylation. The former is catalyzed by CYP2D6, 1A1, 1A2, 2C9, and 2C19 [81]. A human study identified fast and slow metabolic phenotypes for harmine as well, suggesting CYP2D6 polymorphism may be a significant factor in its clinical presentation [82].

Ibotenic acid and muscimol are the major active constituents of *Amanita muscaria* and *A. pantherina*, products of fungal secondary metabolism. Their endogenous analogues are glutamic acid and gamma-aminobutyric acid (GABA). The minimal psychedelic dose for muscimol is 6 mg, 30–60 mg for ibotenic acid [58]. Muscimol, unlike GABA, is able to cross the BBB, possibly via active transport [83–85]. GABA-gamma-oxoglutarate transaminase appears to be involved in the rapid conversion of muscimol to metabolites [86]. One metabolite, tricholomic acid, has been shown to be active in inhibiting neurons [87, 88]. Ibotenic acid is metabolized in vivo to muscimol [89]. Both are renally excreted and have been detected in human urine 3–8 h after ingestion [90].

Pharmacokinetics of Indole Hallucinogens Lysergic acid diethylamide (LSD)

Volume of distribution: 0.27 L/kg after 2 μ g/kg intravenously, elimination half-life calculated at 103 min, hepatic elimination via hydroxylation, glucuronidation, and excretion in bile, small amounts excreted unchanged in urine [91]

Absorption: well absorbed via gastrointestinal tract

Peak levels: 30–60 min after 2 μ g/kg orally, reduced slightly and delayed by food [92]

Plasma protein binding: >80%

(continued)

Elimination half-life: approximately 2.5 h, approximately 0.01% crosses blood–brain barrier [93]

Psilocybin

Duration of action: briefer than LSD's, usually approximately 4 h [94] (6–12 h for LSD)

Bioavailability (of psilocin after oral psilocybin): 50%

Peak levels: 50–100 min, slowly decreases after 5–6 h

Elimination: 65% excreted in the urine, 15–20% in bile and feces within 8 h from ingestion [58]. 10–20% remains longer (psilocin has been detected in urine 7 days after oral psilocybin administration) [95]

Dimethyltryptamine

Intense and shorter trip than LSD, lasting 30–60 min

Smoked, snorted, or injected [94]

Smoking DMT produces symptoms within one minute and peak effect in 2–5 min. The duration of action is 20–60 min [65]. *Mechanism of clearance:* dimethyltryptamine and 5-MeO-DMT eliminated:^[96] (1) via monoamine oxidase by oxidative deamination (major route of metabolism in brain, liver, and kidney), (2) by *N*-oxidation (major metabolic route in peripheral tissues [e.g., liver and kidney], minor in brain), and (3) only 8% of administered dose of either recovered as metabolites in urine

Bufotenines

(5-methoxydimethyltryptamine)

Single deep inhalations of vaporized venom is powerfully psychoactive within 15 s [96]

5-HT_{2C} receptor acts as a modulator [43, 44, 69, 98]. Risperidone, a potent 5-HT₂ receptor and dopamine-D₂ antagonist, completely blocks the discriminative stimulus properties of LSD in rats [99]. Antagonism of LSD's behavioral effects by 5-HT₂ antagonists, without change in the typical LSD-induced suppression of serotonin neuronal activity, suggests that these effects are mediated postsynaptically [100]. That 5-HT₂ agonism is the primary mode of action of LSD's behavioral effects is not firmly established, however. There is some evidence against a mechanism of direct pure 5-HT₂ agonism. LSD does not stimulate 5-HT₂-mediated phosphatidylinositol turnover in rat cortex, yet it inhibits serotonin's ability to produce these effects [101]. A study in monkeys found indolealkylamine administration to be transiently reinforcing in only 1 of 4 animals, suggesting that this class of hallucinogen has either weakly reinforcing effects or mixed reinforcing and aversive effects [102].

Psilocybin acts as a prodrug. Its dephosphorylation results in psilocin which is lipophilic and easily crosses the BBB. Psilocin's psychotic effects are thought to be mediated by 5-HT_{2A} receptors [103] and are blocked by the 5-HT_{2A} antagonist ketanserin in human subjects [24, 104]. Other effects on cognition and attention are not fully diminished and may even intensify when psilocybin and ketanserin are coadministered [18, 105]. It is felt that the psychotic effects result from both 5-HT_{2A} cortical stimulation and 5-HT_{1A} inhibition in the dorsal raphe nuclei, resulting in decreased serotonin release in the prefrontal cortex. Binding studies have shown that psilocin binds 5-HT_{2A} and 5-HT_{2C} receptors with high affinity and 5-HT_{1A} receptors with lower affinity [56, 103]. 5-HT_{2A} receptors are expressed by excitatory glutaminergic pyramidal neurons, but psychoactivity is felt overall to result from inhibitory influence via 5-HT_{2A} receptors on GABAergic interneurons [106]. Monoamine oxidase inhibitors are taken by psilocin users to intensify the induced hallucinations. MAO catalyzes serotonin degradation in the synaptic cleft. Psilocin, as an MAO substrate, is also an MAO inhibitor with respect to other MAO substrates such as serotonin resulting in increased levels of the latter [58].

Pathophysiology of Toxic Effects

At least three different pharmacological mechanisms of hallucinogenesis are believed to exist: dopamine D₂ receptor activation, 5-HT_{2A} receptor activation, and glutamate *N*-methyl-D-aspartic acid (NMDA) receptor inhibition [97]. Indolealkylamines and phenylethylamines produce hallucinations primarily via stimulation of the 5-HT_{2A} receptor, while the

In contrast to other IAAs, the effects of 5-MeO-DMT are mediated primarily by the 5-HT_{1A} receptor [107–110], though 5-HT_{2A} effects may be contributory as well [109], particularly with respect to the induction of hyperthermia in high doses [111]. 5-MeO-DMT is also a serotonin reuptake inhibitor.

5-Methoxy-*N,N*-dimethyltryptamine and the MAOI inhibitor harmaline are both serotonin analogues and are often abused together. Adding harmaline increases and prolongs the duration of action of 5-MeO-DMT. In a mouse study, harmaline was shown to decrease body temperature in low dose and cause hyperthermia in higher dose. Coadministration of harmaline dramatically potentiated 5-MeO-DMT-induced hyperthermia. Harmaline-induced hypothermia was only attenuated by 5-HT_{1A} antagonist administration, while hyperthermia induced by harmaline and 5-MeO-DMT was attenuated by coadministration of a 5-HT_{1A} or 5-HT_{2A} antagonist. Stress-induced hyperthermia was not attenuated by 5-HT_{1A} antagonism. The results suggest the synergistic hyperthermic response to harmaline and 5-MeO-DMT involves activation of both 5-HT_{1A} and 5-HT_{2A} receptors [112].

More recent work with receptor subpopulations has determined that LSD and the phenylethylamine DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) serve as potent partial agonists for cortical 5-HT_{2A} receptors, inhibiting pyramidal cells in layer II, via stimulation of GABAergic interneurons in layer III, of the rat piriform cortex [113]. Indole hallucinogens initiate a 5-HT_{2A} receptor-mediated enhancement of nonsynchronous, late components of glutaminergic excitatory postsynaptic potentials in layer V pyramidal cells, which may help explain the changes in higher level cognition, perception, and mood experienced from these drugs [114].

DMT is a postsynaptic 5-HT_{2A} agonist and a 5-HT_{2C} partial agonist. The latter receptor shows a deep desensitization to DMT over time. This direct agonism decreases the rate of serotonin synthesis and turnover in the brain [115] which could account for the psychodysleptic effects of DMT [116]. DMT remaining in the brain 48 h after injection is concentrated in the olfactory

bulb. The long-term persistence of DMT in the brain is postulated to result from uptake by serotonin transporter and storage in vesicles preventing degradation by MAO. DMT has three putative receptor targets – 5-HT₂ (5-HT_{2A} and 5-HT_{2C}), trace amine-associated receptors, and sigma σ -1R receptors [117].

Muscimol is a GABA_A agonist and partial GABA_C agonist [58]. It binds to high-affinity and low-affinity sites on GABA_A receptors and functionally activates them [118]. Muscimol via GABA_A binding in cerebral cortex and hippocampus induces sedation and ataxia in mice. Muscimol inhibits GABA neuronal uptake and is a substrate for GABA's metabolic enzyme, GABA transaminase [86, 119–121]. Ibotenic acid is an NMDA receptor agonist resulting in its observed neurotoxicity [122]. High-dose muscimol potentiates psychosis in schizophrenics [123]. Muscimol causes increase in brain serotonin and decreased catecholamine levels [124] in mice and rats and decreases striatal GABA_A release in rats [125]. Muscimol when given alone decreases motor activity and when given in combination with cocaine prevents the motor hyperactivity caused by the latter which is known to depend on dopaminergic neurotransmission. It is thought that muscimol modulates dopamine release [126]. Ibotenic acid excites spinal interneurons and Renshaw cells in cats. Its excitatory activity is eight times greater than glutamate. After recovery from excitability in the case of the former, the neurons become refractory to excitation, an effect felt to be due to metabolism of ibotenic acid to muscimol [89].

Muscimol possesses analgesic properties owing to its inhibitory influence. Muscimol potentiates morphine in rats and mice [127, 128]. It also potentiates the anesthetic effects of propofol [129]. Muscimol blocks or delays drug-induced convulsions in animals [130–132]. It has been shown to improve tardive dyskinesia in schizophrenics [133, 134]. It is able to prevent cell death in ischemia–reperfusion conditions where glutamate in high dose shows toxicity [135, 136].

It is clear in any case that the effects of the indolealkylamines are much more complex than can be explained by interaction with one receptor

or binding site. LSD and dimethyltryptamine have been found to have high affinity for the DOB (a phenylalkylamine, 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane) binding site and 5-HT_{1A} and 5-HT_{1D} receptors in addition to 5-HT₂ receptors. This high affinity for the DOB site may be crucial to the ability to produce hallucinations. It is believed that the DOB binding site represents 5-HT₂ receptors when they are in an agonist high-affinity state. The high affinity of indolealkylamines and other hallucinogens for this site may explain why they are hallucinogenic, whereas serotonin itself is not because the latter does not have high affinity for this site [52]. LSD is a potent partial agonist for 5-HT_{2A} and a partial agonist for 5-HT_{2C} receptors [137]. LSD also displays high affinity for α_2 -adrenergic receptors and submicromolar affinity for α_1 -adrenergic and β -adrenergic receptors [101]. It also has been suggested that hallucinogens are partial agonists at 5-HT₂ receptors because they occasionally seem to act as antagonists [138].

Given their status as serotonergic agonists, the indolealkylamine hallucinogens have the potential to produce a serotonin syndrome. A report of eight patients with massive LSD overdose noted many clinical findings suggestive of serotonin syndrome [139]. Interaction also has been noted between serotonergic and dopaminergic agonists with respect to hyperthermia [140]. Drug-induced hyperthermia is antagonized by serotonin receptor antagonists [141]. Psychoactive agents with dopaminergic effects, such as 3,4-methylenedioxymethamphetamine, are noted to be more potent in producing hyperthermia [142].

A case report described what the authors called neuroleptic malignant syndrome after consumption of ethanol and LSD. This case had clinical features similar to those of serotonin syndrome [143]. It was the opinion of the authors of that report that the central nervous system effects of LSD resulted in continuous muscle contraction and hyperthermia, producing muscle damage and its sequelae. Clinical effects from the indolealkylamines are attributed primarily to their effects on serotonergic neurotransmission and the sympathetic nervous system.

Clinical Presentation and Life-Threatening Complications

Many life-threatening complications are possible with poisoning from indolealkylamine hallucinogens. Most commonly, trauma or self-harm may occur secondary to the mental and behavioral changes associated with the hallucinatory state and accompanying panic reactions or paranoia. Patients for whom little or no history is available should be assumed to have associated trauma until proven otherwise. Serotonergic excess may result in life-threatening serotonin syndrome, characterized by hyperthermia, muscle rigidity, and rhabdomyolysis leading to myoglobinuric renal failure, hepatic necrosis, and disseminated intravascular coagulation. Elevation of blood pressure is common from these agents, and hypertensive crisis is theoretically possible, although it has not been reported.

LSD

True hallucinations are marked by changes in perception without significant impairment of intellect or memory. Usual doses of hallucinogens typically are not associated with alterations in consciousness or excessive stimulation at these doses. To the extent that they do occur, autonomic side effects tend to be mild and not disturbing to the patient. Addictive craving is minimal [144]. Colorful and luminous pattern hallucinations are characteristic of IAA intoxication [71]. Distortion of time perception occurs as well [48].

Typical presentations for acute LSD toxicity include psychiatric and constitutional effects. Psychiatric manifestations include acute hyperanxiety, paranoia, panic reactions, dangerous or self-destructive behavior, hallucinations, sensory distortions (e.g., misperception of shape or color), and major depressive or dysphoric reactions [145]. Constitutional signs and symptoms include nausea, diaphoresis, mydriasis, severe headache, muscle weakness, fatigue, and impaired concentration. Cases of severe toxicity also have presented with coma, hyperactivity, seizures, marked visual and auditory hallucinations,

respiratory depression requiring intubation, sinus tachycardia, fixed and dilated pupils, vomiting, vasodilation, and coagulopathy [139]. A single patient was documented as presenting unconscious with severe extrapyramidal rigidity and hyperthermia [143].

Hallucinogenic Mushrooms

Ingestion of hallucinogenic mushrooms containing psilocin or psilocybin results in perceptual distortions or hallucinations, dysphoria, mydriasis, dry mouth, hyperreflexia, tachycardia, drowsiness, euphoria, nausea, cramping, abdominal pain, and distortions of body image [146, 147]. One fatal case of mushroom poisoning was reported in a 6-year-old child who ingested *Psilocybe baeocystis* and developed hyperthermia and status epilepticus [148]. Psilocybin/psilocin intoxication results in dose-dependent increases in pulse and blood pressure [149–155] which are maximal 1–2 h after administration [152]. These clinical effects are dose dependent: 8–10 mg (0.1–0.2 mg/kg) of oral psilocybin causes only physiologic mydriasis, rarely nausea and vomiting, slight increases in pulse and blood pressure, and paresthesias [149, 150, 152–155]. Higher doses (10–20 mg in a 70 kg adult) elevate the plasma concentration 5–12 ng/mL, and psychotic symptoms begin when the plasma concentration reaches 4–6 ng/mL [156]. The induced psychosis intensifies over 30–60 min and declines after 2–3 h [27, 149, 152, 153, 156]. It is estimated that 2 g of *Psilocybe semilanceata* mushroom fruit bodies (equivalent to about 10–20 mg of psilocybin) results in mild psychosis usually experienced as pleasurable (“good trip”). Increasing the dose to 12 g (equivalent to 60–120 mg of psilocybin) typically produces a negative experience (“bad trip”). The psychosis abates after 5–6 h. The psychotic symptoms include disturbances of visual perception (illusions, hypnagogic experiences), alteration of time, color and motion perception (e.g., kaleidoscope vision), synesthesias, derealization and depersonalization, euphoria sometimes changing

to drowsiness, anxiety, mood changes, dysphoria, or extreme fear [23, 25, 104, 150, 153, 157–160]. Body image perception is distorted with sensation of swelling and numbness reported [161]. Psilocybin impairs cognition, decreasing reaction times, impairing focus and attention by eliciting strong and unusual emotions and visual stimuli, and disturbing thinking by distortion of ego and delusions [18–27, 104, 105]. Psilocybin, like schizophrenia, impairs the ability to use contextual information [22]. At high doses, the psychotic manifestations, called the schizophrenic phase, give way to a panic attack-like phase characterized by dysphoria, paranoia, and a loss of ego control perceived as negative [149, 161, 162]. Accidental death from jumping out a window has been reported after ingestion of “magic mushrooms” [163, 164]. Recurrence of induced psychotic symptoms after even a single psilocybin ingestion (aka “flashbacks”) can occur especially under the influence of other toxicants such as alcohol or marijuana [153, 164, 165].

Psilocybin is a low potency toxicant with an LD₅₀ in mice of 285 mg/kg and in rats of 280 mg/kg [166]. It may transiently elevate hepatic transaminases [152]. Psychotomimetic doses in humans (30 mg orally in a 70 kg adult) produce only slight, transient elevations in pulse and blood pressure [149, 150, 152, 154]. Blood clotting disturbances have been reported [167]. Single cases of cardiac disturbances such as supraventricular tachycardia, myocardial infarction, and takotsubo cardiomyopathy have been reported [168, 169]. Serotonergic vasoconstriction can contribute to venous ulcers and delay in wound healing, headaches, and increased risk of abortion [153, 161, 170]. Psilocin is associated with breakdown of the BBB. A 33-year-old patient developed left leg weakness and visual field defects 2 weeks after magic mushroom consumption which was attributed to multifocal cerebral demyelination within the corpus callosum and both optic nerves [171].

The first effects of intoxication with *A. muscaria* and *A. pantherina* are muscarinic: nausea, vomiting, diarrhea, vasodilation, sweating, and salivation [84, 172, 173]. Thirty minutes after ingestion, anticholinergic signs and

symptoms arise, including mydriasis, xerostomia, hyperthermia, a slight blood pressure increase, drowsiness, memory loss, dizziness, photophobia, euphoria, motor hyperactivity, hallucinations, and delirium [84, 172–174]. These tend to intensify over 2–3 h. Somnolence followed by deep sleep and skeletal muscle atony and hyporeflexia follows, a state which can resemble a stroke [84]. A study of human volunteers found that hallucinations, muscle twitching, delirium, and sleep occurred after pure ibotenic acid and muscimol administration [175]. Signs of poisoning decrease after about 8 h [84, 172, 173, 175, 176].

Muscle twitching, spasms, cramps, abdominal pain, and seizures can result from intoxication with fly agaric, especially in children [123, 175, 177]. Animal studies show that ibotenic acid administration systemically or locally can induce seizures [178, 179]. The LD₅₀ of muscimol in rats is 4.5 mg/kg after intravenous administration and 45 mg/kg after oral administration. For mice, the LD₅₀ is 2.5 mg/kg intraperitoneally, 3.8 mg/kg subcutaneously, and 5.62 mg/kg intravenously [180, 181]. The oral LD₅₀ in rabbits is 10 mg/kg. For ibotenic acid, the LD₅₀ in rats is 128 mg/kg orally and 42 mg/kg intravenously and for mice 38 mg/kg orally and 15 mg/kg intravenously [180]. Cortical injections of ibotenic acid are used to model Alzheimer's disease in rats given its cytotoxicity [182].

Bufotenine

As stated previously, because of its poor penetration of the blood–brain barrier, bufotenine (5-hydroxydimethyltryptamine), found in many toad and plant species, is not believed to be psychoactive if ingested. One species of toad, the Sonoran Desert (also known as Colorado River) toad (see Fig. 2) *Bufo alvarius*, is unique within its genus, however, in possessing the enzyme *O*-methyltransferase, which converts bufotenine to the potent hallucinogen 5-methoxydimethyltryptamine [183]. A 5-year-old boy was reported to have developed profuse salivation and status epilepticus within 15 min of licking a toad identified positively as *B. alvarius*



Fig. 2 The Colorado River Toad (*Bufo Alvarius*) (Source U.S. National Park Service)

[96]. He survived but remained symptomatic for 1 week. It has been shown that inhalation of the vaporized venom results in an intense but short-lived “trip” after 15 s, marked by auditory and visual hallucinations [183]. This mode of intake apparently denatures the venom's more toxic fractions, avoiding serious toxicity. Toad venoms contain many toxic substances in addition to indolealkylamines (bufotenines), including biogenic amines (epinephrine, norepinephrine), cardioactive steroids similar to digitalis (bufotalins or bufogenins), and conjugates of bufogenins (bufotoxins) [184].

Dimethyltryptamine

The prevalence, user characteristics, and abuse potential of dimethyltryptamine were recently reviewed [65]. Intramuscular administration of DMT produces visual hallucinations and illusions, distortions of spatial perception and body image, thought disturbance and euphoria [185], visual and auditory hallucinations, and bodily dissociation [186]. DMT is known to produce sympathomimetic effects including tachycardia, hypertension, and mydriasis [185–187].

Symptoms of DMT intoxication include cognitive changes described as “deep introspection” [188]. DMT can be snorted, ingested, or smoked, but the latter is the most commonly utilized, likely owing to improved clinical effect. DMT was

found in one study to have a shorter duration of effect compared to LSD, ketamine, and magic mushrooms (23.8 ± 33.9 min) and was judged by users to have the strongest effect and deemed as pleasurable as LSD, more pleasurable than ketamine or magic mushrooms, with the fewest negative effects attributed to its being smoked.

Ayahuasca Brew

Oral intake of ayahuasca brew, a botanical hallucinogenic preparation, is associated with nausea and vomiting [65]. Ayahuasca has been associated with severe intoxication, though some reports lack sufficient supporting forensic/toxicological information. Available case experience suggests patients with cardiac or liver disease are especially susceptible to toxicity and that co-ingestion of other serotonergic agents also poses an additional risk [189].

5-Methoxy-*N,N*-Dimethyltryptamine

5-MeO-DMT is a potent, fast-acting hallucinogen of short duration. It can be used by inhalation and injection, sublingually, intranasally, or orally [69]. 5-Methoxy-*N,N*-dimethyltryptamine has high affinity for the 5-HT_{1A} receptor, 4–10 times more potent than DMT [190, 191]. It causes visual and auditory changes, distorting perception of time 3–4 min after it is inhaled, effects which peak after 35–40 min and last 60–70 min [192]. Because of the first-pass effect, oral administration produces no effect. Oral coadministration with harmaline is about one-third as potent as administration via the intranasal or sublingual routes. Animal models of 5-MeO-DMT toxicity document symptoms including ataxia, mydriasis, head nodding, tremor, convulsions, and shivering [193, 194]. Bufotenine has 5–10 times greater affinity for 5-HT_{2A} receptors than 5-MeO-DMT but poor penetration of the blood–brain barrier. Its administration intravenously, intranasally, or sublingually results in psychoactive effects [71, 195, 196].

Ibogaine

Among the natural IAA hallucinogens, ibogaine has proven to be particularly toxic. Overdose of ibogaine resulted in altered mental status, sinus bradycardia, QTc prolongation, brief self-limited episodes of polymorphic tachycardia initially associated with tonic–clonic seizures deteriorating into torsades de pointes, and cardiac arrest. The patient responded initially to defibrillation, but torsades recurred despite intravenous magnesium, atropine, epinephrine, and isoprenaline. The patient was defibrillated several more times and intubated, and first transcutaneous then transvenous pacing shortened his QTc and prevented return of dysrhythmia [197]. It is believed that ibogaine causes QT interval prolongation by blocking human ether a-go-go-related potassium channels during their activation during cardiac repolarization. When studied in mammalian kidney tsA-201 cells, the mechanism appeared to result from preferential binding of ibogaine to the open and inactivated state of the cytosolic side of the channel resulting in a shift of steady-state activation and inactivation to more negative membrane potentials [198]. Though the proximate cause was not determined for this case, ibogaine when used as an alternative medicine in alcohol detoxification with documented serum level elevation was associated with sudden death in a patient who on autopsy was found to have hepatic cirrhosis and heavy fatty infiltration [199].

The clinical presentation of patients intoxicated with other indolealkylamine hallucinogens is similar to the presentations described earlier for LSD and psilocybin. One exception, though, is ibotenic acid which can cause convulsions and hyperexcitability similar to its endogenous analogue glutamate [58]. The main long-term risk of abuse of hallucinogens is impairment of mental functioning and psychosis [200]. A subset of users can have persistent symptoms long after stopping drug use [201]. Users have called this persistent drug trips or “flashbacks,” labeled in the American Psychiatric Association’s Diagnostic and Statistical manual V (DSM-V) as “Hallucinogen Persisting Perception Disorder” (HPPD) (APA DSM-V, 2013, ICD-10-CM F16.983). Reported

symptoms are generally visual, but auditory symptoms can occur. The diagnosis is difficult given the existence of other conditions which alter perception and no specific diagnostic test to identify HPPD [202].

Diagnosis

The differential diagnosis of severe poisoning with the indolealkylamines includes intoxication with the phenylalkylamine (e.g., amphetamine derivatives) or cycloarylhexyl (e.g., phencyclidine) hallucinogens, which present in a similar manner, with the exception that small fixed pupils and nystagmus can be prominent distinguishing features of phencyclidine (and congener) intoxication. Other toxicologic causes in the differential diagnosis include anticholinergic poisoning (e.g., jimsonweed, scopolamine), sympathomimetic poisoning (e.g., cocaine), the serotonin syndrome, malignant hyperthermia, and neuroleptic malignant syndrome. Possible nontoxicologic causes with similar signs and symptoms include psychosis, central nervous system infections, withdrawal syndromes, and delirium from metabolic causes.

The diagnosis of indolealkylamine poisoning depends first on the acquisition of a thorough history if available. Smoking or licking of toad venom, use of blotter “acid,” or ingestion of “psychedelic mushrooms” suggests the diagnosis. Adult patients with uncomplicated hallucinogenic experiences usually do not present to health-care facilities. Adults who do present to health-care facilities usually have presentations similar to those described in the prior section. Hallucinations, fixed and dilated pupils, muscle rigidity, and hyperthermia in the absence of other explanations should raise a high index of suspicion for this type of intoxication. Given the possibility of co-ingestion of an MAO-A inhibitor in those using IAAs recreationally, the possibility of serotonin syndrome should be considered especially in patients with severe manifestations such as delirium, neuromuscular rigidity, and/or hyperthermia (see ► Chap. 24, “Serotonin Syndrome”). Evaluation of a patient with hallucinations should include an electrocardiogram with measurement

of the QT interval given the possibility of its prolongation and resulting life-threatening arrhythmias in the context of ibogaine intoxication.

Standard drug-of-abuse screening tests do not detect these agents. LSD and its major metabolite, 2-oxy-LSD, remain in the urine for 12 h and can be detected by specific directed radioimmunoassay [145]. LSD degrades on exposure to light, so specimens should be wrapped in opaque paper or aluminum foil and frozen. Identification of hallucinogenic mushrooms requires a proper specimen and the services of an experienced mycologist. Exposure to a toad in the area of the Sonoran Desert should raise suspicion of toad toxicity. The toad should be identified if available. Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) has been used to sensitively and reliably quantitate blood 5-MeO-DMT and bufotenine levels [68]. Effective liquid chromatography–mass spectrometry methods to detect psilocybin and psilocin have been developed, but are not routinely available in a clinically meaningful time period [58]. Thin-layer chromatography can be used for qualitative identification of ibotenic acid. High-performance liquid chromatography (HPLC) (reversed phase) can be used to quantitate ibotenic acid or muscimol [203–205].

Treatment

Treatment of intoxication by indole hallucinogens does not routinely require gastrointestinal decontamination with activated charcoal but may include it if the patient presents soon after oral ingestion, particularly if there is concern for co-ingestants. However, there are no data indicating that it alters the clinical outcome in these patients. Activated charcoal should be given cautiously, if at all, to patients who may develop seizures or altered mental status for to avoid aspiration. Gastric lavage, considered to be of very limited utility, if any, in the management of poisoned patients in general, should be avoided in patients intoxicated by indole hallucinogens. These procedures are unlikely to be beneficial and could

worsen the agitation of the patient as well as increase the possibility of serious adverse events such as aspiration. Extracorporeal removal techniques play no role in the treatment of poisoning with the indolealkylamines.

Specific treatments have been reported to be helpful for various complications of indolealkylamine intoxication. Hyperanxiety states and panic attacks are helped by treatment with someone at bedside in a quiet room with a soothing, reassuring, nonjudgmental approach (Level III recommendation). Patients are “talked down” by repeated orientation to person and place, explaining that symptoms are drug related and the patient is not losing their sanity [146] (Level III recommendation). Given the serotonin receptor agonism of indoles, serotonin reuptake inhibitors logically should be avoided. Benzodiazepines are likely to be beneficial if sedation is required [145] or if treatment is needed for sympathetic excess (Level II-III recommendation).

Among the most dangerous complications of IAA intoxication is serotonin syndrome (see ► Chap. 24, “Serotonin Syndrome”), made more likely when co-ingestion with an MAO-I occurs, and especially life-threatening when accompanied by the severe hyperthermia which can result. It is recommended that patients with serotonin syndrome and severe hyperthermia (temperature is more than 41.1 °C) be treated with sedation, neuromuscular paralysis, and orotracheal intubation [206] (Level III recommendation). There is no role for antipyretics since temperature elevation in this context results from muscular hyperactivity rather than a derangement of the hypothalamic set point.

There is evidence to suggest that the rate of cooling in hyperthermia is an important determinant of mortality. A retrospective study of non-exertional heatstroke found a statistically nonsignificant trend toward increased mortality for patients whose cooling to a temperature of less than 38.9 °C (102 °F) was delayed more than an hour compared to patients cooled to that temperature within an hour of presentation [207]. No controlled clinical trials exist to guide selection of method or endpoint for temperature reduction in drug-induced hyperthermia. However,

guidelines recommended for heat stroke include lowering the core temperature to <39.4 °C by promoting heat loss by conduction and evaporation, maintaining a skin temperature of 30–33 °C to avoid vasoconstriction, control of any seizures, airway protection and maintenance of oxygenation (saturation > 90%), intravenous fluids and pressors as appropriate to maintain vital organ perfusion (MAP > 60 mmHg), volume expansion +/- furosemide, mannitol or bicarbonate to prevent myoglobin-induced renal injury, and monitoring and maintenance of electrolyte (K^+ , Ca^{++}) balance to prevent life-threatening arrhythmias [208]. Two cases of severe drug-induced hyperthermia, one from an amphetamine derivative and another from cocaine, were cooled using ice-water submersion. The observed cooling rates were faster than those previously reported for the mist and fan technique [209].

Because it has been suggested that hallucinogens are psychoactive because of their affinity for 5-HT₂ receptors, treatment of toxicity from these agents may benefit from the use of 5-HT₂ receptor antagonists [210]. Cyproheptadine is given for serotonin syndrome orally or crushed via nasogastric tube in a dose of 12 mg, followed by 2 mg every 2 h until clinical response is seen [206]. Its administration is associated with sedation and transient hypotension responsive to intravenous fluids. Although there are reported human cases of benefit from cyproheptadine in serotonin syndrome [210–215], animal data suggest that a pure 5-HT₂ antagonist might be more effective. In a fatal rat model of serotonin syndrome, treatment with chlorpromazine and cyproheptadine prevented lethality only at high doses [216]. However, the potent 5-HT_{2A} receptor antagonists ritanserin and pipamperone prevented lethality and increase in temperature while muting the associated rise of hypothalamic norepinephrine better than the other treatments. Both are available for oral use, though their therapeutic use in humans for serotonin syndrome is undocumented. In another study using a lethal rat model of serotonin syndrome, the potent 5-HT_{2A} antagonist, risperidone,

prevented serotonin syndrome and mortality as did ketanserin, a selective 5-HT_{2A} antagonist [94]. Of interest, in the same study, animals given the D₂ antagonist, haloperidol, died sooner than saline control animals.

Care should be taken in treating tachycardia and hypotension in the context of serotonergic excess and even more so if co-ingestion of an MAOI is suspected. Hypertension and tachycardia can be transient and fluctuating in this context, so short-acting intravenous agents such as nitroprusside and esmolol are preferred. If pressors are used to treat hypotension in the context of co-ingestion with an MAOI, indirect agents such as dopamine should be avoided given the exaggerated catecholaminergic response which can result [206]. Direct agonists such as phenylephrine, epinephrine, or norepinephrine are preferred (Level III recommendation).

Indications for ICU Admission in Indole

Hallucinogen Poisoning

Respiratory depression requiring mechanical ventilation
Hyperthermia requiring external cooling
Muscle rigidity/hyperthermia requiring neuromuscular blockade
Myoglobinuric renal failure
Hypertensive crisis
Malignant arrhythmia
Seizures/status epilepticus

Criteria for ICU Discharge in Indole

Hallucinogen Poisoning

Adequate oxygenation and ventilation without ventilator support
Normalization of vital signs (tachycardia, hypertension) without pressor or inotropic support
Core temperature <39 °C with no evidence of life-threatening end-organ damage*:
No evidence of cerebral edema, hemorrhage or infarction, and seizures
No evidence of pulmonary aspiration or edema
No evidence of cardiac failure or infarction

No evidence of hepatic or renal injury
No evidence of rhabdomyolysis
No evidence of disseminated intravascular coagulation

*Should end-organ damage occur, timing of intensive care unit discharge is situation dependent.

Special Populations

Pediatric Patients

Given the reemergence of hallucinogen use among teenagers and the availability of unsupervised access to information regarding synthesis and administration of these agents on the Internet [217], heightened awareness of the presentation and knowledge of treatment of toxicity from these agents are needed. There is no evidence basis for a different approach in the pediatric population to indolealkylamine poisoning. Per the 2014 NPDS report, there was no pediatric mortality from hallucinogens until adolescence when there were deaths from hallucinogen amphetamines [41].

Pregnant Patients

Available data concerning use of these agents in pregnancy are inconclusive. A review of the genetic toxicity of LSD found the available information on teratogenicity to be contradictory and inconclusive [218].

Common Errors in Indole Hallucinogen Poisoning

Exacerbating agitation in hallucinogen intoxication from overaggressive gastrointestinal decontamination
Failure to recognize and treat hyperthermia aggressively

(continued)

Overlooking therapy to limit renal effects of myoglobin in treating hyperthermia
 Treatment-induced hypertension from use of β -blockers for psychostimulant-induced hypertensive crisis
 Mistaken use of serotonin reuptake inhibitors or phenothiazines in indolealkylamine-induced hyperthermia

Key Points in Indole Hallucinogen Poisoning

1. Intoxication with indolealkylamines in most instances responds to reassurance and good supportive care
2. Serotonergic excess from these drugs requires aggressive treatment: hyperthermia necessitates active external cooling, benzodiazepines, neuromuscular blockade, and possibly serotonin (5-HT₂) receptor antagonists
3. Consultation with an experienced mycologist may be necessary to confirm *Psilocybe* mushroom poisoning (and rule out hepatotoxic mushroom ingestion) if there is any concern for the latter

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Cannabinoids are a diverse group of synthetic and naturally occurring molecules that interact with endogenous human cannabinoid receptors. The clinical effects of cannabinoids are varied and depend upon the individual cannabinoid molecule, the specific cannabinoid receptor (CR) that is agonized, and the route of cannabinoid exposure.

There are many cannabinoids that cause clinical effects. Plant-derived cannabinoids (phytocannabinoids) are most commonly found in *Cannabis* spp. plants, commonly known as marijuana. Cannabis is produced in virtually every country and is the most commonly abused illicit drug worldwide. Approximately 25% of worldwide production occurs in Africa closely followed by North and South America which produces approximately 23% of the world's cannabis [1]. Cannabis products are increasingly available throughout the USA as some states have legalized the use of medical and/or recreational marijuana products. This increased availability has led to increased rates of hospitalization associated with cannabinoid ingestion [3].

Synthetic cannabinoids (SC) are a heterogeneous group of molecules that are agonists at CRs. They were first developed as research tools to study the endocannabinoid system and subsequently for therapeutic purposes [8]. However, the emergence of significant adverse effects, especially neuropsychiatric effects, caused most to be quickly abandoned as therapeutic agents. They are increasingly produced in clandestine

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laboratories and abused worldwide [9]. Because the production is illicit, locations of manufacture are difficult to ascertain though a significant proportion of SCs are believed to originate from Chinese laboratories [10]. SC use results in higher rates of medical morbidity than marijuana products; new chemical variants have resulted in numerous public health outbreaks characterized by renal injury/failure, seizures, and occasionally, death [5, 6, 11–13].

There are dozens of SCs with additional novel SC molecules identified every few months [9, 10, 13]. The predominant demographic characteristics of users are males between 20 and 30 years of age [9, 14]. SCs are the second most abused illicit drug after marijuana in adolescents [15] and are commonly abused by active military service members [16, 17]. Reports of abuse to international poison centers have increased every year since 2008 [5, 14, 18]. Thus, SCs are the most commonly abused synthetic designer drug and fastest growing drug of abuse [19].

Biochemistry and Clinical Pharmacology (Includes Pharmacokinetics)

Endogenous Cannabinoid Receptors and Agonists

The endocannabinoid system consists of cannabinoid receptors and cannabinoid agonists.

Endogenous cannabinoid receptors are found throughout the human body including the brain, solid organs, connective tissue, and immune system including the thymus, tonsils, B lymphocytes, T lymphocytes, macrophages, monocytes, natural killer (NK) cells, and polymorphonuclear cells [20–22]. The best characterized receptors are the cannabinoid receptor 1 (CB1) and the cannabinoid receptor 2 (CB2) though the transient receptor potential cation channel subfamily V member 1 (TrpV1, capsaicin receptor) and the G-protein-coupled receptor 55 (GPR55) have been demonstrated to play a role in endocannabinoid signaling

[23, 24]. CB1 is a G-coupled protein that is expressed in the nervous system and the periphery. Activation of the receptor triggers a variety of downstream processes mediated through inhibition of adenylate cyclase and subsequent decrease in intracellular cAMP [25]. Clinical intoxication by cannabinoids is mediated through this pathway [26–28]. Additional cannabinoid receptors, such as CB-2, TrpV1, and GPR55, are found throughout the body and likely contribute to organ-specific toxicity.

Toxicity from inhalation cannabis is dose dependent, peaks around 30 min, and resolves over 2–6 h. Edible cannabis products have significantly delayed kinetic parameters, onset occurs at approximately 30 min, serum peak occurs between 2 and 3 h, and clearance occurs in 8–12 h [29]. See Box [Pharmacokinetics](#) for kinetic parameters associated with cannabinoids products.

Endocannabinoid agonists are derived from integral components of cell membranes; they act as hydrophobic lipid messengers. These molecules activate CBs locally or on nearby cells. These messengers are made on demand and act as retrograde messengers and synaptic modulators [22]. The major endogenous cannabinoid neurotransmitters are anandamide and 2-arachidonoylglycerol. Abused SCs uniformly have a higher affinity [30–32] and higher potency [5, 6, 33] at the CB1 than delta-9-tetrahydrocannabinol (THC) and the endogenous cannabinoid neurotransmitters. In addition, some SCs, such as WIN55,212-2, inhibit serotonin and dopamine uptake leading to higher levels of these neurotransmitters within the synapses and at the neuromuscular junction [34, 35]. Subsequently, the clinical effects elicited by SCs are less predictable than the phytocannabinoids, potentially leading to more toxicity. Depending upon the SC molecule, potency at the CB1 receptor ranges from full agonism to antagonism [36].

The prototypical SC was WIN55,21-2, an aminoalkylindole cannabinoid that inspired the production of indole cannabinoids [37]. This compound binds CB2 with more affinity than CB1. Naturally, alternative indole molecules with greater CB1 affinity were soon developed

[38]. Pyrrole derivatives of the molecule resulted in variable affinities for the CB1 receptor depending upon the length of the R1 side chain; longer side chains lead to greater CB1 affinity [39]. Addition of a phenyl group to the pyrrole molecules led to variably increased CB1 binding affinity, depending upon the substitution location [38]. Potency is further increased via cyclic stacking of the naphthoyl indole molecules at the CB1 receptor [40]. The newest and most SCs to date are the indazoles, such as AB-FUBINACA and ADB-PINACA, which uniformly have higher CB1 and CB2 binding affinity [41]. Toxicity has increased as the CB1 affinity and the potency of these molecules have increased [13, 41, 42].

Pathophysiology of Toxic Effects

Excessive activation of central and peripheral cannabinoid receptors results in toxicity. Activation by endocannabinoids, THC, and SCS inhibits adenylate cyclase which subsequently decreases intracellular cAMP. This, in turn, increases conductance through calcium-dependent potassium channels [43–45]. This leads to the release of acetylcholine, L-glutamate, gamma-aminobutyric acid, norepinephrine, dopamine, and 5-hydroxytryptamine. The increased release of these neurotransmitters results in central nervous system (CNS) toxicity and may contribute to organ-specific toxicity.

Clinical Presentation and Life-Threatening Complications

Clinical presentation from cannabinoid agonists consists primarily of neurotoxicity. However, additional organ toxicity occurs as a result of local agonism of CBs and as a manifestation of neurotoxicity, for example, progressive acidemia due to seizures has led to renal tubular acidosis [46]. See Table 1 for clinical features resulting from acute cannabinoid agonist toxicity.

Clinical Toxicity from Phytocannabinoids

The majority of patients presenting with evidence of toxicity from naturally occurring cannabinoid products demonstrate central nervous system (CNS) toxicity in the form of agitation followed by CNS depression and neuropsychiatric features [7]. THC causes psychosis, even those without underlying psychiatric disease, and the symptoms increase with increased dose [47–49]. CNS depression seems to predominate in children [50]. While adult patients very rarely require critical care for ingestion of *Cannabis* spp. products, young children may require monitoring in an intensive care setting, and occasionally endotracheal intubation, for airway protection [50, 51]. Edible THC products disproportionately result in more medical presentations for toxicity. This is likely due to the unpredictable dosing and the delayed clinical effects resulting in “dose stacking” by users [3].

Synthetic Cannabinoids

While naturally occurring cannabinoids rarely lead to severe clinical illness, synthetic cannabinoid products may result in organ failure and have resulted in intensive care unit admission in approximately 15% of cases during several outbreaks [6, 13, 52]. While the clinical features and organ toxicity are diverse dependent upon the specific SC(s) involved, neurotoxicity generally predominates. This is characterized by delirium and seizures in the acute phase. Patients typically demonstrate a hyperadrenergic state characterized by tachycardia, hypertension, and occasionally hyperthermia during this phase. After 3–6 h, CNS depression predominates. Patients may develop bradycardia during this phase, similar to cocaine washout syndrome. The vast majority of severely poisoned patients recover completely over 12–24 h, with good supportive care.

Table 1 Life-threatening clinical symptoms and management^a

System	Clinical effects	Management
Central nervous system	Excitotoxicity characterized by agitation, hallucinations, and seizures [6, 13, 53]. There have been cases of acute ischemic cerebral vascular accidents [12]	Benzodiazepines, antipsychotics, and GABA agonists
Pulmonary	Aspiration risk in children and severely poisoned adults [3, 50]. Nonspecific organizing pneumonia with a tree-in-bud pattern may occur with SC inhalation [54]	Airway management to prevent aspiration. Cessation of use of these agents
Cardiac	Bradycardia has been demonstrated with several SCs [6, 11]	Bradycardia can be treated with electrolyte repletion and observation. While unlikely, bradycardia leading to impaired organ perfusion can be treated with atropine 0.5 mg IV
Gastrointestinal	Nausea and vomiting are common presenting complaints for both marijuana and SCs [5, 55]	Antiemetics and antipsychotics can be used to control nausea and vomiting. Ondansetron 4–8 mg IV bolus, metoclopramide 5–20 mg IV bolus, and haloperidol 2.5–10 mg IV bolus. These agents may be given as often as needed until symptoms are controlled or until limited by toxicity of the treatment
		Heavy users that develop cannabinoid hyperemesis syndrome report acute improvement of nausea with hot showers though the only proven cure is cessation of marijuana use [56]
Hepatic	There are no definitive reports of cannabinoid-induced hepatotoxicity	NA
Renal	Acute tubular necrosis and interstitial inflammation have been seen with SC abuse [46, 57]	Hemodialysis should be employed for severe metabolic acidosis, severe electrolyte abnormalities, or oligo/anuria. Fluid resuscitation with isotonic fluids should be employed aggressively for oliguria
Musculoskeletal	Rhabdomyolysis [58, 59]	Fluid resuscitation
Dermal	Marijuana may lead to hypersensitivity dermal reactions, particularly in workers [60]. There are no reports of progression to Stevens-Johnson syndrome or toxic epidermal necrolysis	Removal of the allergen. Topical steroids such as fluocinonide topical 0.1% daily

^aAll medical management recommendations should be considered Level 3 evidence and are based upon case series, case reports, and clinical experience of the author

Diagnosis

The diagnosis of cannabinoid intoxication is based upon clinical history. Marijuana can be detected by the majority of clinically available qualitative urine immunoassays. These immunoassays typically detect 11-nor-THC-9-carboxylic acid (THC-COOH), a pharmacologically inactive metabolite of parent THC. Chronic users may have THC-COOH detected in the urine for

greater than a month [61–63]. False positives for THC due to nonsteroidal anti-inflammatories, antiemetics, proton pump inhibitors, and other agents have been reported (see “Drugs Known to Cause False Positives on THC Immunoassays”) [64, 65]. Confirmation of the qualitative immunoassay can be performed with liquid or gas chromatography and mass spectrometry (LC or GC-MS). A clinician may infer the timing of ingestion based upon the parent compound/metabolite ratio detected with liquid

chromatography tandem mass spectrometry (LC-MS/MS) methodologies though this inference is prone to individual variability and is not recommended in routine clinical practice. This is not clinically useful since patients recover rapidly though the LC-MS/MS testing may be useful in legal settings. Further, most clinical laboratories do not conduct LC-MS/MS testing in-house, making the results unavailable in a clinically useful timeframe.

In contrast, clinical immunoassays almost uniformly do not detect synthetic cannabinoid receptor agonists [66]. Several reference laboratories now offer blood, urine, and saliva LC-MS/MS assays for a variable panel of synthetic cannabinoid receptor agonists. However, these panels are not comprehensive; additionally, minor alterations in the chemical structure can yield false negatives on these assays because these new SCs do not have verified standards for the LC-MS/MS method leading to delay molecular identification. The rapid evolution of new SCs, and the resulting lack of reliable analytical standards, hampers the laboratory detection and identification of these agents.

Drugs Known to Cause False Positives on THC Immunoassays

Ibuprofen
Naproxen
Ketoprofen
Niflumic acid
Promethazine
Riboflavin
Dronabinol
Pantoprazole
Omeprazole
Esomeprazole
Efavirenz
Baby soaps

Treatment

Supportive care is the mainstay of treatment for cannabinoid toxicity. Most patients with CNS depression alone can be observed without

intervention. Agitated patients may require benzodiazepines and/or antipsychotic medication to prevent harm to themselves or others. IV boluses of benzodiazepines such as lorazepam (0.05–0.1 mg/kg), midazolam (0.05–0.1 mg/kg), or diazepam (0.1–0.5 mg/kg) may be used in conjunction with antipsychotics. Appropriate antipsychotic medications for cannabinoid toxicity may include haloperidol 5–10 mg, droperidol 2.5–5 mg, or olanzapine 5–10 mg IV boluses. Benzodiazepines are favored in patients also manifesting seizure activity. These doses may be repeated every 5–15 min, as needed to halt seizures and provide adequate sedation.

Patients with recurrent seizures or status epilepticus should be intubated and sedated with a GABA agonist such as propofol (Grade I recommendation).

Special Populations

Young children with CNS depression may be at risk for airway obstruction and aspiration [50]. In addition, children more commonly ingest the product, often a large dose, leading to prolonged toxicity. Monitoring in an intensive care setting is warranted for many symptomatic toddlers following exposure. Asymptomatic children may be medically cleared after 6 h of observation.

Indications for ICU Admission

- Toddlers with CNS depression requiring airway monitoring
- Recurrent seizures
- Hemorrhagic or ischemic cerebrovascular accidents

Criteria for ICU Discharge

- Lack of seizure activity for 6+ hours
- Adequate protection of airway manifested as easy arousal with appropriate verbal communication

Key Points

- Synthetic cannabinoids are more potent and lead to more severe acute toxicity than phytocannabinoids.
- Ingestion of marijuana edibles results in presentation for toxicity more often than inhalation.
- Children are at risk of airway compromise due to cannabinoid ingestion.

Pharmacokinetics

- Inhalation of marijuana [2]
 - Onset: <10 min
 - Peak: 30–90 min
 - Elimination: 4 h
- Ingestion of marijuana edibles [2]
 - Onset: 30 min
 - Peak: 3 h
 - Elimination: 12 h
- Inhalation of synthetic cannabinoids [4–7]
 - Onset: <10 min
 - Peak: 30–90 min
 - Elimination: 4–12 h (active metabolites)

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Part XIV

Chemical Agents: Metals and Related Substances

Matthew D. Sztajnkrycer

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Antimony

Antimony (stibium [Sb]) is a brittle, crystalline, silver-white metalloid naturally present in the Earth’s crust and found at low levels throughout the environment. At least 114 different ores have been identified [1]. Stibnite (SbS_3) is the predominant ore; the others are mostly oxides.

Antimony has been used by human civilization for millennia. Al-kohl, antimony powder used as a cosmetic, is the etymological origin of the word alcohol [1]. The ancient Romans used antimony compounds as emetic drugs (*calices vomitorum*) and expectorants [2]. In the fourteenth century, John of Rupescissa used it as an alternative to bleeding to remove toxins from the body, a use subsequently promoted by Paracelsus. The Danish physician Severin described the effects of ingested antimony as “vomare, cacare, sudare,” reflecting its ability to cause vomiting, diarrhea, and sweating. In the nineteenth century, antimony potassium tartrate (“tartar emetic”) was used in the treatment of schistosomiasis [3].

Two pentavalent antimony-containing drugs, sodium stibogluconate (US trade name Pentostam[®]) (US trade names are given herein as examples; they may be the same, or different, in other countries) and meglumine antimoniate (US trade name Glucantime[®]), have until recently been the mainstays for treatment of visceral, mucosal, and cutaneous leishmaniasis (kala-azar) [4, 5]. Sodium stibogluconate is largely used in English-speaking countries, while meglumine

antimoniate is used in French- and Spanish-speaking countries [6].

Elemental antimony is used in the production of semiconductors, infrared detectors, and diodes [7]. Antimony commonly is alloyed with other metals, such as lead, copper, and silver, to increase their hardness, mechanical strength, and corrosion resistance and to decrease their coefficient of friction. The common forms of antimony found in industry are antimony trioxide, pentoxide, trisulfide, oxysulfide, pentasulfide, and trichloride. Antimony trioxide is used as a fire retardant for plastics, textiles, rubber, building materials, adhesives, pigments, and papers, while antimony trisulfide is used in the manufacture of lead batteries, type metal, paints, ceramics, and glass [8, 9].

Biochemistry and Clinical Pharmacology

Antimony (atomic number 51, atomic weight 121.76) is found in group VA (formerly group 15) of the periodic table of elements, directly below arsenic and above bismuth. Antimony has been described as less toxic than arsenic but more toxic than bismuth [10]. It has four oxidation states: 0, +3, +5, and -3 ; the +3 state is the most common [11]. Pentavalent antimony is more commonly found in aerobic conditions, while trivalent antimony is more commonly found under anaerobic conditions and as a consequence of human activities [7]. The important toxicologic properties of antimony and common antimony-containing compounds are presented in Table 1.

In contrast to the closely related element arsenic, available human data regarding the toxicology of antimony compounds are sparse and are derived mainly from animal studies, occupational exposures, and patients treated with antimony potassium tartrate (Sb(III)), sodium stibogluconate (SB(V)), and meglumine antimoniate (SB(V)). Evaluation of toxicity is further complicated by the fact that antimony is frequently found in association with other potentially toxic materials, including lead and arsenic. The word antimony is derived from the Greek “anti” and “monos,” meaning “not alone.”

Soil antimony concentrations are typically less than 1 ppm, although soil near antimony processing sites or hazardous waste sites on the US Environmental Protection Agency’s National Priorities List may have concentrations as high as 2550 ppm [12]. Airborne concentrations range from 1 to 170 ng/m³ [7]. Antimony can be found dissolved in water at concentrations less than five parts per billion (ppb), typically attached to particles of dirt. The average human daily intake is 5 mcg, reflecting levels of 0.2–1.1 ppb in food sources [13].

Antimony compounds are poorly absorbed (15%) and readily excreted [10]. The absorption of antimony from the respiratory tract depends on particle size and water solubility, with aerosols containing small particles of low water-solubility compounds (e.g., antimony oxides) retained in the lungs for longer periods than larger particles with higher water solubility (e.g., antimony tartrate) [14–16]. After oral ingestion, less than 10% of antimony tartrate and 1% of all other forms of antimony are absorbed [17]. Valence states determine the distribution of antimony in blood and tissues [15, 18]. After inhalation, the trivalent and pentavalent forms concentrate in the erythrocytes and plasma. Antimony has been reported to accumulate in the liver when absorbed in the trivalent form and in the skeleton when given in the pentavalent form, although different distribution patterns were noted by other authors [14–16]. Similar to the distribution pattern after inhalation, the distribution of antimony after gastrointestinal absorption also seems to depend on valence state [19]. Parenterally administered antimonial drugs demonstrate poor skin bioaccumulation, resulting in the need for different treatment regimens for cutaneous leishmaniasis as compared with visceral leishmaniasis [6]. The volume of distribution is greater in trivalent than pentavalent compounds. Studies on patients receiving antimonial therapy for leishmaniasis revealed a volume of distribution of 0.22 ± 0.05 L/kg [20]. Pentavalent antimony is excreted preferentially in urine; the trivalent forms are excreted in the feces [21, 22].

Pentavalent compounds are considered less toxic than trivalent compounds, acting as prodrugs

Table 1 Properties of antimony and common antimony compounds^a

Property	Antimony	Antimony pentasulfide	Antimony pentoxide	Antimony potassium tartrate
Atomic/molecular weight	121.75	403.80	323.5 (anhydrous)	333.93
Color	Silvery white	Yellow	Yellow	Colorless
Physical state	Solid	Solid	Solid	Solid
Valance state	0	+5	+5	+3
Melting point	630.5 °C	75 °C decomposes	380 °C decomposes ^f	100 °C (−1/2H ₂ O)
Boiling point	1750; 1325 ^b ; 1635 ^d	No data	No data	No data
Density (g/cm ³)	6684 (25 °C); 6688 (20 °C) ^b	4.12	3.78	2.6
Odor	No data	Odorless ^d	No data	Odorless ^c
Odor threshold				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Taste	No data	No data	No data	Sweetish, metallic ^d
Taste threshold	No data	No data	No data	No data
Solubility				
Water	Insoluble	Insoluble	Very slightly soluble	83 g/L (cold)
Organic solvents	No data	Insoluble in alcohol	No data	Insoluble in alcohol
				Soluble in glycerine
Partition coefficients				
Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure, mm Hg	1 (886 °C) ^c	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flash point	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors, ppm to mg/m ³	None ^g	None ^g	None ^g	None ^g
Explosive limits	No data	No data	No data	No data

From ATSDR: Toxicological Profile for Antimony. Report TP-92/14. Atlanta, GA, US Public Health Service, Agency for Toxic Substances and Disease Registry, 1992

^aAll information obtained from Weast, 1988, except where noted

^bHerbst et al. [9]

^cFreedman et al. [127]

^dWindholz [97]

^eHSDB ([128], 1991)

^fSAX [129]

^gBecause these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m³

that require biological reduction to the active trivalent form [23]. The site and mechanism of reduction of Sb(V) within the amastigote remain controversial [23]. Particularly, in acidic environments, both glutathione and trypanothione can reduce Sb(V) to Sb

(III) nonenzymatically [24, 25]. The presence of an intracellular antimony reductase has also been proposed [26]. In humans, the reduction of antimony appears to occur at low levels, with only 5–10% Sb (V) converted to Sb(III) [27].

A two-compartment pharmacokinetic model has been proposed to describe the fate of antimony after being administered intramuscularly in the pentavalent form, consisting of a fast phase and a slow phase with elimination half-lives of 2.02 ± 0.25 h and 76 ± 28 h, respectively [20]. The slow terminal elimination phase was hypothesized to be due to conversion of Sb(V) to Sb(III). In rhesus monkeys, the terminal elimination phase half-life during a 21-day course of meglumine antimoniate therapy was found to be 35.8 days [28]. Posttreatment, antimony is localized within the liver, thyroid, and nails. In contrast to arsenic, methylation of antimony is limited, suggesting that Sb(III) is less effectively detoxified than As(III) [27]. Within the rat, Sb(III) is conjugated with glutathione and excreted in the bile [29]. The antimony-glutathione bond was noted to be unstable, with potential for enterohepatic reabsorption of Sb(III). More than 80% of intravenously administered stibogluconate was excreted in the urine within 6–8 h [30]. The half-life of antimony in urine is approximately 95 h [31].

Pathophysiology of Toxic Effects

Being chemically, physically, and physiologically similar to arsenic, antimony toxicity is similar to arsenic toxicity [32]. As with other metals, antimony interacts with sulfhydryl groups of enzymes and other proteins. In vitro, antimony inhibits succinic oxidase, pyruvate oxidase, and phosphofructokinase, suggesting interference with cellular respiration [2, 33]. In guinea pigs, trivalent antimony is able to prolong the action potential of ventricular myocytes by increasing calcium currents, possibly through interactions with calcium channel cysteine residues in a mechanism analogous to arsenic trioxide [34, 35]. Anti-leishmanial effects are attributed to depletion of intracellular ATP due to interference with glycolysis and beta-oxidation of fatty acids in amastigotes [36]. The generation of reactive oxygen species has also been postulated to play a role in antimony toxicity [37]. Antimony-associated apoptosis is attributed to depletion of glutathione capacity and subsequent enhancement of reactive oxygen species formation [38, 39].

Clinical Presentation and Life-Threatening Complications

Antimony poisoning may occur in the industrial and occupational setting, primarily with exposures to trivalent forms (antimony trioxide, trisulfide, and trichloride) and in patients treated with pentavalent antimony compounds for leishmaniasis. Numerous organ systems are involved in antimony toxicity and may vary with the route of exposure (inhalation vs. ingestion vs. parenteral administration).

Antimony is historically known for its emetic properties after oral ingestion [40]. Acute ingestion of antimony salts primarily affects the gastrointestinal tract. Toxicity manifests as nausea, vomiting, watery diarrhea, abdominal pain, melena, and hematemesis and may lead to volume depletion and hypovolemic shock [41]. One or two grains of tartar emetic were sufficient to cause death in a child and adult, respectively [44]. Seventy people became ill after ingesting lemonade contaminated with antimony trioxide [42]. Patients presented with abdominal pain, nausea, and vomiting; the majority recovered within 3 h of ingestion.

Chronic oral exposure to trivalent and pentavalent antimony compounds is speculated to result in cardiovascular and gastrointestinal toxicity. A causal relationship to antimony could not be definitively established due to the presence of other agents [43, 44]. Cardiovascular effects include elevated blood pressure and electrocardiogram abnormalities, including T wave changes with prominent U waves and QT interval prolongation [44]. Stokes-Adams syndrome, responsive to atropine, has been described with acute and long-term administration (orally or intravenously) of antimony potassium tartrate [3]. Chronic antimony exposure in itself does not appear to be associated with increased risk of ischemic heart disease [7].

Inhalational antimony exposure is irritating to the mucous membranes. It is associated with pharyngitis, conjunctivitis, rhinitis, and epistaxis. Although nasal septal perforation was observed among smelter workers, this finding was attributed to concomitant arsenic exposure [1].

Studies of pulmonary antimony toxicity have been plagued by the presence of confounding



Fig. 1 Antimony Dermatitis

exposures, including arsenic oxide, iron oxide, hydrogen sulfide, and particulates [1, 45, 46]. Chronic occupational exposure to airborne antimony is associated with development of pneumoconiosis [47]. Radiographic studies performed on smelter workers demonstrated a 15.7% prevalence of pneumoconiosis, with associated decreased FEV and FVC [48]. Elevated antimony concentrations were found in the lungs of smelter workers 20 years after retirement. These concentrations seemed to increase with duration of exposure [49]. Other respiratory findings include chronic bronchitis, chronic emphysema, pleural adhesions, and respiratory irritation (including coughing, wheezing, and upper airway inflammation) [7, 46].

Antimony dermatitis is a pustular eruption of the trunk and limbs near sweat and sebaceous glands [50, 51] (Fig. 1). It is more commonly noted in workers exposed to high temperatures or in hot weather. The dermatitis improves within 2 weeks after transfer to a cooler environment.

Commonly reported adverse effects associated with sodium stibogluconate and meglumine antimoniate treatments are musculoskeletal pain, nausea, vomiting, diarrhea, abdominal pain, headache, anorexia, fatigue, fever, erythema, and urticaria [52]. A high incidence of severe cutaneous reactions in patients treated with meglumine

antimoniate 20 mg/kg/day was subsequently determined to be due to high concentrations of other heavy metals in the particular drug lot, including trivalent antimony, lead, cadmium, and arsenic [53]. However, all skin reactions noted in this cohort occurred in historical controls, albeit at a lesser frequency.

The most concerning toxicity associated with pentavalent antimonial therapy is cardiotoxicity, which may occur at the recommended dose of 20 mg/kg/day [4]. Studies in India and Africa have reported frequent adverse cardiac events in patients using pentavalent antimonials, including ventricular tachycardia, torsade de pointes, and sudden cardiac death [54]. Electrocardiographic manifestations of parenteral antimony cardiotoxicity include ventricular premature contractions, first-degree atrioventricular block, T wave and ST-T changes, and prolonged QTc interval [4, 55–57]. These changes are reversible with cessation of treatment. In one cluster of cardiotoxicity and death, QTc prolongation was followed by ventricular ectopy and then malignant ventricular dysrhythmias, including torsade de pointes and ventricular fibrillation [58]. The cluster was attributed to incorrect formulation, with resultant unexpected increase in osmolarity. Another cluster of cardiotoxicity occurred after introduction of a new generic formulation of sodium stibogluconate [59]. Eight of 23 patients treated with the new generic product died, with five deaths secondary to drug cardiotoxicity.

A retrospective analysis of returned travelers with New World cutaneous or mucosal leishmaniasis who received intravenous sodium stibogluconate (pentavalent) for more than 21 days demonstrated progressive QTc prolongation from 389 ± 3.1 to 404 ± 2.9 msec [60]. During the third week of treatment, 10% of patients reached the threshold for potential cardiac toxicity, defined as a QTc prolonged >50 msec above baseline or an absolute value >450 msec. An 81-year-old male with hypertension, cardiomegaly, and a baseline QTc of 429 msec developed short runs of ventricular tachycardia on day 9. This patient, on a thiazide diuretic concurrently with sodium stibogluconate therapy, had a serum potassium of 2.7 mmol/L and a QTc of

567 msec. In contrast, cardiotoxicity was not observed among 96 US military personnel with cutaneous leishmaniasis treated with Pentostam® (sodium stibogluconate) [61]. These differences have been attributed to the greater systemic morbidity of visceral versus cutaneous leishmaniasis, different drug formulations, and different cardiovascular risk profiles of studied populations. Another study noted the development of arrhythmia in a patient without any apparent comorbidity, requiring cessation of treatment.

Hepatobiliary, hematologic, and renal toxicity have been noted with pentavalent antimonial therapy. In one study, increases in serum AST or ALT above the upper limit of normal were noted in 85% of patients, and increases greater than three times the upper limit of normal were noted in 33% [60]. Peak transaminase levels occurred on day 12. No patients developed clinical signs of hepatitis, including right upper quadrant tenderness, hepatic enlargement, or jaundice. Elevated amylase, with and without evidence of clinical pancreatitis, has been observed [60, 62–64]. Sixteen of 17 patients treated with sodium stibogluconate manifested elevated amylase and lipase; 12 patients developed clinical symptoms consistent with pancreatitis [62]. Elevated amylase without clinical pancreatitis was noted in 67% of patients, with an increase greater than three times the upper limit of normal occurring in 19% of patients [60]. Although amylase elevations are typically asymptomatic, deaths due to acute pancreatitis have been reported [63].

Diverse hematologic abnormalities have been observed. Acute anemia due to erythroid precursor bone marrow toxicity was noted in a 6-year-old male treated with sodium stibogluconate for visceral leishmaniasis [65]. Over the course of treatment, the hemoglobin decreased from 7.2 to 3.5 g/dL. Within 4 days of treatment cessation, the patient's hemoglobin had increased to 5 g/dL with a corrected reticulocyte count of 10%. Parenteral sodium stibogluconate administration was associated with significant decreases in lymphocyte and platelet counts [66, 67]. Mean decrease in platelet count by day 4 was 31,000 [66]. Antimony trioxide nanoparticles demonstrated *in vitro* toxicity to hematopoietic progenitor cells,

specifically impairing the proliferation of erythroid progenitors [68]. No effect was noted on erythroid differentiation or on granulocyte-monocyte precursors.

Acute renal tubular acidosis and acute tubular necrosis have rarely been reported [52, 69, 70]. Other observed laboratory abnormalities include elevated creatine phosphokinase and alkaline phosphatase [71]. A 19-year-old male who intentionally ingested 500 mg of tartar emetic as therapy for alcohol dependence developed hyperkalemia (6.1 mEq/L) without ECG changes [72]. All abnormalities were transient and returned to normal after completion of treatment.

In summary, analogous to arsenic, antimony effects diverse organ systems, resulting in cardiovascular, pulmonary, gastrointestinal, dermatologic, renal, and hepatobiliary toxicity. Cardiac dysrhythmias and sudden cardiac death, related to progressive QTc prolongation, remain the greatest concern in the evaluation and management of antimony toxicity.

Diagnosis

Antimony toxicity should be considered in patients presenting with gastrointestinal or pulmonary symptoms or electrocardiogram changes, who are being treated for leishmaniasis or work with antimony compounds. Consider the concomitant presence of other heavy metals. The diagnosis of antimony poisoning is made by measuring antimony concentrations via atomic absorption spectroscopy in blood, urine, or both [73]. The normal serum antimony concentration is 3 mcg/L, while the normal 24-h collection urine concentration is 0.8 mcg/L [74]. In 2009, the US Centers for Disease Control and Prevention (CDC) investigated a possible outbreak of antimony toxicity among Florida firefighters, presumed due to the fire retardant in the outer protective clothing [75, 76]. The index case complained of neurological symptoms and was noted to have elevated antimony on hair sample analysis. Extensive evaluation revealed no evidence of elevated urinary antimony levels in firefighters wearing antimony-containing fabrics. The CDC specifically

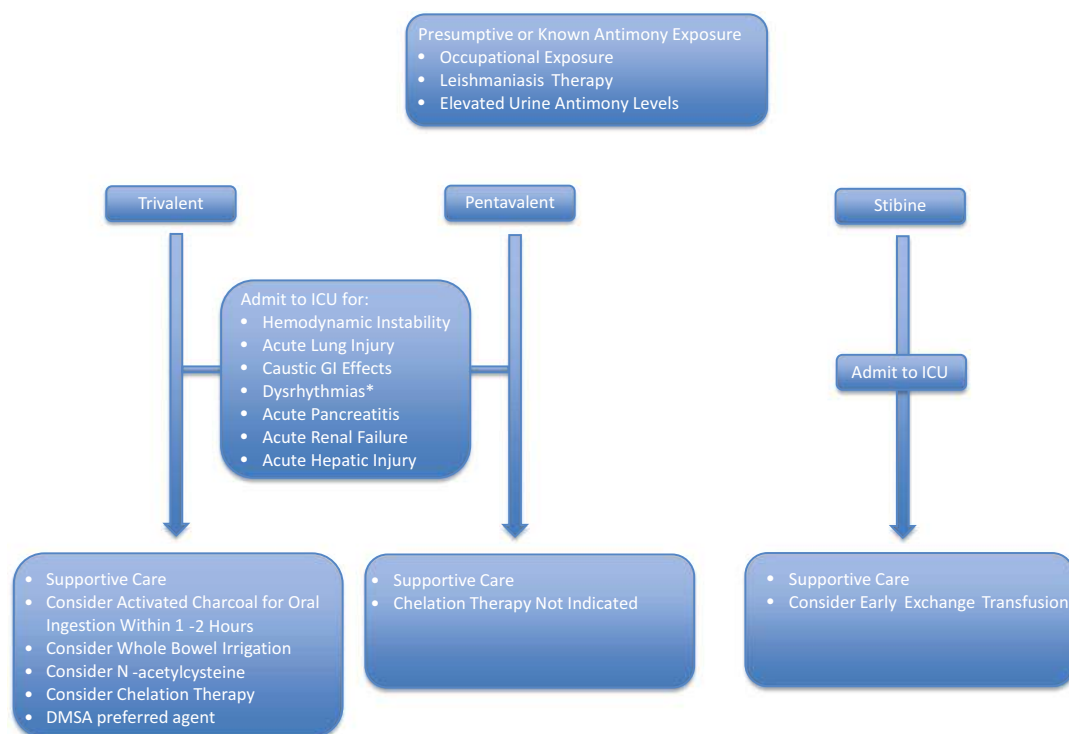


Fig. 2 Treatment Algorithm for Presumptive or Known Antimony Toxicity

cautioned about the use of non-validated methods, including hair testing, to determine antimony toxicity.

Treatment

After antimony ingestion, the majority of patients will develop emesis. The ability of activated charcoal to reduce antimony absorption from the gastrointestinal tract in acute antimony poisoning has not been studied (see Fig. 2). Theoretically, activated charcoal may be efficacious in reducing absorption if it is administered within the first 1–2 h after oral ingestion (Level III) [77]. However, there are no data indicating that administration of activated charcoal changes patient outcome. Whole-bowel irrigation may have a role in management, analogous to arsenic poisoning (Level III) [78]. Aggressive intravenous administration of crystalloids with appropriate cardiovascular

monitoring may be necessary to replace volume loss. Vasopressors and/or inotropes may be necessary to treat shock not responsive to fluid volume replacement. The treatment of shock is discussed in detail elsewhere (► Chap. 14, “The Assessment and Management of Hypotension and Shock in the Poisoned Patient”). Because QTc prolongation may lead to the development of torsade de pointes, continuous cardiac monitoring should be implemented if there are electrocardiogram changes or other significant manifestations of antimony poisoning. The treatment of this dysrhythmia is outlined in ► Chap. 22, “Toxicant-Induced Torsade de Pointes.” In one case report, N-acetylcysteine was used as a glutathione precursor to facilitate the conjugation and enterohepatic excretion of antimony [79].

Box 1: Indications for ICU Admissions: Antimony

1. Symptomatic patients after acute oral exposure (Level III)

2. Evidence of severe toxicity with hemodynamic or respiratory compromise (Level III)
3. Evidence of ECG abnormalities (including QT prolongation*) or dysrhythmias (Level III)
4. Evidence of acute kidney injury, pancreatitis, or hepatic injury (Level III)
5. Known or presumptive stibine exposure (Level III)

*Otherwise stable patients with isolated QT prolongation may alternatively be admitted to a telemetry bed.

In an attempt to enhance antimony elimination, the use of chelating agents has been proposed. Dimercaprol (British anti-lewisite [BAL]) was reported to decrease the toxicity of antimony potassium tartrate in rabbits and to be effective in ameliorating the toxicity and adverse reactions during treatment with other trivalent antimonial drugs [80, 81]. Administration of dimercaprol 30 mg/kg IM 1-h postexposure followed by 15 mg/kg at 6, 24, and 48 h increased the LD50 of intramuscular antimony from 90 to 160 mg/kg [80]. In another study, dimercaprol 10–15 mg/kg administered 4 times at 4-h intervals resulted in a 50% reduction in mortality [81]. 2,3-Dimercaptosuccinic acid (DMSA, succimer) and 2,3-dimercaptopropane-1-sulfonate (DMPS), two derivatives of dimercaprol, have been shown to decrease mortality in mice given antimony tartrate in a dose twice the median lethal dose. Intraperitoneal DMSA administered 20 min after administration of antimony potassium tartrate 120 mg/kg resulted in the survival of 28 of 30 mice [82]. Nineteen of 30 mice receiving intraperitoneal DMPS survived; D-penicillamine was less effective than DMPS, while dimercaprol did not decrease mortality in this model.

Human chelation studies are limited. In four patients who were accidentally overdosed with antimony tartrate, intramuscular dimercaprol 200–600 mg per day did not seem to change the course of their toxicity [40]. DMSA administration 72-h postexposure did not increase antimony excretion in a patient who accidentally received an overdose with sodium stibogluconate [83]. However, the authors noted that most of

the antimony was eliminated in the first few hours. A 34-year-old male presented to the emergency department with abdominal pain and vomiting after ingesting tartar emetic [79]. Due to ongoing emesis, the patient was initially treated with intramuscular dimercaprol. This was discontinued after the third dose due to chest pain, tachycardia, hypertension, and nonspecific ECG changes. The patient was subsequently switched to DMSA, but this too was discontinued due to the development of transaminitis, subsequently attributed to the antimony.

In the absence of more robust data, DMSA (10 mg/kg orally every 8 h for 5 days followed by 10 mg/kg every 12 h for 14 days) may be considered in the management of trivalent antimony compound poisoning (Level III evidence). DMSA should be administered as early as possible after toxic exposure. Dimercaprol may be considered in patients with intractable emesis unable to tolerate oral DMSA. In the absence of specific dosing data, dimercaprol may be administered at doses used for arsenic poisoning (3 mg/kg every 4 h for 48 h, followed by twice daily for 7–10 days; alternate regimen 5 mg/kg every 4–6 h for 24 h, with a tapering dose and duration based upon patient symptomatology). Based upon animal data, penicillamine (250 mg in adults and 20–30 mg/kg in children four times a day) may also serve as an alternative to DMSA, although DMSA is considered the most effective chelating agent (Level III evidence) [82]. The current available data do not support chelation for pentavalent antimony toxicity. The duration of therapy should be guided by the clinical response.

Box 2: Criteria for ICU Discharge

The patient may be discharged from the ICU when acute symptomatology, evidence of end-organ or hemodynamic compromise, and ECG abnormalities resolve (Level III recommendation).

Stibine

Stibine (SbH_3 , hydrogen antimonide, antimony hydride) is a colorless gas formed when antimony

alloys are treated with acids and subjected to electrolytic action, such as during the charging of certain lead-containing batteries. In 1990, stibine was implicated as the cause of sudden infant death syndrome (SIDS), due to the purported actions of the fungus *Scopulariopsis brevicaulis* on fire retardant PVC cot mattress covers [83]. In vitro studies demonstrated the generation of stibine, phosphine, and hydrides of antimony oxides, which were speculated to cause antimony toxicity and subsequent sudden infant death. Further study demonstrated that antimony volatilization did not occur unless cot mattress PVC was heated to 80–100 °C and that antimony trioxide in cot mattress PVC was not bioavailable [84]. Subsequently, urine antimony concentrations in SIDS infants were found to be similar to control and healthy infants, refuting this theory [85]. Detection of antimony in hair of healthy babies further suggested no link between antimony and SIDS [41].

Clinical Presentation and Life-Threatening Effects

In animals, stibine was shown to be lethal and to cause pulmonary edema and hemolysis in a dose-dependent manner, analogous to arsine gas [86]. Several cases of poisoning from a mixture of gases including stibine (others being arsine and hydrogen sulfide) have been reported [87]. The hallmark of arsine poisoning is intravascular hemolysis secondary to binding of arsine with oxidized hemoglobin. In a case report of acute arsine poisoning, antimony was detected in the urine of one patient, suggesting the co-formation of stibine through the same mechanism as arsine formation [87]. Although studies of pesticide workers exposed to phosphine demonstrated decreased RBC and pseudocholinesterase activity, suggesting a possible mechanism for stibine toxicity [88], subsequent studies found this to be incorrect [89].

Clinical features of stibine toxicity include headache, nausea, weakness, abdominal and back pain, and severe hemolysis.

Treatment

The treatment for acute stibine poisoning is supportive (See Fig. 2). Fluid hydration and maintenance of urine output are important to prevent renal injury secondary to hemolysis. Erythrocyte transfusions may be required if the hemolytic anemia is severe or if the patient has compromised cardiopulmonary function. In the case of arsine, early exchange transfusion has been recommended in patients with evidence of severe toxicity due to the difficulty in detecting acute hemolysis (Level III recommendation) [90]. It is unknown whether chelating agents have any role in the management of stibine poisoning.

Box 3: Key Points for Antimony Poisoning

1. Antimony toxicity is analogous to that of arsenic.
2. Acute ingestion is associated with GI toxicity, including hematemesis and shock.
3. Chronic inhalational exposure is associated with pneumoconiosis.
4. The most concerning toxicity associated with pentavalent antimonial therapy is cardiotoxicity.
5. Stibine is associated with acute lung injury and hemolysis.
6. Antimony toxicity should be considered in patients presenting with gastrointestinal or pulmonary symptoms or electrocardiogram changes, who are being treated for leishmaniasis or work with antimony compounds.
7. Antimony toxicity should not be diagnosed based upon non-validated techniques, including hair analysis.
8. In the absence of more robust data, DMSA may be considered in the management of trivalent antimony compound poisoning (Level III).
9. Penicillamine is an alternative to DMSA, although DMSA is considered the most effective agent (Level III).
10. Current data do not support chelation for pentavalent antimony toxicity (Level III).
11. Early exchange transfusion may be considered for acute stibine exposure (Level III).

Nickel

Nickel is the fifth most common metal in the Earth's crust and is distributed widely in soils and sediment. It is used in many different industries, including mining, petroleum, electroplating, and ceramics and is used as yellow pigment in paint. Two general types of nickel ore exist: magmatic sulfide ores, which are mined underground, and lateritic hydrous nickel silicates or garnierites, which are surface mined [91, 92]. Nickel carbonyl is a volatile liquid nickel compound formed from the reaction of carbon monoxide and nickel compounds. It is often described as having a sooty or musty odor.

Biochemistry and Clinical Pharmacology

Nickel's physical properties allow for its broad use in industry. Pure nickel is a hard, silvery-white metal that is combined with other metals to form alloys. It is a hard, yet malleable, metal that is relatively resistant to corrosion. Nickel and its compounds have no characteristic odor or taste. The most familiar nickel ferrous alloys are stainless steel and coinage metal. Nickel may be found in the metallic, inorganic, and organic forms. Although nickel can exist in oxidation states -1 , 0 , $+2$, $+3$, and $+4$, its only medically important oxidation state is $+2$.

Nickel has typical metallic properties. It also is ferromagnetic and a good conductor of heat and electricity. Nickel is positioned after hydrogen in the electrochemical series and slowly displaces hydrogen ions from dilute hydrochloric and sulfuric acids. It reacts more rapidly with nitric acid. Nickel is highly resistant to attack by strong alkali [93]. Nickel ($+2$) forms an extensive series of compounds and is the only important oxidation state in aqueous systems. Other oxidation states occur in special complexes and oxides. In alkaline solutions, nickel ($+2$) hydroxide can be oxidized to a hydrated nickel ($+4$) oxide, a reaction used in the Edison storage battery.

In aqueous solutions, nickel occurs as the octahedral hexahydrate ion $[\text{Ni}(\text{H}_2\text{O})_6]$, which is poorly absorbed by most living organisms [94, 95]. Nickel subsulfide is formed during the roasting and smelting of nickel ore and may be shipped as the matte for further processing, but it does not have any other significant commercial uses [96]. Data on the chemical properties of nickel and some important nickel compounds are presented in Table 2.

Nickel may be absorbed via inhalation or ingestion. Absorption by the respiratory route with secondary gastrointestinal absorption (insoluble and soluble) is the major pathway of exposure during occupational exposures. Similar to many inhaled particles, significant quantities may be swallowed after mucociliary clearance from the respiratory tract. The soluble nickel ion (Ni^{2+}) may be absorbed through the gastrointestinal tract, while less soluble compounds may be phagocytized in the lung. Percutaneous absorption is negligible for most nickel compounds, but for some forms, such as nickel chloride and nickel sulfate, 77% of an applied dose may be absorbed [96].

Due to high volatility and high lipid solubility, the organonickel compounds, such as nickel carbonyl, have the greatest propensity for absorption. It has been reported that 35% of inhaled nickel is absorbed into the blood [97–99]. Ingestion of nickel results in absorption of variable amounts. Bioavailability of nickel is altered by the presence of food in the gastrointestinal tract [97]. When nickel sulfate is given with water, 27% is absorbed, whereas only 0.75% is absorbed with food. After absorption, nickel enters the vascular compartment, where it is bound principally to albumin (34%) and nickeloplasmin (26%), with none as an unbound ultrafiltrable fraction [100]. Nickel carbonyl is distributed into the central nervous system to a greater extent than its other forms.

Metallic nickel is not metabolized. Nickel carbonyl is oxidized to nickel and carbon monoxide [100]. However, in a study of five subjects with nickel carbonyl poisoning, none developed elevated carboxyhemoglobin levels [101]. This finding was confirmed in a series of 25 cases [102, 103]. Biomonitoring after nickel carbonyl

Table 2 Physical and chemical properties of nickel and selected compounds^a

Property	Nickel	Nickel oxide	Nickel sulfate	Nickel chloride
Molecular weight	58.69	74.69	154.75	129.60
Color	Silvery	Green or black	Greenish yellow	Golden yellow
Physical state	Solid	Solid	Solid	Solid
Melting point	1455 °C	1995 °C	840 °C	1001 °C
Boiling point	2730 °C	No data	Decomposes at 840 °C	Sublimes at 973 °C
Density	8.91 g/cm ³	6.72 g/cm ³	4.01 g/cm ³	3.55 g/cm ³
Odor	Odorless	No data	Odorless	None
Odor threshold				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility				
Water	1.13 mg/L at 37 °C ^b	1.1 mg/L at 20 °C	293 g/L at 0 °C	642 g/L at 20 °C
Organic solvent(s)	No data	No data	Insoluble in ether and acetone; 0.2 g/L at 35 °C in ethanol; 0.9 g/L at 35 °C in methanol	Soluble in ethanol; 180 g/L at 20 °C in ethylene glycol
Partition coefficients				
Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
Vapor pressure	1-mm Hg at 1810 °C	No data	No data	1-mm Hg at 671 °C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	Nonflammable	Nonflammable
Flash point	No data	No data	Nonflammable	Nonflammable
Flammability limits	No data	No data	Nonflammable	Nonflammable
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

From ATSDR: Toxicological Profile for Nickel. Report TP-92/14. Atlanta, GA, US Public Health Service, Agency for Toxic Substances and Disease Registry, 2005.

^aAll information obtained from HSDB 1996 except where noted

^bIshimatsu et al. [130]

exposure should focus on the detection of nickel in blood or urine samples [104]. In a rat model, 35% of nickel carbonyl was eliminated via the kidney [101]. Parenteral nickel is eliminated almost exclusively in the urine, where it is cleared rapidly from the body [105]. Nonabsorbed nickel (approximately 90%) is eliminated in the feces [104].

Pathophysiology of Toxic Effects

Nickel's toxicity may be related to its interference with physiologic processes involving other metal cations, such as manganese, zinc, calcium, and magnesium. The pathophysiology of nickel carbonyl-induced acute lung injury is complex. Nickel ions generate reactive oxygen species, including

superoxide anion radicals [106]. Animal studies suggest a complex pathway leading to acute lung injury, including generation of reactive oxidative species, subsequent lipid peroxidation generating malondialdehyde, which in turn causes DNA damage [107]. Altered expression of cell cycle proteins Chk1 and Cdc2 was also noted, suggesting a mechanism of cell cycle arrest and apoptosis.

Clinical Presentation and Life-Threatening Complications

For the most part, nickel exposure is self-limited and benign. Allergic contact dermatitis to nickel is common, estimated to affect 10% of the human population [108]. More significant allergic reactions, including reactive airway disease, have been reported [109, 110].

Inhalation of nickel alloys or dust is associated with upper airway and pulmonary irritation, reactive airway disease, pneumoconiosis, and pulmonary fibrosis. Analogous to metal fume fever, acute lung injury in a welder has been reported after exposure to nickel fumes [111, 112]. Ingestion is associated with systemic toxicity, particularly involving the central nervous system. Exposure to nickel was associated with generalized tonic-clonic seizures and nonconvulsant focal status epilepticus in two patients working in the same shop [113].

Nephrotoxic effects, such as renal edema with hyperemia and parenchymatous degeneration, have been reported in 32 cases of electroplaters who accidentally drank water contaminated with nickel sulfate and nickel chloride [114]. The workers developed nonspecific signs and symptoms (e.g., nausea, vomiting, abdominal discomfort, diarrhea, giddiness, lassitude, headache, cough, shortness of breath) that were transient in most but persisted 1–2 days in seven cases. Ten workers with initial urine nickel concentrations greater than 0.8 mg/g of creatinine were hospitalized and treated with intravenous fluids. This treatment resulted in a mean elimination half-life for serum nickel of 27 ± 7 h, which was significantly shorter than the mean half-life of 60 ± 11 h in 11 subjects who did not receive intravenous

fluids. All subjects recovered rapidly, without evident sequelae, and returned to work by the 8th day after exposure.

Box 4: Indications for ICU Admission: Nickel

1. Known or suspected exposure to nickel carbonyl, even if asymptomatic (Level III)
2. Evidence of hemodynamic instability or respiratory compromise (Level III)
3. Significant inhalational exposure of nickel fumes (Level III)
4. New-onset seizures after nickel exposure (Level III)
5. 8-h urinary nickel concentration greater than 50 mcg/dL (Level III)

Few nickel exposures result in a critical care admission. The exception is nickel carbonyl, which may cause multisystem toxicity, particularly involving the pulmonary system, within hours after significant inhalational exposure [115–117]. The severity of toxicity of nickel carbonyl has been compared with hydrogen cyanide [117]. In one study, 40% of patients developed symptoms within 1 h of exposure, while 20% did not manifest symptoms for up to 1 week from exposure [118]. Acute lung injury is typically delayed, occurring after a prodrome of flu-like symptoms, but may occur immediately after exposure. Radiographic pneumonitis may persist for 4 weeks [103]. Transient pulmonary infiltrates and eosinophilia (Löffler's syndrome) have been reported after low-dose inhalational exposure to nickel carbonyl [94]. Cardiac manifestations of nickel carbonyl exposure may include myocarditis and electrocardiographic abnormalities, including QT prolongation and heart block [118]. Deaths are frequently due to acute lung injury or cerebral edema [103, 114, 115]. In survivors, a prolonged neurasthenic syndrome has been reported, lasting several months in some cases [118].

Treatment

The most important intervention after nickel exposure is the interruption of any potential ongoing absorption (see Fig. 3). Removal from

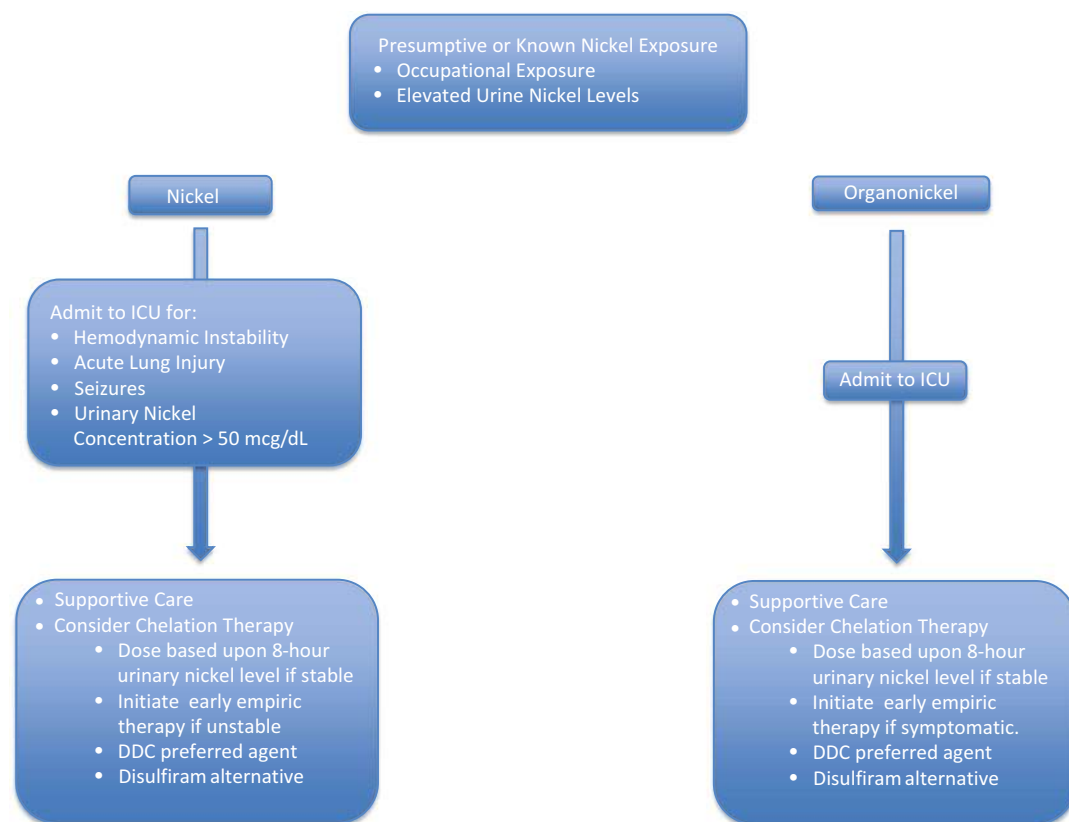


Fig. 3 Treatment Algorithm for Presumptive or Known Nickel Toxicity

exposure and decontamination is of primary importance. With nickel or nickel carbonyl poisoning, it is important to remove any contaminated clothing. In a descriptive study of seven patients presenting 72 h after nickel carbonyl exposure, four patients were admitted to the ICU; all three patients requiring endotracheal intubation died [119]. Surviving patients were asymptomatic on follow-up 6 months later.

Box 5: Criteria for ICU Discharge

1. The patient may be discharged from the ICU when asymptomatic for 24 h or when all evidence of toxicity has resolved and urinary nickel levels are less than 10 mcg/dL (Level III).

Few specific therapeutic measures are available. Most traditional chelating agents are not of

value. Sodium diethyldithiocarbamate (DDC) and disulfiram (US trade name Antabuse) appear effective as nickel chelators, with DDC being the preferred agent (Level III evidence). In a rat model, DDC given parenterally at a dose of 50–100 mg/kg immediately after nickel carbonyl administration resulted in reduction of mortality from 73% to 8% [120]. In another animal study, mice were given 50–100 mg/kg of DDC, which was protective when given 8 h after exposure. The efficacy declined at 24 h. The 100-mg/kg dose was more efficacious than a lower dose [121].

Disulfiram (bis (dimethylthiocarbamoyl) disulfide) is metabolized to two molecules of DDC. Given at a dose of 1000 mg/kg to rats, disulfiram offered complete protection against nickel carbonyl-induced toxicity when administered after exposure; however, 500 mg/kg offered no protection [122]. Doses greater than 1500 mg/kg

Table 3 Diethyldithiocarbamate (DDC) and disulfiram dosing regimens for acute nickel carbonyl poisoning (Level III)

Urinary nickel concentration	Anticipated clinical severity	Chelating agent	Suggested dosing regimen
<10 mcg/dL	Mild	None	Treat as moderate if severe symptoms develop
10–50 mcg/dL	Moderate	DDC	Day 1: 35–45 mg/kg orally in divided doses to decrease nausea. Day 2 and beyond. ¹ Give 400 mg every 8 h until symptom free and urinary nickel concentration <10 mcg/dL
>50 mcg/dL	Severe	DDC	Initial dose 25 mg/kg IV. ² Severe cases may require 100 mg/kg in the first 24 h. Additional dosing based upon clinical severity
Unknown level	Concern for moderate to severe exposure	DDC	Administer 2 mg orally in divided doses. Additional dosing based upon clinical severity and urinary levels
DDC unavailable	Evidence of toxicity	Disulfiram	750 mg orally every 8 h for 24 h, then 250 mg every 8 h until symptom free

Refs. [118, 119, 125, 126]

1. Suggested dosage schedule for an approximately 70-kg patient is:

- (a) Dose 1: 1000 mg (5×200 -mg capsules) in first hour
- (b) Dose 2: 800 mg (4×200 -mg capsules) from hour 1 to 4
- (c) Dose 3: 600 mg (3×200 -mg capsules) from hour 4 to 8
- (d) Dose 4: 400 mg (2×200 -mg capsules) from hour 8 to 16

2. DDC solution can be prepared by adding 10 mL of sterile solution of phosphate buffer (500 mg per NaH_2PO_4 per 100 mL) to 1-g powdered sterile DDC

seemed to enhance mortality. In one case report, disulfiram was administered after inhalational exposure to nickel carbonyl for the first 2 days until sodium DDC was obtained. The patient gradually improved over 10 days [117]. Because of the use of DDC, the efficacy of disulfiram could not be determined.

There are no adequately controlled clinical studies of the use of disulfiram or DDC in acute nickel carbonyl poisoning. Disulfiram or DDC may be considered as a possible therapeutic intervention in seriously ill patients (Table 3). DDC treatment guidelines are listed in Table 3 (Level III) [116, 123]. If DDC is unavailable, disulfiram may be used as an alternative (Level III) [124–126]. Current dosing strategies are based upon an 8-h urinary nickel level collected immediately after exposure [125]. Animal studies suggest that treatment is most effective when administered as soon as possible after exposure, leading to the recommendation that treatment should not be delayed while awaiting diagnostic data [120]. In reconciling these conflicting approaches, it would appear reasonable to delay treatment pending urinary nickel study results in

mildly and moderately symptomatic patients and initiate treatment immediately in severely symptomatic or critically ill patients (Level III recommendation). Nausea is common with DDC therapy and should be managed expectantly. Patients receiving treatment with DDC or disulfiram should be advised to avoid ethanol for at least 1 week after treatment. Although nickel carbonyl may be oxidized to carbon monoxide, no evidence of carbon monoxide poisoning has been noted [101–103]. The utility of routine carbon monoxide screening in nickel carbonyl poisoning remains unclear (Level III).

Box 6: Key Points in Nickel Exposure

1. For the most part, nickel exposure is self-limited and benign.
2. Exposure to nickel fumes may cause acute lung injury analogous to metal fume fever.
3. Nickel carbonyl exposure is associated with delayed pulmonary edema.
4. Sodium diethyldithiocarbamate (DDC) and disulfiram appear effective as nickel chelators, with DDC being the preferred agent (Level III).

5. Chelation therapy should not be delayed in symptomatic patients with suspected nickel carbonyl exposure (Level III).
6. Patients receiving treatment with DDC or disulfiram should be advised to avoid ethanol for at least 1 week after treatment (Level III).
7. Although nickel carbonyl may be oxidized to carbon monoxide, no evidence of carbon monoxide poisoning has been observed (Level III).

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Arsenic has captured the attention of the medical community for more than two millennia as a cause of disease and as a cure. Hippocrates and other ancient Greek physicians described the use of arsenic sulfides such as realgar (As_2S_2) or orpiment (As_2S_3) as a topical treatment for ulcers. During the first millennium AD, the roasting of realgar led to the discovery of the so-called white arsenic, or arsenic trioxide. Odorless, tasteless, and soluble in solution, it became a tool of deliberate poisoning and gained particular notoriety as a homicidal agent in Europe in the fifteenth through seventeenth centuries. In the late eighteenth century, Fowler [1] described the medical use of a 1% solution of potassium arsenite as an oral treatment for fever and chorea. Known as *liquor arsenicalis* or *Fowler's solution*, it was used extensively until the mid-twentieth century as a remedy for asthma and psoriasis. In the nineteenth century, arsenic compounds were used widely in commerce as pigments (e.g., copper arsenite or “Scheele’s green”). Several arsenic compounds were used through most of the twentieth century as pesticides (e.g., lead arsenate, calcium arsenate) or herbicides (e.g., sodium arsenite). Until recently, the wood preservative chromated copper arsenate represented the largest commercial use of arsenic, although use in new residential products has been discontinued. Ammoniacal copper zinc arsenate is still used as a wood preservative in limited industrial applications. Organic arsenic antibiotics were used extensively in humans in the first half of the twentieth century in the treatment of protozoan

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and spirochetal diseases, and until recently phenylarsenic agents were used as feed additives for poultry and swine. The link between environmental and occupational arsenic exposure and chronic nonmalignant and malignant disease became well established in the latter half of the twentieth century, leading to a reduction in many commercial applications and recent regulatory efforts to reduce permissible exposure levels in drinking water, where arsenic of geologic origin may occur as a natural contaminant.

Semiconductor manufacturing is one industrial sector that has seen expanded the use of arsenic-containing compounds in recent decades. Hydride forms of arsenic, such as arsine gas, have been used as a source of arsenic dopants for silicon chips, and gallium arsenide has been used increasingly as a substrate for semiconductors. Inorganic arsenic has reemerged as a medicinal agent for the treatment of acute promyelocytic leukemia, and its potential utility in the therapy of other selected malignancies is under investigation. Arsenic trioxide was approved by the U.S. Food and Drug Administration as an orphan drug for the secondary treatment of acute promyelocytic leukemia in September 2000.

Biochemistry

Arsenic

Elemental arsenic (atomic weight 74.92) is a naturally occurring silver-gray solid metalloid. The elemental (zero valence) form, which rarely exists in nature and has low solubility, is seldom a cause of human toxicity. Rather, human exposure may occur predominantly to a variety of inorganic arsenic salts and natural and synthetic organoarsenic compounds, whose toxicity varies considerably depending on the molecular form, valence state, solubility, and exposure circumstances.

The principal inorganic forms of arsenic of toxicologic concern are the soluble crystalline solids and salts of trivalent (As^{+3}) arsenite and pentavalent (As^{+5}) arsenate. Trivalent arsenic compounds generally have greater acute toxicity

than the pentavalent forms, but *in vivo* interconversion occurs, and the two forms are capable of producing a similar pattern of acute and chronic intoxication. In the approach to a poisoned patient, there is seldom a clinical reason to distinguish whether the exposure has been to arsenite or arsenate. Arsenic trioxide (As_2O_3) is a commercially important crystalline solid that usually is produced from the smelting of copper or lead ores containing arsenic sulfides, such as arsenopyrite (FeAsS). Arsenic trioxide is moderately soluble in water (37 g/L at 20 °C), and arsenic pentoxide (As_2O_5) is very soluble in water (1500 g/L at 16 °C) [2]. Commonly encountered soluble arsenic salts include sodium arsenite (NaAsO_2) and sodium arsenate (Na_2HAsO_4). Inorganic arsenic of geologic origin occurs in natural waters, particularly groundwater in the vicinity of arsenic-bearing soils or sediments, where local redox conditions influence the relative preponderance of arsenite or arsenate species. Inorganic compounds of low solubility seldom have been associated with overt acute toxicity because of poor absorption and limited systemic distribution. These compounds include the former pesticide and herbicide calcium arsenate, which still may be encountered as a natural contaminant of some coal fly ash, and gallium arsenide (GaAs), which is used in semiconductors.

Pharmacokinetics and Metabolism of Arsenic Compounds

Volume of Distribution

In humans given an intravenous bolus of radio-labeled arsenite in a clinical study, the initial volume of distribution was calculated to be 0.2 L/kg [3]. Because initial plasma clearance was rapid (half-life approximately 0.45 h), however, the volume of distribution after 2–3 h appeared to increase to approximately 6 L/kg. Pharmacokinetic analysis of plasma arsenic in ten chemotherapy patients receiving an intravenous dose of As_2O_3 (0.15 mg/kg) over 2 h observed a volume of distribution of 15.2 ± 6.7 L/kg at the terminal elimination

(continued)

phase during the first day of therapy [4]. However, since calculations were based on arsenic concentration in plasma, and not the higher values usually found in whole blood [5], the volume of distribution reported may have overestimated the actual extravascular distribution.

Protein Binding

At low background levels, arsenic in the blood follows a red blood cell-to-plasma ratio of approximately 1:1, but this ratio increases at higher levels of arsenic exposure in humans and animals [6]. In two patients receiving arsenic chemotherapy, the concentration of total arsenic in whole blood (approximately 100–200 µg/L) was about two- to threefold higher than total arsenic in plasma [5]. Within the plasma of these patients, approximately two-thirds of the arsenic appears to be protein bound [7]. Studies in patients undergoing peritoneal dialysis indicated that approximately 5% to 6% of the inorganic arsenic in serum is bound to protein, predominantly to transferrin [8]. The total serum arsenic in these patients (mean 4.7 µg/L) was higher than that of a reference population (0.96 ± 1.52 µg/L) [9] and was much lower than levels encountered in the early phases of acute arsenic intoxication.

Mechanisms of Clearance

In humans, inorganic arsenic and its methylated metabolites are excreted overwhelmingly (>95%) via the urine. Minor to trace amounts are eliminated via the feces, sweat, skin, and appendages (hair and nails) [3, 10, 11]. In a study involving ingestion of radiolabeled arsenate, elimination was characterized by a three-component exponential function, with 66% of the arsenic eliminated with a half-life of 2.1 days, 30% with a half-life of 9.5 days, and 4% with a half-life of 38.4 days [11]. In other human ingestion studies, the half-life of urinary arsenic excretion after ingestion of 500–1000 µg arsenite was 2–3 days [12, 13]. The elimination of arsenic is prolonged, however, after high-dose exposure [6]. In

acutely poisoned humans, elevated urinary arsenic levels still may be detectable several weeks after the termination of exposure [14–16]. Some data suggest that arsenic may undergo enterohepatic or enteroenteric circulation in humans, but the extent of this process has not been well characterized.

Active Metabolites

Inorganic arsenic undergoes *in vivo* biomethylation to form monomethylated and dimethylated metabolites (Fig. 1). The principal metabolites are the pentavalent species, monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}), which are less acutely toxic than inorganic arsenic by an order of magnitude [2]. After chronic low-dose exposure to inorganic arsenic, the methylated metabolites account for approximately 70–90% of arsenic excreted in the urine [17]. The biomethylation process also produces small amounts of the trivalent methylated species, monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}), however, which have been found to be more acutely toxic than inorganic arsenic (arsenate or arsenite) [18–20]. Methylation cannot be viewed exclusively as a detoxification process. Genetic polymorphisms resulting in decreased methylation efficiency and a relative increase in the ratio of MMA to DMA in urine have been associated with an increased risk of chronic arsenic-related health impacts [21]. Recent human studies have found that thioarsenite compounds including dimethylmonothioarsinic acid (DMMTA^{V}) occur *in vivo* as minor metabolites that may also contribute to arsenic toxicity [22, 23].

Methods to Enhance Clearance

Because arsenic is excreted via the kidney, intravenous hydration and other supportive care that maintain adequate urine output help to optimize clearance. Chelation may accelerate arsenic excretion. Arsenic is cleared rapidly from the blood, and hemodialysis contributes little to clearance in patients with intact renal function.

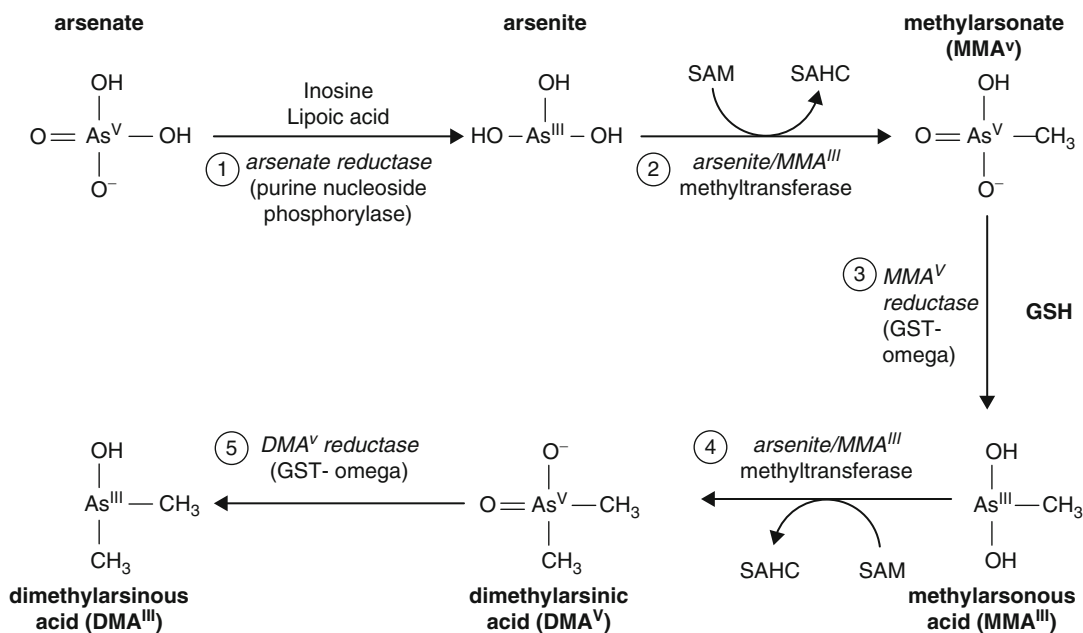


Fig. 1 Known pathways of arsenic metabolism in vertebrates. Abbreviations: *GSH* glutathione, *GST-omega* glutathione S-transferase omega, *SAHC* S-adenosylhomocysteine, *SAM* S-adenosylmethionine. Note the need to consider six

arsenic forms when exposure may be to arsenate alone. Reproduced from https://openi.nlm.nih.gov/detailedresult.php?img=PMC2137106_ehp0115-001770f1&req=4 under a Public Domain license

Noteworthy organoarsenicals include synthetic and natural products. In humans, inorganic arsenate or arsenite undergoes *in vivo* biomethylation in certain tissues to monomethyl and dimethyl forms that ultimately are excreted in the urine. The main biomethylation products are the pentavalent species monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V), which have lower acute toxicity than inorganic arsenic. More recent studies have shown that trivalent methylated forms, monomethylarsonous acid (MMA^{III}) and dimethylarsinous acid (DMA^{III}), which exist in small but stable amounts *in vivo*, have acute toxicities greater than the toxicity of arsenite. Synthetic DMA^V (also known as *cacodylic acid*) or its sodium salt were formerly used as agricultural chemicals, and it is still used as a laboratory buffer. The sodium salt of MMA^V, known as monosodium methane arsenate, is registered for use as a herbicide at sod farms, golf courses, highway rights of way, and cotton fields. It has occasionally been associated with accidental or

deliberate ingestion that results primarily in gastroenteritis that is relatively minor compared to the intoxication that appears after similar doses of inorganic arsenic [24, 25]. Many marine organisms and a few terrestrial biota (principally fungi) biosynthesize the trimethylated arsenic compounds arsenocholine and arsenobetaine $[(\text{CH}_3)_3\text{As}^+\text{CH}_2\text{CO}_2^-]$. The latter, an amino acid analogue, exists in dietary seafood at concentrations ranging from approximately 1–100 ppm but appears not to be metabolized after ingestion and exerts no known toxicity. Arsenosugars and arsenolipids occur in edible marine organisms and certain plants; although arsenosugars are partially metabolized to DMA, they are not associated with acute human toxicity. The occurrence and chemistry of organoarsenicals in the diet have been reviewed [26].

Trivalent and pentavalent arylarsenical antibiotics (e.g., arsphenamine and carbarsone) were used widely to treat spirochetal and protozoal infections in the first half of the twentieth century. Today the only organoarsenical manufactured as a

human pharmaceutical is melarsoprol, reserved for the treatment of the meningoencephalitic stage of African trypanosomiasis. Pentavalent arylarsenicals, such as roxarsone (4-hydroxy-3-nitrophenylarsonic acid), sodium arsanilate, and nitarsone, were formerly used as growth-promoting feed additives or antibiotics for poultry and swine, but as of 2016 all arsenic-containing drugs have been withdrawn from use in food producing animals in the United States.

Arsine

Arsine (AsH_3) is an extremely toxic colorless gas with a density heavier than air. In contrast to the other arsenicals, which principally result in acute toxicity after ingestion of a sufficiently large dose, arsine gas is an acute inhalational hazard. Arsine gas is liberated when any inorganic arsenic-containing material comes in contact with nascent hydrogen. Severe accidental poisonings have occurred when metal ores, alloys, or metallic objects (particularly objects made of aluminum or zinc) have come in contact with acidic (or occasionally alkaline) solutions, producing arsine gas from arsenic impurities in the metal or the solution or both [27]. As discussed subsequently, arsine poisoning is distinguished from other forms of arsenic intoxication by its characteristic production of intravascular hemolysis.

Lewisite

The chemical warfare agent lewisite (dichloro [2-chlorovinyl] arsine ClCH:CHAsCl_2), named after Lewis, its American inventor, a chemist, is a volatile vesicant liquid that causes immediate severe irritation and necrosis to the eyes, skin, and airways. The median lethal dosage by inhalation is 1200–1500 mg-min/ m^3 ; eye injury occurs at dosages less than 300 mg-min/ m^3 [28]. In recent decades, rare but significant accidental exposure to lewisite from old munitions has occurred. A current review of the acute and chronic effects of lewisite is available [29].

Pathophysiology

Arsenic

The acute and chronic noncancer toxicity of arsenic is a consequence of a multitude of interactions with cellular proteins, cofactors, and nucleic acids. Arsenite combines with the sulfhydryl groups of enzymes and cofactors, such as the vicinal dithiol lipoate component of the α -keto acid oxidation systems, that are vital to the main oxidative pathways of the tricarboxylic acid cycle [30]. In particular, arsenite has long been known to inhibit strongly pyruvate dehydrogenase [31], and more recently MMA^{III} has been shown to be even more potent in this regard [19]. Arsenite and to a greater extent MMA^{III} are potent inhibitors of enzymes necessary for cellular protection against oxidative stress, such as glutathione reductase and thioredoxin reductase [32, 33]. Arsenite exposure *in vitro* is associated with oxyradical production, mutagenesis, and cell death [34]. Arsenate and pentavalent methylarsenicals are reduced *in vivo* to trivalent species [26], which subsequently may bind proteins, interfere with enzymatic function, or increase oxidative stress. Arsenate also may impair cellular energy production through unstable substitution for phosphate in phosphorylation reactions, resulting in cellular depletion of adenosine triphosphate [35]. Inorganic arsenic may interfere with heme biosynthesis, reflected in part by elevated excretion of urinary porphyrins [36].

In addition to the aforementioned effects, inorganic arsenic or its methylated metabolites are associated with numerous other cellular perturbations, such as alterations in gene expression, cell-cycle regulation, signal transduction, and apoptosis, that may contribute to acute and chronic cancer and noncancer effects [37]. Arsenite induces DNA-protein cross-links [38] and interferes with microtubule assembly [39]. Arsenic has been associated with chromosomal aberrations in multiple *in vitro* and *in vivo* studies, and one investigation has suggested that trivalent methylated arsenicals may damage DNA directly [20]. The numerous cellular effects induced by arsenic in

experimental studies often depend on the intensity and duration of arsenic exposure, and the precise mode of action responsible for the spectrum of clinical effects of arsenic has not been elucidated. The fact that the biochemical targets of arsenic are ubiquitous in cells throughout the body is consistent, however, with the fundamental clinical observation that the effects of arsenic typically are multisystemic in their presentation.

Humans seem to be more susceptible than experimental animals to the toxic effects of inorganic arsenic. The median lethal dose of arsenite in hamsters is 8.5 mg/kg [19] and ranges from 15 to 75 mg/kg in mice and rats [2]. By comparison, potentially lethal complications have been observed in adult humans after the acute ingestion of approximately 200–300 mg (3–4 mg/kg) of a soluble form of inorganic arsenic.

Arsine

Arsine gas is a potent hemolytic agent. In vitro studies with human erythrocytes suggest that a large increase in intracellular calcium associated with an alteration in membrane sulfhydryl groups is a key feature of the hemolytic process [40]. In these experiments, arsine-induced changes in transmembrane ion flux appeared within 5 min of exposure, followed by significant hemolysis at 1 h. The strong susceptibility of erythrocytes to the toxic effects of arsine, but not arsenite, suggests that the hemolysis might be induced by a reaction product of arsine formed in the presence of heme, which is highly abundant in these cells [41]. The pathophysiology of the adverse effects that follow arsine inhalation is multifactorial. The intrarenal deposition of hemoglobin and other cellular debris from lysed erythrocytes may produce acute tubular damage and oliguric renal failure. Severe hemolysis diminishes peripheral oxygen delivery and creates generalized hypoxic stress. Before hemolysis, some arsine is transported via the bloodstream to other tissues [42], which may be damaged by the direct action of arsine or its reaction products. The kidney and possibly other organs convert arsine to arsenite, which further contributes to adverse effects [41, 43].

Clinical Presentation and Life-Threatening Complications

Arsenic

Acute Arsenic Intoxication

The clinical presentation of arsenic intoxication after a single acute ingestion is characterized by multisystemic findings that appear in stages over the course of hours to weeks (Table 1). The most common scenario results from the deliberate or accidental ingestion of several hundred milligrams or more of a soluble arsenic salt. The first stage typically begins 30 min to several hours postingestion, with prominent gastrointestinal distress consisting of nausea, vomiting, abdominal pain, and watery or mucoid diarrhea. There is often abdominal tenderness to palpation. The slightly delayed onset of these gastrointestinal symptoms and their appearance after parenteral arsenic overdose [16] are consistent with an acute mode of action dependent on acute cytotoxicity and increased vascular permeability rather than direct mucosal irritation.

During the initial stage of acute arsenic intoxication, diffuse capillary leak, alone or in combination with gastrointestinal fluid loss, produces cardiovascular signs and symptoms within a matter of hours. In mild-to-moderate cases, there may be thirst, tachycardia, or decreased urine output. More severe cases may result in hypotension, shock, malignant ventricular arrhythmias, and death [44–51]. The oliguria or anuria that occurs during the first 1–2 days after acute arsenic intoxication is most likely a consequence of decreased renal blood flow due to hypotension or diffuse extravascular fluid accumulation, rather than a consequence of acute tubular necrosis. The initial neurologic features of acute arsenic poisoning are highly variable and nonspecific. The mental status may be intact, or there may be lethargy, agitation, or delirium. Generalized convulsions have been reported but are relatively rare [46, 52]. Low-grade fever may be present but is not an invariable finding.

Commonly the initial phase of gastrointestinal symptoms and hypotension stabilizes or improves within 24–48 h but is followed within 1–7 days by

Table 1 Clinical and laboratory findings in acute arsenic poisoning^a

Phase 1: Immediate (within hours postingestion)
Gastrointestinal
Nausea, vomiting, diarrhea, abdominal pain
Cardiovascular
Hypotension (shock), tachycardia, diminished urine output, malignant cardiac arrhythmias
Metabolic acidosis
Rhabdomyolysis
Neurologic
Altered mental status (lethargy or agitation), seizures
Phase 2 (1 day to 1 week postingestion)
Cardiovascular
Prolonged QTc interval, cardiac arrhythmias (torsades de pointes), congestive cardiomyopathy, noncardiogenic pulmonary edema
Neurologic
Encephalopathy (agitation, delirium, stupor, coma)
Renal
Low-grade proteinuria
Hepatic
Elevated hepatic transaminases (slight to moderate), hyperbilirubinemia (slight)
Dermatologic
Desquamation (especially palmar or plantar), maculopapular rash, periorbital edema
Phase 3 (1–4 weeks postingestion)
Hematologic
Anemia, leukopenia, thrombocytopenia, relative eosinophilia, basophilic stippling of erythrocytes, disseminated intravascular coagulation
Neurologic
Sensorimotor peripheral neuropathy, autonomic instability (hypertension, diaphoresis)
Dermatologic
Transverse striate leukonychia (Aldrich-Mees' lines), herpetic lesions (zoster and/or simplex)

^aMore common findings are in **bold** type

a second phase of cardiovascular compromise characterized by mild congestive heart failure, noncardiogenic pulmonary edema, or both. The severity is variable, ranging from mild cardiomegaly or pleural effusions to full-blown acute respiratory distress syndrome [47, 53, 54]. In some cases, the peak manifestations of acute respiratory distress syndrome may be delayed 8–10 days postingestion [55]. The delayed appearance of isolated or recurrent malignant cardiac arrhythmias up to 10 days after an

initial high-dose arsenic ingestion merits particular concern and clinical vigilance. A relatively specific feature is the development of the polymorphic ventricular tachycardia, torsades de pointes. Torsades de pointes frequently is preceded by the common arsenic-associated finding of prolongation of the QT interval, with the QT_c interval frequently greater than 500 ms [56–60]. Sudden cardiac arrest in the absence of QT prolongation or torsades de pointes also may occur within a few days of the initial onset of gastrointestinal symptoms [61].

Patients may exhibit a decline in mental status, characterized by delirium or obtundation, 2–6 days after the onset of acute arsenic poisoning [62–64]. This delayed encephalopathy often resolves spontaneously within a week, but on rare occasions it may persist for a prolonged period [65–67].

A third phase of acute intoxication, generally appearing 1–4 weeks after the initial high-dose ingestion, is heralded by hematologic abnormalities and peripheral neuropathy. The classic hematologic finding is pancytopenia, with the suppression of erythrocytes, leukocytes, and platelets usually reaching a nadir within 1–3 weeks. Complete recovery of all cell lines usually follows within weeks to months. The salient laboratory features are discussed further in the section on diagnosis.

In many but not all cases of acute arsenic intoxication, a symmetric distal sensorimotor axonal peripheral neuropathy evolves 1–5 weeks after the ingestion. Initial findings consist of dysesthesias in the distal extremities in a stocking-glove distribution. Dysesthesias often rapidly progress to “burning” paresthesias, with hyperpathia to mild stimuli, such as bed sheets rubbing against the feet [62, 68]. Other sensory modalities (e.g., proprioception) also are affected, and within days to a week patients experience the onset of motor weakness. The lower extremities may be more affected than the upper extremities in the initial stages. Depending on the severity of the poisoning, sensory and motor deficits ascend symmetrically to involve the proximal musculature, and a marked quadriplegia can occur. In the most severe cases, neuromuscular respiratory

failure requires mechanical ventilation, sometimes for several weeks [53, 69, 70]. Autonomic instability, characterized by episodic diaphoresis, temperature instability, and hypertension, may appear during the peak stages of neuropathy [66]. Although there have been rare reports of visual disturbances [44, 71] and facial nerve paralysis [72], cranial nerve function almost always is well preserved. Signs of slow improvement in the peripheral neuropathy begin to appear within a few weeks after deficits have reached their maximum. The extent of recovery depends on the severity of the peak insult. Patients with mild-to-moderate insults, such as cases with predominantly sensory involvement, have recovered completely, but in patients with severe motor and sensory deficits, distal weakness, wasting, and diminished sensation may persist for years [62, 64, 73].

Several dermatologic signs variably appear after a delay of approximately 1–6 weeks following acute arsenic ingestion. A diffuse maculopapular rash, sometimes with areas of vesiculation, may be noted [55, 74]. Mild-to-moderate desquamation of the skin, mainly in the hands and feet but occasionally in a more diffuse pattern, is common [74–76]. In many cases, the cutaneous reactions have appeared before treatment with chelating agents, which may induce allergic dermal manifestations. Patients may exhibit periorbital edema. Herpetic vesicular lesions, secondary to herpes simplex or herpes zoster, often erupt on the face or trunk days to weeks after substantial arsenic ingestion. This eruption may be triggered by arsenic-related suppression of leukocytes and immune function. Transverse white striae (white bands 1 or 2 mm in width) classically appear on the emerging nail beds of the fingers and toes after 4–6 weeks. Although frequently referred to as *Mees' lines* after the report of Mees [77], this finding of transverse striate leukonychia was described earlier by Aldrich [78] and by Reynolds [79] in arsenic-poisoned patients. The bands, which are thought to reflect an abrupt disruption of keratinization, are not pathognomonic for arsenic poisoning and may occur after other toxic insults, such as thallium poisoning [80]. Multiple bands on the nail

beds may be visible in patients who have had multiple discrete episodes of acute poisoning in the preceding months.

Subacute and Chronic Arsenic Poisoning

Subacute arsenic poisoning shares many of the features of acute arsenic intoxication but is less often life-threatening. The magnitude of the recurrent dose influences the severity and time course of the presentation. A 2–4-month period of consumption of drinking water delivering arsenic doses that were probably on the order of 10–50 mg/day resulted in peripheral neuropathy, sometimes with antecedent gastrointestinal symptoms [81] and sometimes without gastrointestinal symptoms [16]. In a subset of 220 adult patients studied by Mizuta and colleagues [82], 2–3 weeks of ingesting an estimated 3 mg of arsenite per day in contaminated soy sauce resulted in periorbital edema, gastrointestinal symptoms, decreased hematocrit, and mild peripheral neuropathy. During the Manchester beer epidemic of 1900, daily consumption for weeks to months of 1–5 mg of arsenic per day in contaminated beer caused a large outbreak of mild-to-moderate peripheral neuropathy. Hyperpigmentation and periorbital edema commonly were noted. Deaths from congestive heart failure were reported, but the contributory role of alcoholic cardiomyopathy in those cases remains uncertain [79, 83]. Among 104 adults accidentally exposed to an estimated 24 mg of arsenic per day in a lunch meal for 5–8 consecutive days, approximately 80% developed self-limited gastroenteritis and mild-to-moderate elevation in serum alanine aminotransferase, and approximately 70% exhibited leukopenia [84]. Assuming a body weight of 55 kg in that Asian population, the daily ingested dose may have been 0.4 mg/kg.

Experimental trials employing intravenous arsenite in the treatment of refractory or relapsed acute promyelocytic leukemia have provided new insights into the subacute toxicity of inorganic arsenic. The therapeutic mode of action of arsenic in treatment of this malignancy may involve a selective induction of apoptosis in the leukemic cells, possibly through degradation of a specific

oncoprotein [85] or through interaction with the tubulin that is abundant in leukemic cells [39]. Experimental protocols generally have administered 10–20 mg of As_2O_3 intravenously daily for 2 months per course of treatment (an arsenic dose of approximately 0.15 to 0.3 mg/kg/day). Although many subjects have tolerated this regimen, some severe arsenic-related adverse effects have been reported, including arrhythmias, peripheral neuropathy, and hepatotoxicity. Ohnishi and coworkers [86] observed QT prolongation in eight of eight patients receiving daily infusions of 0.15 mg/kg As_2O_3 administered over 2 h, and four of eight patients exhibited nonsustained monomorphic ventricular tachycardia, generally after 3 or more weeks of treatment. Unnikrishnan and associates [87] observed torsades de pointes in 3 of 19 patients, after 42, 16, and 12 days of treatment, respectively. In two of the three cases, the arrhythmia was refractory to treatment, and the patient died. Niu and coworkers [88] observed hepatic transaminase elevation in 7 of 11 newly diagnosed patients entering an arsenite treatment protocol. In five of the patients, hepatic dysfunction was reversible on cessation of treatment, but in two cases it seemed to be progressive. Sensorimotor peripheral neuropathy has occurred 6–8 weeks after initiation of treatment, and nausea, vomiting, and abdominal pain have been common [89].

Chronic arsenic poisoning has been characterized extensively through studies of populations exposed to elevated levels of naturally occurring arsenic in drinking water and through historical accounts of the use of medicinal arsenic (e.g., Fowler's solution) for the treatment of asthma, psoriasis, and other maladies. The adverse effects of chronic arsenic ingestion have been reviewed in detail [26, 37]. Noncancer chronic effects include a distinctive pattern of spotted hyperpigmentation and palmar-plantar hyperkeratosis, hematologic findings of anemia and leukopenia, a sensory predominant axonal peripheral neuropathy, vascular disease, and noncirrhotic periportal hepatic fibrosis and portal hypertension. Nonspecific gastrointestinal complaints, such as diarrhea and cramping, may also occur, but in many instances the cutaneous, neurologic,

vascular, or hematologic effects of chronic arsenic poisoning develop without a history of antecedent gastrointestinal symptoms [90]. Epidemiologic studies have suggested a link between chronic arsenic ingestion and diabetes mellitus, hypertension, and increased cardiovascular disease mortality [26, 37, 91–93]. In the short term (days to months), gastrointestinal, hematologic, and neurologic symptoms may emerge with arsenic doses of 0.05 mg/kg/day. When exposure occurs over several years, noncancer symptoms may emerge at doses of approximately 0.01 mg/kg/day. Chronic arsenic ingestion is well established as a risk factor for lung cancer, bladder cancer, and skin cancer, and occupational studies have identified arsenic inhalation as a cause of lung cancer [26, 37, 94]. Epidemiological studies increasingly link arsenic exposure to an increased risk of certain types of renal cancer [95] and liver cancer [96]. The latency period for arsenic-induced cancers may range from one to four or more decades [97, 98].

Arsine

Although exposure to arsine occurs by inhalation, the gas is nonirritating, and there generally are *no immediate symptoms*. Although a garlic-like odor has sometimes but not invariably been reported, the reported odor threshold of 0.5–1.0 ppm does not provide sufficient warning properties [99]. Most arsine intoxications are associated with acute occupational exposure occurring over 30 min to a few hours. After a typical delay of 2–24 h, patients often report nonspecific constitutional symptoms that may include malaise; headache; fever or chills; and gastrointestinal disturbance, particularly nausea, vomiting, and crampy abdominal pain [100]. In some cases, the pain has occurred predominantly in the low back or flank, rather than the abdomen [101]. Patients also may complain of numbness or coldness of the extremities. In severe exposures, sudden cardiovascular collapse and death may ensue within 1 or 2 h [102]. The clinical features of acute arsine poisoning are summarized in Table 2.

Table 2 Clinical and laboratory features in acute arsine poisoning^a

Constitutional
Malaise, fever or chills , acute sensation of numbness or cold in extremities
Gastrointestinal
Nausea and vomiting, crampy abdominal pain , low back/flank pain, hyperbilirubinemia (slight to moderate)
Hematologic
Hemolysis, elevated plasma hemoglobin
Renal
Hemoglobinuria (dark red urine), oliguria or anuria (active urine sediment [cells and casts; may be delayed], increasing serum creatinine and BUN)
Dermatologic
Bronze discoloration of skin
Neurologic
Headache , altered sensorium (delirium or agitation), delayed sensorimotor peripheral neuropathy

^aMore common findings are in **bold** type

In the absence of rapid fatality, a characteristic finding in the first 2–24 h is the passage of dark, reddish urine, usually followed by oliguria and sometimes anuria [103, 104]. There is often a concomitant appearance of a copper, bronze, or jaundiced discoloration to the skin [105, 106]. The urine discoloration is attributable to hemoglobinuria, and the skin discoloration possibly is due to elevated plasma hemoglobin; both of these effects follow the significant intravascular hemolysis. Oliguria and anuria, which may last days to several weeks, are the hallmark of acute tubular necrosis. Within the first 1–2 days after presentation, a few patients with acute arsine poisoning may develop an altered mental status, ranging from agitation to frank hallucinosis [106, 107]. Electrocardiogram changes during this time may include nonspecific T-wave changes or occasionally peaked T waves [108], but in contrast to the picture in acute inorganic arsenic poisoning (see earlier), significant conduction abnormalities or malignant arrhythmias are uncommon. The delayed appearance (within weeks) of a mild-to-moderate sensorimotor peripheral neuropathy has been reported after acute arsine poisoning [106, 109]. Transverse

white striae of the fingernails, known as *Aldrich-Mees lines*, also may emerge during that time interval.

Chronic arsine poisoning has been described only rarely. Bulmer and colleagues [110] reported chronic arsine poisoning in 14 workers engaged in the cyanide extraction of gold. Five workers with the longest exposures (5–9 months) complained of persistent headache, weakness, shortness of breath, and nausea and vomiting and were noted to have severe anemia. Among the 14 subjects, the degree of anemia was proportional to the length of exposure, but specific exposure levels were not determined. In experimental models, subacute and subchronic exposure of rodents to arsine in the range 0.025–5 ppm has been associated with reversible hematopoietic effects [99].

Diagnosis

Poisoning by Inorganic Arsenic

The diagnostic approach to arsenic poisoning should integrate (1) characteristic signs and symptoms, (2) a history consistent with sufficient exposure, (3) confirmatory laboratory findings, and (4) the relative exclusion of other factors in the differential diagnosis. Acute arsenic poisoning should be suspected in a patient with the abrupt onset of nausea, vomiting, watery diarrhea, abdominal pain, and hypotension, possibly in association with the evolving pattern of cardiovascular, hematologic, and neurologic findings discussed earlier. In symptomatic subacute and chronic poisoning, clinical or laboratory evidence of *multisystemic* adverse effects almost always is present.

Laboratory findings in the initial stage of acute arsenic poisoning often reveal evidence of an elevated anion-gap metabolic acidosis. The initial complete blood count (CBC) may be normal or may reveal an elevated hematocrit due to extravascular fluid loss and hemoconcentration. Rhabdomyolysis may be evidenced by increasing levels of creatinine phosphokinase [111, 112]. The urinalysis may be normal or may reveal low levels of protein or heme. Microscopic

examination of the urine usually lacks the prominent cellularity and sediment of acute tubular necrosis, however. Initially, blood urea nitrogen and serum creatinine may be normal or slightly elevated. These parameters of renal function often increase in the presence of diminishing urine output and shock, sometimes with a disproportionate rise in serum creatinine associated with rhabdomyolysis. The electrocardiogram commonly exhibits sinus tachycardia, sometimes with a prolonged QT_c interval, and nonspecific S-wave and T-wave changes [56, 59].

The chest x-ray in the initial phase of acute arsenic intoxication is generally unremarkable, but over the next several days the chest x-ray may exhibit mild cardiomegaly, pleural effusions, or both. The presence of radiopaque material in the gastrointestinal tract, detected incidentally in the region of the stomach on chest x-ray or in the stomach or small intestine on abdominal x-ray, sometimes may provide a clue to acute arsenic ingestion [49, 113, 114]. The presence of a radiopacity, owing to poorly dissolved arsenic compounds, is neither a sensitive nor a specific diagnostic finding, however.

Liver function tests in acute arsenic poisoning typically reveal slight-to-moderate increases in hepatic transaminases (alanine aminotransferase and aspartate aminotransferase), which may reach several hundred international units per liter within the first days to a week. Moderate hyperbilirubinemia (e.g., 1–3 mg/dL [17–51 µmol/L]) may be present initially or after a delay of several days. More severe elevations in bilirubin have been noted rarely [111], and in two such cases, liver biopsy revealed slight cholestasis and a marked pattern of hepatocellular mitotic figures [115].

Several abnormal hematologic test results usually are present in the second phase of acute arsenic poisoning and in subacute or chronic intoxication. Pancytopenia, particularly anemia and leukopenia, characteristically is evident on the CBC within 1–2 weeks after acute ingestion. The anemia is usually normochromic and normocytic, but megaloblastic changes also have been reported, with the peripheral smear showing regenerative macrocytes [116]. Basophilic

stippling of erythrocytes may be visible on the peripheral smear [117, 118], as may be nucleated red blood cells with karyorrhexis (irregular pyknotic nuclei). Leukopenia is evident as lymphocytopenia and neutropenia, and the differential white blood cell count often reveals a relative eosinophilia. Bone marrow examination typically reveals erythroid karyorrhexis and megaloblastoid dyserythropoiesis in the context of a hypercellular background. Hemostatic disorders have included a prolonged partial thromboplastin time and disseminated intravascular coagulation [16, 45, 51, 55, 119].

The cerebrospinal fluid in the second or third phase of acute arsenic intoxication may be normal, or there may be mild-to-moderate elevations in protein, usually in the range 50–100 mg/dL. Only rarely does the cerebrospinal fluid protein reach a few hundred milligrams per deciliter [62, 69, 71]. Cerebrospinal fluid cellularity classically is absent or scant. Electrodiagnostic studies and nerve biopsies performed to assess arsenic-induced peripheral neuropathy usually reveal distal axonal degeneration, although some investigators have reported that the early stages of acute arsenical polyneuropathy may exhibit features of a segmental demyelinating process [64, 69, 75, 120].

Measurement of urinary arsenic should be obtained for confirmatory diagnosis. Although a 24-h urine collection sometimes yields information of forensic, toxicokinetic, or research interest, a spot urine collection that measures arsenic concentration is usually sufficient for diagnostic purposes. Most clinical laboratories report the result in terms of *total urinary arsenic*. Diagnostic interpretation sometimes requires a more specific assessment of the chemical forms or “species” of arsenic detected, however. Absorption of inorganic arsenate or arsenite by humans results in excretion of arsenate and arsenite, plus the products of *in vivo* biomethylation, principally MMA and DMA. Certain foods of marine origin, including many finfish, shellfish, and algal products, may contain large amounts of nontoxic organoarsenicals, such as arsenobetaine and arsenosugars. After a seafood meal, arsenobetaine may be excreted unchanged in the urine in concentrations

of several hundred to several thousand micrograms (as arsenic) per liter over the next several days. Arsenosugars, abundant in bivalve mollusks and edible seaweed (e.g., kelp, nori, laver), are metabolized at least partially to DMA [121]. A few types of edible seaweed, notably Hijiki and Laminaria, have been found to contain inorganic arsenate at concentrations of approximately 50 ppm. Regular consumption could result in a daily dose on the order of 100 micrograms that is associated with chronic but not acute health risk [122]. After ingestion of clams or mussels or edible seaweed, the DMA concentration of the urine may be increased to several hundred micrograms per liter. The arsenobetaine and DMA excreted after seafood ingestion is included in the laboratory measurement of total urine arsenic. In North Americans and Europeans with average, “background” exposure to arsenic, the sum of inorganic arsenic (arsenate and arsenite), MMA, and DMA in the urine is generally less than 20 µg/L [26, 123].

Because of the potential presence of large amounts of seafood-derived arsenic in a patient’s diet, the following approach is recommended when ordering urinary arsenic measurement on a potentially poisoned patient. If readily available, a speciated urine arsenic result that reports the concentration of inorganic arsenic (arsenite plus arsenate), MMA, and DMA should be requested. (It may be technically difficult, and not clinically necessary, for the laboratory to differentiate between arsenite and arsenate.) If only a total urinary arsenic measurement is readily available, this should be obtained, but a separate aliquot of the urine should be stored at -4°F (-20°C). If the total urine arsenic concentration is elevated significantly above background values (e.g., $>50\text{ }\mu\text{g/L}$), the retained aliquot should be sent to a toxicologic laboratory that can report the amount of inorganic arsenic, MMA, and DMA present. This practice reduces the potential for a total urine arsenic concentration that is elevated on the basis of recent arsenobetaine ingestion in seafood to be misinterpreted as evidence of recent overexposure to inorganic arsenic. Because DMA derived from arsenosugars in seafood still may appear in the urine in large amounts for 3 days

[121, 124], it nonetheless is important to obtain and consider a careful history of any recent seafood ingestion. If relevant, a follow-up urine specimen obtained after 3 or 4 days of strict abstinence from any seafood should be submitted for speciated arsenic analysis. Urine collected for speciated analysis should not be treated with dilute acids to prevent adsorption onto the sample container because this may alter the speciation profile [125].

In the first 2–3 days after acute, symptomatic arsenic intoxication, the urinary arsenic concentration (expressed as a sum of inorganic arsenic, MMA, and DMA) usually exceeds 1000 µg/L, and the urinary arsenic excretion in 24 h is typically greater than several thousand micrograms. Depending on the severity of the poisoning, the urine arsenic concentration may not return to background levels (total urine arsenic concentration $<50\text{ }\mu\text{g/L}$) for several weeks. In the initial four hours following therapeutic administration of 10 mg As_2O_3 i.v. to cancer patients, As(III) was the major species excreted in urine; however by 24 h DMA predominated [126]. In patients acutely poisoned by ingestion of hundreds of milligrams to gram quantities of inorganic arsenic, it may take several days to a week for DMA to be the predominant urinary arsenic species [14, 127]. The dose-dependent, temporal change in the pattern of arsenic species in the urine following acute exposure indicates that sequential examination of speciated analyses (inorganic arsenic, MMA, and DMA) from an experienced reference laboratory may offer useful clinical and forensic information.

Blood arsenic values are seldom of clinical utility in diagnosis or management for several reasons. Arsenic is cleared rapidly from the blood, and the relationship between symptomatic arsenic intoxication and blood arsenic levels is highly variable and time dependent. Blood values may decline to what some laboratories define as the “normal” range when the urine still contains hundreds of micrograms of arsenic per liter and the patient remains symptomatic. Blood arsenic also is technically more difficult to measure accurately, and speciation, while possible [4], is seldom available. Measurement of blood arsenic

concentration should be reserved for cases when a urine arsenic measurement cannot be obtained, such as an anuric patient. Background levels of arsenic in whole blood usually are less than 5 µg/L (0.07 µmol/L) [26]. In acutely poisoned patients, values greater than 100 µg/L (1.3 µmol/L) (serum or whole blood) have been reported [44, 54, 67, 70, 119, 128].

Arsenic is incorporated from the circulation into fingernails, toenails, and the growing hair shaft at the root. As the hair and nails grow outward, portions that were formed during the time of increased circulating arsenic contain elevated arsenic concentrations. Scalp hair grows at the approximate rate of 1 cm/month [129, 130], fingernails grow at the approximate rate of 4–5 mm/month [10], and toenails grow at the approximate rate of 1.1 mm/month [131]. As a consequence, segmental analysis of hair shafts (e.g., analysis of longitudinally aligned hairs cut into centimeter or subcentimeter sections) or analysis of distal toenail or fingernail clippings may reveal evidence of increased arsenic exposure that occurred months earlier. Because arsenic levels in the urine generally return to baseline levels within a matter of weeks, the elevated arsenic levels remaining in hair or nails may yield important forensic evidence of past exposure. Arsenic can bind to hair and nails from external contamination, however, in a manner that is indistinguishable from that present as a result of internal incorporation. Some data also suggest that arsenic extruded in the sweat during acute poisoning may contaminate distal segments of the hair and nail that were formed long before the arsenic exposure occurred [10, 132]. Thus, the information obtained from analysis of the arsenic content of the hair and nails should be interpreted cautiously [133]. Background levels of arsenic in hair and nails are less than 1 ppm.

The differential diagnosis of acute arsenic intoxication includes other causes of multisystemic illness and organ dysfunction. Many clinical illnesses and poisonings can manifest with the severe gastrointestinal symptoms, hypotension, and metabolic acidosis that are typical of the initial stage of acute arsenic intoxication; examples include bacterial and viral

gastroenteritis, naturally occurring food toxins (e.g., bacterial food poisoning), salicylate overdose, and iron overdose. Acute colchicine overdose may result in acute gastrointestinal distress and hypotension, followed within days by cardiovascular disturbances, altered mental status, and delayed bone marrow depression.

When the early symptoms of acute arsenic poisoning are followed by delayed peripheral neuropathy, the differential diagnosis shifts to several other entities. Guillain-Barré syndrome often occurs as an ascending polyradiculopathy in a patient with a history of an antecedent gastrointestinal illness. In contrast to Guillain-Barré syndrome, arsenical polyneuropathy features prominent early sensory deficits, absence of cranial nerve involvement, and generally lower cerebrospinal fluid protein levels. Noting that some of the early electrodiagnostic features of Guillain-Barré syndrome and arsenic polyneuropathy may be difficult to distinguish, Goddard and associates [134] recommended examination of the proximal F-loop latency, which is prolonged in Guillain-Barré syndrome but not in arsenic poisoning.

Thallium poisoning shares many of the features of arsenic poisoning, including marked initial gastroenteritis, central nervous system dysfunction, and cardiac toxicity, followed by painful peripheral neuropathy and Mees' lines on the nails. In contrast to arsenic poisoning, thallium poisoning does not cause prominent hematologic abnormalities, and it is more likely than arsenic poisoning to produce alopecia.

Patients presenting with alcoholic peripheral neuropathy can have histories of antecedent gastrointestinal distress, anemia, cardiac abnormalities, and liver dysfunction. Compared with arsenic peripheral neuropathy, alcoholic peripheral neuropathy has a slower tempo and may have less prominent motor involvement.

Patients with acute intermittent porphyria may present with a history of abdominal pain, central nervous system disturbance, and peripheral neuropathy, but the condition lacks the prominent sensory involvement of arsenic poisoning. Because acute intermittent porphyria is a genetic disease, it is often associated with a past history of recurrent attacks in adults. Certain nutritional

deficiency syndromes, such as pellagra (dermatologic changes, gastrointestinal symptoms, peripheral neuropathy) and beriberi (mental status changes, cardiac failure, peripheral neuropathy), may share some features of arsenic intoxication.

The following two case summaries (of patients for whom the author provided consultation later in their courses) illustrate some classic clinical features of acute arsenic poisoning.

Case 1

A 39-year-old woman presented to the emergency department complaining of 3 days of nausea, vomiting, diarrhea, and intermittent abdominal pain. Aside from her anxious and bizarre affect, physical examination was unremarkable. On laboratory testing, CBC and electrolytes were remarkable only for a hematocrit of 34% and a serum potassium of 2.8 mEq/L. She was administered 500 mL of intravenous fluids, given a prescription for prochlorperazine, and discharged with a presumptive diagnosis of viral gastroenteritis. She returned the next day with identical complaints. Physical examination remained unremarkable with the exception of a mild postural tachycardia. Laboratory testing revealed electrolytes (in mEq/L) of sodium 134, potassium 3, chloride 107, and bicarbonate 21; serum chemistry panel was remarkable for abnormal liver function tests, with total bilirubin of 1.9 mg/dL [32.5 μ mol/L] (direct 0.3 mg/dL [5.1 μ mol/L]) (reference range for total bilirubin 0.2–1.2 mg/dL [3.4–20.5 μ mol/L], aspartate aminotransferase of 194 IU/L (reference range 5–35 IU/L), and alanine aminotransferase of 225 IU/L (reference range 5–35 IU/L). Serum β -human chorionic gonadotropin was negative. The diagnostic impression remained viral gastroenteritis, with inadequate oral intake at home. The patient was admitted to the medical ward for hydration. Past medical history was unremarkable.

During the first 3 hospital days, intermittent crampy abdominal pain, nausea, vomiting, and diarrhea continued. The patient remained afebrile. On hospital day 4, hematocrit was 28.7%, and white blood cell (WBC) count was 4900/mm³. Urinalysis revealed 2+ proteinuria. Stool cultures and ova and parasite examination were negative.

Slowly progressive periorbital and pedal edema, unresponsive to furosemide, were noted. The patient complained of a dry mouth, and a faint malar rash was observed. On hospital day 7, the patient complained of lightheadedness, and an electrocardiogram revealed supraventricular tachycardia. She was transferred to the cardiac care unit, where additional monitoring over the next 2 days revealed frequent runs of nonsustained polymorphic ventricular tachycardia, including an episode of torsades de pointes. Chest x-ray revealed slight cardiomegaly and small bilateral pleural effusions.

Gastrointestinal complaints resolved by the second week of hospitalization. Aspartate aminotransferase peaked at 542 IU/L on day 7. CBC revealed slowly progressive pancytopenia, reaching a nadir on day 10 with hematocrit 22% and WBC count 1100/mm³. A bone marrow biopsy specimen showed erythroid hyperplasia and karyorrhexis; later, basophilic stippling and reticulocytosis appeared in the peripheral blood smear. A prodigious number of additional tests recommended by multiple consultants were essentially negative; the diagnosis of arsenic poisoning came to light with a blood arsenic level of 160 μ g/L (2.1 μ mol/L) on hospital day 11. Repeat testing on day 16 yielded a blood arsenic level of 3 μ g/L (0.04 μ mol/L), and on day 17, a 24-h urine arsenic collection contained 2279 μ g (urine arsenic concentration was 426 μ g/L [5/7 μ mol/L]).

Palmar desquamation was observed on day 23. A progressive sensorimotor peripheral neuropathy first became evident on day 30. Weakness progressed proximally, and on day 46, neuromuscular respiratory failure necessitated intubation and mechanical ventilation. Cranial nerves were intact. Head computed tomography scan and electroencephalogram were normal. Lumbar puncture revealed acellular fluid with a protein of 121 mg/dL. Seven to 10 days of autonomic instability, characterized by transient episodes of hypertension (systolic blood pressure 140–210 mmHg), tachycardia (140 beats/min), and diaphoresis, appeared to respond to metoprolol. By day 62, motor strength began to return in a proximal-to-distal direction, and on day 73, the patient was weaned successfully from the ventilator. Gross

voluntary limb movement returned on day 83. Six months after the acute poisoning incident, the patient had recovered most motor strength in the upper extremities and proximal lower extremities, but residual weakness remained in the toes.

Comment: The source of the arsenic poisoning was never detected, but foul play was suspected. Because the initial attempt to investigate heavy metal poisoning was performed with a blood arsenic measurement, the diagnosis was almost missed. Although the blood arsenic level still was elevated on day 11, it had returned to normal range by day 16, a day before the preferred test, urine arsenic concentration, remained markedly elevated. The patient received 3 days of chelation with intramuscular dimercaprol (British antilewisite [BAL]) from day 17 to day 19, which did not avert the subsequent development of peripheral neuropathy (see later under Treatment).

Case 2

A 27-year-old man self-injected approximately 0.6 mL of an arsenic-containing herbicide (arsenite dose 330 mg) in a suicide gesture. He presented to the emergency department 30–60 min later with an alert mental status and profuse vomiting. Vital signs included blood pressure 104/50 mmHg, pulse 103 beats/min, temperature 98 °F (37 °C), and respiratory rate 40 breaths/min. Physical examination was normal except for slight diffuse erythema. Initial laboratory tests revealed an anion gap acidosis with serum electrolytes (mEq/L) of sodium 141, potassium 2.8, chloride 106, and bicarbonate 14 and an arterial blood gas on 6 L/min oxygen of pH 7.57, PCO₂ 14 mmHg, and PO₂ 156 mmHg. CBC included hematocrit 45.2%, WBC count 6000/mm³, and platelets 257,000/mm³. Prothrombin time was 11.7 s. Prompt chelation with dimercaprol, 300 mg intramuscularly every 4 h (approximately 4 mg/kg every 4 h), was begun 10 min after presentation. The patient became transiently delirious over the next 12 h. A spot urine arsenic concentration on admission was 13,100 µg/L (174 µmol/L), and a 24-h urine collected between the second and third day contained 11,396 µg of arsenic. Vomiting subsided within 36 h. Transient oliguria that developed 24–48 h

postadmission was accompanied by a rise in serum creatinine from 1.6 mg/dL [141.4 µmol/L] to 2.1 mg/dL [185.6 µmol/L]. Urine output increased, however, with vigorous fluid hydration, and serum creatinine decreased to 1.0 mg/dL [88.4 µmol/L] on day 4.

A progressive thrombocytopenia developed during the first 6 days, with platelet count declining to 66,000/mm³. Fibrinogen was 175 mg/dL (5.15 µmol/L) (reference range 200–400 mg/dL; 5.88–11.8 µmol/L), and fibrin split products were increased slightly, leading to an impression of low-level disseminated intravascular coagulation. The patient developed episodic disorientation and hallucinations on day 6 and became markedly tachypneic. Dimercaprol was discontinued. Urine arsenic excretion on day 7 was 9623 µg/24 h. Chelation with oral succimer, 800 mg every 8 h (10 mg/kg three times a day), was begun on day 8, and the platelet count subsequently increased over the next 2 days to 137,000/mm³. The hematocrit decreased to 28%, however, and the WBC count reached a nadir of 3700/mm³. On day 10, there was an episode of ventricular tachycardia, and the chest x-ray after intubation revealed patchy bilateral infiltrates consistent with adult respiratory distress syndrome. Invasive hemodynamic monitoring revealed high-output congestive heart failure. Succimer was continued via a nasogastric tube. On day 14, cardiopulmonary and mental status improved, and the patient was extubated. On day 17, there was abrupt onset of a progressive sensorimotor peripheral neuropathy. Succimer dose was decreased to 250 mg three times a day on day 20 (when urine arsenic excretion was 992 µg/24 h) and was continued through day 48 (when urine arsenic excretion was 129 µg/24 h). The peripheral neuropathy advanced to quadriplegia by day 59. Slow improvement in limb strength began on day 64, and the patient was able to stand with the assistance of ankle braces by day 96.

Comment: In this rare case of intravenous arsenic overdose, the patient developed initial vomiting and intravascular volume depletion, followed more than 1 week later by life-threatening cardiopulmonary complications and delirium. These complications occurred despite

the prompt initiation of chelation with intramuscular dimercaprol. Thrombocytopenia and low-level disseminated intravascular coagulation, which necessitated discontinuation of dimercaprol, coincidentally resolved when the chelation regimen was changed to oral succimer. A delayed sensorimotor peripheral neuropathy still ensued.

Poisoning by Arsenic

Arsenic poisoning should be suspected strongly in a patient with a history of premonitory constitutional complaints and gastrointestinal disturbance, notably cramping abdominal pain, which is followed within hours by passage of declining volumes of reddish urine and the development of a coppery or jaundiced discoloration to the skin. A history of recent work in which acidic solutions have come in contact with metallic ores or slag is highly suggestive of exposure but is neither specific nor essential.

Common laboratory tests almost always reveal a pattern of evolving, severe hemolysis. The urine is usually heme positive on dip-stick, but microscopic examination may be devoid of formed red blood cells in the initial hours. As oliguria develops, the scant urine usually is strongly dip-stick positive for heme and positive for protein, and microscopic examination reveals an active sediment with red blood cells, red blood cell casts, or granular casts. The urine hemoglobin level should be assessed quantitatively: It may be approach 3 g/L with significant hemolysis, and values ultimately may exceed 10 g/L [105, 135].

In the first few hours after acute overexposure, the CBC may reveal a hematocrit or hemoglobin that is normal or only moderately decreased, but within approximately 12–36 h these values may decline dramatically, with hematocrits in the 20s and hemoglobin values in the range 5–10 g/dL (50–100 g/L). Measurement of plasma or serum hemoglobin should be obtained because elevations greater than 1.5 g/dL (>15 g/L) are common in clinically significant arsenic poisonings and may have prognostic significance. Plasma or serum hemoglobin initially rises, then remains elevated

during the course of active hemolysis, which may persist for several days in the absence of treatment by exchange transfusion (see later). Erythrocyte morphology may include characteristic “ghost cells,” which appear as an enlarged membrane enclosing a pale or vacant interior [101, 102, 106]. Erythrocyte fragmentation, spherocytes, and acanthocytes variably may be found. Leukocytosis is common, and reticulocytosis may appear within a few days. Coombs’ test is negative.

Serum chemistries often reveal mild-to-moderate elevations in total bilirubin (e.g., 2–5 mg/dL [34.2–85.5 μ mol/L]) within the initial 48 h. Although the skin discoloration of arsenic-poisoned patients sometimes has been described as “jaundiced,” the typical elevation in serum bilirubin is inadequate to account for the dermal appearance. Plasma hemoglobin or degenerated heme products instead may be responsible. Serum transaminases may be slightly elevated, but lactate dehydrogenase typically is markedly elevated, consistent with the hemolytic state. Blood urea nitrogen and serum creatinine increase as acute tubular necrosis proceeds and renal output declines. As with most cases of acute tubular necrosis, the acute renal insufficiency of arsenic poisoning generally is reversible after days to weeks of supportive care, although some residual insufficiency may persist.

Blood and urine arsenic concentrations are elevated in symptomatic arsenic poisoning, but the range of values reported in the literature for similarly affected patients is extremely variable. This variability may reflect differences in the timing of collections, renal function, the impact of treatment, and laboratory precision. The total arsenic concentration in whole blood in severely affected patients has been reported to range from a few hundred to a few thousand micrograms per liter, and total urinary arsenic has ranged from a few hundred micrograms per liter to several thousand micrograms per liter. In one of the only reports of speciated urine arsenic measurements after acute arsenic poisoning, marked elevations of inorganic arsenic and its methylated metabolites were detected, with the latter increasing in preponderance over 5 days [136]. Although total (and potentially speciated) urine arsenic levels and total whole-blood arsenic

Table 3 Treatment of acute arsine poisoning

Supportive Care
In patients with evidence of hemolysis (especially plasma hemoglobin ≥ 1.5 g/dL [≥ 15 g/L]), perform exchange transfusion with whole blood
Maintain vigorous urine output with intravenous fluids and mannitol (osmotic diuresis)
Perform hemodialysis as needed for progressive renal insufficiency
Chelation
Currently available chelating agents are of uncertain benefit in arsine poisoning (see text)
In first 24 h, BAL may be beneficial: 3.0–5.0 mg/kg intramuscularly every 4–6 h
Beyond first 24 h, DMPS (oral or parenteral) or DMSA (oral) in patients with evidence of severe intoxication may offer some clinical benefit.
<i>DMPS</i> dimercaptopropanesulfonic acid or unithiol, <i>DMSA</i> dimercaptosuccinic acid or succimer

levels should be ordered for confirmatory or forensic purposes, the diagnosis usually can be established by the history, the clinical picture, and the pattern of common laboratory tests (urinalysis, CBC, and serum chemistries). In any case, the prompt and often intensive supportive care (Table 3) required in acute arsine poisoning should not be delayed pending the return of arsenic analyses. If industrial hygiene data on the patient's actual or estimated arsine exposure are available, this may help to confirm the diagnosis. The acute exposure guideline levels (AEGL) for arsine developed by the U.S. National Research Council [99] reported that disabling effects (AEGL-2) might result from 30 min of exposure to equal to or greater than 0.21 ppm, 1 h of exposure to equal to or greater than 0.17 ppm, or 8 h of exposure to equal to or greater than 0.02 ppm. Life-threatening or lethal effects (AEGL-3) could result from 30 min of exposure to equal to or greater than 0.63 ppm, 4 h of exposure to equal to or greater than 0.13 ppm, or 8 h of exposure to equal to or greater than 0.06 ppm. No toxicity or systemic arsenic absorption was observed in a hairless mouse model involving exclusive dermal exposure to 300 ppm arsine for 5 min, suggesting that percutaneous absorption will not pose a risk to workers or first responders with adequate respiratory protection [137].

An important element in the differential diagnosis of arsine poisoning is poisoning by stibine (SbH_3), the hydride gas of antimony. Stibine, a potent hemolytic agent that may cause signs and symptoms similar to those of arsine, is also liberated under similar occupational circumstances, such as contact of antimony-containing alloys or compounds with acidic solutions. Acute high-dose exposure to lead may result in a constellation of signs and symptoms that overlap with arsine poisoning, including acute central nervous system effects (headache or encephalopathy or both); abdominal pain; acute hemolysis; mild-to-moderate elevations in liver function tests; and short-term, mild-to-moderate renal insufficiency. The tempo of severe acute lead intoxication is seldom as rapid as that seen with acute arsine intoxication, however. The hemolysis associated with severe acute lead intoxication is not as extensive as that due to arsine, and the acute renal insufficiency is not a consequence of hemoglobin deposition or acute tubular necrosis. Certain stages of malaria due to infection with *Plasmodium falciparum* may resemble clinically arsine poisoning, with patients displaying hemolysis ("blackwater fever"), renal failure, gastrointestinal symptoms, and occasionally central nervous system symptoms. Patients with paroxysmal nocturnal hemoglobinuria may present with hemolysis and abdominal pain.

Treatment

Arsenic

The treatment of acute arsenic poisoning is summarized in Table 4.

Supportive Care and Decontamination

Treatment of acute arsenic poisoning requires supportive care (usually in the intensive care unit), possibly decontamination, and prompt use of specific chelating agents. Immediate supportive care should address the hypotension or incipient shock that often accompanies the increased vascular permeability and the gastrointestinal fluid loss from vomiting and diarrhea that is common in acute arsenic poisoning. Large volumes of

Table 4 Treatment of acute poisoning by inorganic arsenic

Supportive Care and Decontamination
Intravenous rehydration with crystalloid solutions
Vasopressor drugs
In patients with gastrointestinal fluid loss and hypotension, use as needed to support blood pressure and optimize urine output (≥ 1 mL/kg/h)
Sodium bicarbonate (as needed for severe metabolic acidosis)
Whole-bowel irrigation may be beneficial if there is a substantial amount of arsenic in the gut
<i>Avoid</i> phenothiazines and type 1a antiarrhythmics
Chelation^a
Agent of first choice: DMPS
(2,3-dimercaptopropanesulfonic acid, unithiol, Dimaval)
Administer intravenously 3–5 mg/kg every 4 h by slow infusion over 20 min
Agent of second choice if DMPS not immediately available: BAL
Administer intramuscularly 3–5 mg/kg every 4–6 h
When patient stable and able to absorb an oral medication, consider change to oral chelation with either
DMPS 4–8 mg/kg orally every 6 h
DMSA (2,3-dimercaptosuccinic acid, succimer):
7.5 mg/kg orally every 6 h, or 10 mg/kg every 8 h

^aDMPS and DMSA are not officially approved in all countries for chelation treatment of acute arsenic poisoning. Indications and dosages are the author's suggestion based on best available data

intravenous fluids may be needed to support blood pressure and maintain urine output. Moderate to high levels of urine output (1 mL/kg/h) are desirable because the kidney is the major route of arsenic excretion (Grade III recommendation). Because arsenic may result in congestive heart failure or noncardiogenic pulmonary edema, however, typically after several hours to days, determination of optimal fluid requirements ultimately may require invasive hemodynamic monitoring. Support with vasopressor agents, such as norepinephrine, or treatment of acidosis with bicarbonate may be indicated in severe cases. It may be prudent to avoid the use of phenothiazines as antiemetics or antipsychotics in these patients because these drugs may lower the seizure threshold or prolong the QT interval.

The potential development of malignant arrhythmias merits continuous cardiac monitoring

for at least the first 24–48 h in arsenic-poisoned patients who present with any initial electrocardiogram abnormality or whose other presenting symptoms or signs (e.g., gastrointestinal distress, hypotension, metabolic acidosis, or altered mental status) indicate significant acute intoxication. Monitoring beyond 48 h is indicated in patients with persistent symptoms or evidence of new (i.e., not preexisting) cardiovascular disturbances. These signs may include electrocardiogram abnormalities (e.g., tachycardia, ectopy, prolonged QT_c interval, U waves) or evidence of congestive heart failure, even to a mild degree. Antiarrhythmic drugs such as procainamide and other type 1a agents, which may exacerbate arsenic-related prolongation of the QT interval, should be avoided.

Indications for ICU Admission in Arsenic or Arsine Poisoning

Intensive care unit (ICU) admission is indicated for any patient with a history of acute ingestion of milligram quantities of inorganic arsenic or any patient with suspected arsenic ingestion who presents with overt signs of gastrointestinal, cardiovascular, or neurologic disturbance. Gastrointestinal manifestations, such as vomiting, diarrhea, or abdominal pain; cardiovascular findings, such as tachycardia or hypotension; or alterations in mental status, such as lethargy or agitation, may be followed abruptly by life-threatening shock, arrhythmias, or seizures.

Because of the potential for delayed cardiovascular or neurologic deterioration (congestive heart failure, noncardiogenic pulmonary edema, malignant arrhythmias, encephalopathy) continued ICU monitoring may be necessary for several days to a week after acute gastrointestinal symptoms or hypotension has been stabilized. Careful ongoing monitoring is indicated particularly in patients whose urinary arsenic concentration has been elevated markedly (e.g., >5000 $\mu\text{g/L}$ [66 $\mu\text{mol/L}$]) or in patients who exhibit prolongation of the QT_c interval on an electrocardiogram. Patients with

(continued)

arsenical peripheral neuropathy who display progressive signs of ascending motor weakness should be observed carefully for the abrupt appearance of neuromuscular respiratory failure.

Patients with known or suspected arsine intoxication should be admitted to the ICU, treated expectantly with vigorous intravenous hydration, and monitored carefully for progressive hemolysis and any compromise in cardiovascular, renal, or neurologic function. Because arsine-induced hemolysis may be associated with a latent interval of 2–24 h, patients who initially are asymptomatic still may merit careful overnight observation.

Gastrointestinal decontamination of retained arsenic is theoretically useful, but in practice the profuse vomiting that accompanies acute arsenic poisoning may obviate or preclude intervention. As noted previously, abdominal x-rays (and occasionally chest x-rays) may reveal the presence of radiopacities consistent with gastrointestinal retention of poorly dissolved arsenic. In these cases, it may be prudent to perform whole-bowel irrigation to hasten removal of this unabsorbed material [114, 138–142]. In one case in which a chemist deliberately ingested the massive quantity of 54 g of arsenic trioxide, intraoperative gastric lavage and endoscopy were unable to remove arsenic adherent to the gastric mucosa, and a gastrotomy was performed [67]. Colonoscopy and colonic irrigation have been used to remove poorly soluble arsenic that persisted in the proximal colon [67, 140]. Administration of oral activated charcoal often has been recommended, but because the binding affinity of activated charcoal for inorganic arsenic is extremely low *in vitro*, the clinical utility of this intervention is doubtful [143]. The detection of arsenic in human gastric aspirates 1 week after the last known ingestion raises the possibility that arsenic may undergo a degree of enterohepatic or enteroenteric circulation [14, 82], but the extent of this process has not been quantified, and a

potential approach to interdict it with alternative binding agents has not been studied in humans.

Hemodialysis may increase arsenic elimination in patients with marked oliguria or anuria secondary to arsenic-induced acute failure, but because of the rapid distribution of arsenic to extravascular compartments, the total amount removed by this route (on the order of a few milligrams) is miniscule compared with the amount responsible for the intoxication or the amount eliminated via the urine in nonoliguric patients [14, 47, 51, 144–146]. Because the oliguria associated with acute arsenic intoxication is generally due to hypotension and decreased renal blood flow rather than to acute tubular necrosis, fluid resuscitation to support blood pressure and maintain urine flow rates should be the focus of therapy (Grade II-3 recommendation). Hemodialysis or continuous veno-venous hemodiafiltration [54] should be considered only for patients with renal failure from another cause or patients whose oliguria or anuria is otherwise unresponsive.

Patients who develop delayed peripheral neuropathy should be monitored carefully for progressive involvement of the proximal musculature. There is a risk that neuromuscular respiratory failure might ensue abruptly when there is evidence of proximal limb weakness. Patients with this level of ascending motor involvement should undergo serial measurements of inspiratory muscle effort, and the possible requirement for mechanical ventilation on an emergent basis should be anticipated. Physical therapy is an important adjunctive measure in the recovery from arsenical neuropathy. Tricyclic antidepressants, such as amitriptyline, have efficacy in the treatment of neuropathic pain (Grade I recommendation) and thus may be of value in treating the painful dysesthesias that often occur in arsenic-induced peripheral neuropathy [147] (Grade III recommendation).

Chelation

The prompt use of chelating drugs in the treatment of acute arsenic poisoning is recommended. The value of this treatment is based on the results of animal experimentation, however, and the therapeutic efficacy of chelation has not been

established through carefully controlled human clinical trials [148]. The first chelating agent, dimercaprol (2,3-dimercaptopropanol), was developed by British scientists during World War II as a specific antidote for acute poisoning by the vesicant organoarsenical warfare agent lewisite [31, 149]. As noted earlier, dimercaprol often has been referred to as *British antilewisite* or *BAL*. Water-soluble analogues of dimercaprol, dimercaptopropanesulfonic acid (DMPS Unithiol, Dimaval), and dimercaptosuccinic acid (DMSA, succimer, Chemet) were developed as heavy metal chelators in the 1950s [150, 151] and offer the advantage of higher therapeutic index and delivery by oral and intravenous routes [152]. Animal experiments have shown that dimercaprol, DMPS, and DMSA increase survival in experimental animals administered lethal doses of arsenite [153, 154]. The effectiveness of chelation on survival declined, however, in proportion to the length of time after arsenic exposure that treatment was begun [153, 154]. In an early study of the effectiveness of chelation against poisoning by organoarsenicals in rabbits, a single dose of dimercaprol given within 5 min of the arsenical resulted in survival of all the test animals, compared with a zero survival rate when treatment was delayed for 6 h [155]. In humans exposed experimentally to low doses of diphenylcyanoarsine smoke, the percent increase in urinary arsenic excretion after dimercaprol was higher the sooner after exposure it was administered [156]. These experimental studies and limited clinical experience [62] suggest that chelation treatment begun within a few hours after acute arsenic ingestion offers an improved chance of a positive therapeutic outcome. Nevertheless, in many cases, death or delayed peripheral neuropathy has occurred despite prompt chelation treatment [14, 46, 48, 50, 66, 119, 157]. The clinical course of an incipient or established arsenical neuropathy, usually characterized by slow improvement over several months to years, generally is not influenced by chelation therapy [53, 62, 64, 70, 71]. Isolated case reports have associated chelation with more rapid resolution of arsenical neuropathy [158, 159], but because improvement would have been anticipated from the natural

history of the illness, the added therapeutic role of chelation in these cases cannot be determined.

Of the chelating agents currently available, DMPS has the most favorable profile for the treatment of acute poisoning by inorganic arsenic. Although available as a pharmaceutical agent (Unithiol; Oktyabr) in the Soviet Union since the 1960s and in Germany since the 1970s (Dimaval; Heyl), DMPS has become available only more recently in the United States. Since 1999, DMPS has been sold legally in the United States as a bulk drug substance available for use by compounding pharmacists [160].

DMPS offers several advantages over BAL the chelating agent traditionally used for the treatment of arsenic poisoning in the United States and the United Kingdom, since its introduction in the 1940s [161]. DMPS has a higher therapeutic index and potency ratio in the treatment of experimental acute arsenic poisoning in animals [152, 154, 162]. DMPS was more effective than dimercaprol in mobilizing and decreasing the arsenic content of numerous tissues in animal models. This increased effectiveness was particularly noteworthy in the brain, where dimercaprol resulted in an *increase* in arsenic content compared with a significant decrease after use of DMPS [152, 154, 163]. The water-soluble nature of DMPS enables it to be given intravenously, in contrast to BAL which is supplied dissolved in oil for administration by deep intramuscular injection only. The intravenous dosing available for DMPS allows more rapid delivery to the target tissues, especially in arsenic-poisoned patients who are hypotensive or in shock. In the therapeutic doses used to treat heavy metal poisoning, DMPS seems to be tolerated better than dimercaprol and in particular avoids the pain and discomfort associated with repeated intramuscular injections. Moreover, the administration of DMPS results in the formation of a DMPS-MMA^{III} complex, the only intact arsenic-chelator complex ever to be isolated in human urine [164, 165]. The clinical pharmacology of DMPS is discussed in detail in ► Chap. 168, “Unithiol.”

For patients in the initial stages of acute inorganic arsenic poisoning, DMPS is usually administered intravenously at total daily doses of

20–30 mg/kg/day. One sixth of the total daily dose every 4 h, or one-eighth of the total daily dose every 3 h, may be given by slow intravenous infusion over 20 min [166, 167]. Moore and associates [61] reported an initial intravenous dose of 5 mg/kg every 4 h; others have used or recommended a fixed dose of 250 mg (one 5 ml vial containing 50 mg/ml) every four hours [159, 165, 168, 169]. Continuous infusion of DMPS at an initial rate of 250 mg/h for 15 h, combined with high volume fluid administration, was used to treat an adult who presented with vomiting and abdominal pain 7 h after ingesting at least 1000 mg arsenic trioxide. Arsenic compounds totaling 987 mg (!) were recovered in the urine during that treatment interval [170].

Because it is important that chelation be started as soon as possible after arsenic ingestion, BAL should be used if DMPS is not immediately available (Grade II-3 recommendation). Dimercaprol is administered at doses of 3–5 mg/kg intramuscularly every 4–6 h. A switch from parenteral to oral chelation is appropriate when the patient has no signs of adverse gastrointestinal effects (e.g., nausea, vomiting, diarrhea, abdominal pain) and no signs of cardiovascular compromise (e.g., hypotension or decreased urine output), which might be associated with decreased absorption of medication administered through the oral route. Chelation can be continued with oral preparations of DMPS. An adult daily dose of 1.2–2.4 g administered in 12 divided increments has been recommended (i.e., 100–200 mg every 2 h) [171], but considering the elimination kinetics of DMPS [172], it is reasonable to administer a daily dose of 20 to 30 mg/kg/day in four divided doses (i.e. at 6 hour intervals).

The dimercapto chelating agent DMSA also can be used for treatment of arsenic poisoning when an oral agent is appropriate. DMSA has exhibited clinical efficacy and pharmacodynamic properties similar to those of DMPS in animal studies of acute arsenic intoxication [152, 154]. It can be administered at a total daily dose of 30 mg/kg/day. Although a dosing interval of every 8 h has been recommended for chronic lead intoxication, more frequent dose intervals (e.g., every 6 h) may be more appropriate for acute arsenic poisoning. The possibility that oral

chelation with DMPS or DMSA might increase absorption of arsenic retained in the intestinal tract has not been studied directly, but negative studies with other metals and these chelators suggest that enhanced absorption of arsenic is not likely to be a problem [173, 174]. D-Penicillamine has been shown to be ineffective in experimental arsenic intoxication [152, 175], and its use in human arsenic poisoning is not recommended. The clinical pharmacology of DMSA is discussed in ► Chap. 165, “Succimer.”

The optimal duration of chelation treatment for acute or subacute arsenic intoxication is not well established. In cases in which the intoxication is not rapidly lethal, hemodynamic stabilization and resolution of gastrointestinal symptoms may enable parenteral chelation to be switched to oral chelation after 2 or 3 days. It may then be appropriate to continue oral chelation at least until urine arsenic excretion decreases to less than 500 µg/24 h, or 400 µg/L (5 umol/L), urinary values that are lower than values associated with overt clinical effects in acutely exposed individuals. Alternatively, oral chelation might be continued until urinary arsenic excretion decreases to background levels (<50 µg/L [0.7 umol/L]), although the therapeutic benefit of extending chelation to this point is undetermined. A randomized, placebo-controlled clinical trial found no benefit of DMSA in the treatment of chronic arsenic poisoning in patients who already had been removed from ongoing exposure and whose urine arsenic levels were less than 50 µg/L [0.7 umol/L] [176].

Arsine

Prompt exchange transfusion of whole blood is a key therapeutic intervention in acute severe arsine poisoning. The value of exchange transfusion is supported by clinical reports [102, 135, 177, 178] and by mechanistic studies suggesting that the *in vivo* reaction of arsine with a hemoprotein, such as oxyhemoglobin, is an important step in the toxic effects of the gas [40, 43] (Grade III recommendation) [179]. Beneficial effects of exchange transfusion include (1) clearance from the blood of a toxic byproduct or complex formed

by arsine's reaction with hemoglobin; (2) removal of plasma hemoglobin or hemoglobin degradation products released by hemolysis, which then may precipitate in the renal tubules and cause acute tubular damage; and (3) restoration of a sufficient supply of intact erythrocytes to provide adequate oxygen delivery to the kidney and other tissues. A relatively simple technique of exchange transfusion in which whole donor blood is infused through a central line at the same rate of blood removal via a peripheral vein using a blood donor set has been described [180]. Other approaches have used modifications of hemodialysis circuits [181]. Exchange transfusion is recommended in any patient with suspected arsine poisoning exhibiting evidence of significant hemolysis. A plasma or serum hemoglobin level of 1.5 g/dL (15 g/L) or greater has been suggested as a level that merits this therapy [135], but given the delay inherent in securing the necessary donor blood, it would be prudent to plan for the implementation of exchange transfusion in patients with lesser but rapidly escalating plasma hemoglobin levels. Evidence of renal insufficiency or incipient acute tubular necrosis also is an indication for exchange transfusion in arsine-poisoned subjects. Prompt exchange transfusion in patients with arsine hemolysis may avert significant renal failure in some, albeit not all, cases [107, 135].

Maintenance of vigorous renal output with intravenous fluids and mannitol-induced osmotic diuresis also may be protective against hemoglobinuric renal failure and should be started promptly in all patients with evidence of hemolysis or significant arsine exposure (Grade III recommendation). Hemodialysis is indicated in cases of progressive oliguria and anuria. The toxic complexes or byproducts formed by the action of arsine on hemoglobin and other proteins in the blood may not be removed adequately by hemodialysis however [182], and hemodialysis should not be considered a substitute for exchange transfusion.

The value of chelating agents in the treatment of arsine poisoning is uncertain. In experimental arsine poisoning, 1 mM of BAL in human blood *in vitro* 5 min after exposure to arsine (2000 ppm) reduced observed hemolysis to 17% compared

with 33.3% in controls (i.e., a 50% decline in hemolysis) [183]. Although experiments with arsine-poisoned rabbits treated with dimercaprol within 30 min yielded a decline in observed lethality, the dose of BAL used was high, and the authors considered the observed results to be erratic [183]. A derivative of dimercaprol, 2,3-dimercaptopropyl ethyl ether, was more effective than dimercaprol in experimental studies of arsine poisoning, but further drug development was not pursued [183]. Soviet researchers reported that a highly lipid-soluble aryl thioether analogue of dimercaprol, 2,3-dimercaptopropyl-p-tolylsulfide (Mercaptide), was effective in experimental acute arsine poisoning in rats, whereas water-soluble DMPS was completely ineffective [184]. Rael and colleagues [40] found that preincubation of human erythrocytes with high concentrations of DMSA or DMPS *in vitro* diminished hemolysis after subsequent exposure to arsine. In human case reports of arsine poisoning, the administration of dimercaprol has not yielded clinical impressions of therapeutic efficacy [102, 185], but because clinical circumstances of poisoning and treatment are variable, little can be concluded from reports of this nature. It seems reasonable to initiate treatment with dimercaprol, a relatively lipid-soluble chelator, in patients who present in the early stages of acute arsine poisoning (i.e., within 24 h). Later in the course of poisoning, treatment with oral DMSA or DMPS may exert some benefit in countering the adverse effects of arsenite, which eventually is produced *in vivo* after arsine poisoning [136]. The treatment of acute arsine poisoning is summarized in Table 3.

Special Populations

Pregnant Patients

Transport of arsenic across the placenta has been documented in animal models [186] and confirmed in studies of pregnant women exposed to elevated concentrations of arsenic in drinking water [187]. The developmental toxicity of arsenic has been reviewed [26, 37, 188]. Animal

studies indicate that inorganic arsenic can cause malformations, prenatal fatality, and decreased fetal weight, usually at maternal exposures greater than 1 mg/kg/day [26]. Arsine exposure of pregnant rats and mice at concentrations of 0.025 ppm, 0.5 ppm, and 2.5 ppm resulted in increases in maternal spleen weight at the highest dose, but fetotoxicity was not observed [189]. A number of epidemiologic studies, including prospective cohort studies, have observed an adverse effect of environmental arsenic exposure on intrauterine growth and fetal and infant survival [190, 191].

Two reports of pregnant women acutely poisoned with inorganic arsenic showed transplacental transport resulting in fetal or neonatal death. A 17-year-old woman who was 30 weeks pregnant developed abdominal pain, vomiting, hypotension, and acidosis shortly after ingestion of approximately 400 mg of arsenic trioxide [192]. A single dose of BAL was given 24 h postingestion. The patient developed renal insufficiency and disorientation but subsequently recovered. A premature infant born 4 days after the arsenic ingestion had an Apgar score of 4 and hyaline membrane disease and died 11 h after delivery. Autopsy revealed elevated levels of arsenic in the infant's organs. A 39-year-old woman who was 28 weeks pregnant developed the acute onset of slight abdominal pain and hypotension after eating chocolate later found to contain a large amount of arsenic trioxide [55]. The mother survived after a stormy course that included cardiopulmonary failure and moderately severe peripheral neuropathy. Intrauterine fetal death was confirmed on day 5, and 3 days later a maternal urine arsenic concentration of 5800 µg/L (77 µmol/L) was reported. Examination of the organs of the aborted fetus revealed markedly elevated levels of arsenic.

The chelating agents DMPS and DMSA reduced, but did not eliminate, embryotoxic and teratogenic effects of sodium arsenite (12 mg/kg) in pregnant mice [193, 194]. The protective effects occurred only with high doses of the chelating agents (≥ 150 mg/kg), administered within 1 h of the arsenite. Nevertheless, these beneficial effects, combined with the apparent lack of adverse reproductive effects of the chelators

given alone at therapeutic doses, suggest that pregnancy should not be considered a contraindication to chelation with DMPS or DMSA in a patient with acute arsenic poisoning [195, 196].

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Together with zinc and mercury, cadmium belongs to group IIb of the periodic table. It can be found in rocks, soil, water, coal, zinc ore, lead ore, and copper ore. In the environment, cadmium is present predominantly as the oxide or as the chloride, sulfide, or sulfate salt. It has no recognizable taste or odor. Cadmium sulfide, carbonate, and oxide salts are practically insoluble in water, whereas the sulfate, nitrate, and halides are soluble in water.

Cadmium is utilized widely in industry for the production of glass and metal alloys as well as many consumer products, such as batteries or pigments in plastics. Exposure to relatively high cadmium concentrations occurs predominantly in the workplace. Workers also can be exposed during welding and soldering. Cadmium oxide is the compound most frequently inhaled. Cadmium is also present in tobacco smoke.

Biochemistry and Kinetics

The major route of cadmium exposure for the nonoccupational setting and nonsmoking persons is via food (e.g., leafy vegetables or potatoes). Normal daily exposure is approximately 30 µg/day, of which about 1–3 µg/day is absorbed. In smokers, 2–6 µg/day can be absorbed. The smoke of one cigarette contains about 1–2 µg of cadmium.

In water, insoluble cadmium salts can be solubilized with changes in pH. Consequently,

This chapter was submitted shortly before the death of Dr. Meulenbelt, a sophisticated medical toxicologist, highly respected intensivist, and a great friend. He will be sorely missed.

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insoluble cadmium compounds, such as cadmium oxide and carbonate, can dissolve at gastric pH. Iron deficiency increases cadmium absorption, whereas oral zinc supplements decrease its absorption [1]. Approximately 25% of cadmium administered with food is still retained after 3–5 days. Retention decreases to approximately 6% after about 20 days [2, 3]. Whole-body retention ranges from 1.2% to 7.6% (mean 2.7%) [4]. Following Satarug et al. a safe daily intake of cadmium should be kept below 25–30 $\mu\text{g/day}$ per person [5, 6]. The Permissible Exposure Limit, or PEL, which defines the limit to which an employee may be exposed to cadmium in the workplace is set at 5 $\mu\text{g}/\text{m}^3$ air [7]. The Separate Engineering Control Air Limit, or SECAL, apply to select and defined industries and processes, is 15 or 50 $\mu\text{g}/\text{m}^3$ for cadmium, depending on the processes involved [7].

Depending on the kind of cadmium compound and particle size, 50% of inhaled cadmium can be absorbed. Some authors stated that exposure to relatively more soluble compounds in biologic fluids seemed to be relatively more harmful [8, 9], but this was not confirmed by others [10]. The initial lung burden declines slowly after exposure [9, 11, 12]. Most inhaled or ingested cadmium is excreted in the feces. The excretion of cadmium via the kidneys is low.

Cadmium (+2) ions bind to anionic groups (especially sulfhydryl groups) in proteins (notably albumin and metallothionein) [13]. They are absorbed by the intestinal mucosa, after which a cadmium-metallothionein complex is transported to the target organs. Cadmium does not undergo any direct metabolic conversion, such as oxidation, reduction, or alkylation. The cadmium concentration in most tissues increases with age, especially in the kidneys and liver. The spleen, pancreas, and testes also contain relatively high concentrations after chronic cadmium exposure. After reviewing the literature, Kjellström and Nordberg [14] concluded that cadmium half-life in the kidney is 6–38 years (mean approximately 12 years) and in the liver is 4–19 years (mean approximately 7.5 years). Placental transfer of cadmium is slow and incomplete [15]. A kidney cadmium concentration of 50 $\mu\text{g}/\text{g}$ wet weight is a

maximum tolerable level in order to avoid abnormal kidney function [16]. This renal concentration corresponds to a urinary cadmium excretion of 2 $\mu\text{g}/\text{d}$ [5].

Clinical Presentation

Symptoms After Acute Exposure

Acute intoxication by inhalation of air with high cadmium levels rarely occurs except in cadmium welding, when exposure to high concentrations may cause severe pulmonary damage. During exposure, the symptoms are generally mild (comparable to symptoms seen in metal fume fever, such as cough, dyspnea, chest pain, and fever), but within a few days severe acute respiratory distress syndrome can develop, leading to respiratory failure, which can be fatal [17]. The lowest observed adverse effect level necessary in acute exposure to cause serious effects in humans seems to be 10 mg/m^3 . If a patient recovers from acute cadmium poisoning, the improvement seems to be rapid and complete. Limited data on follow-up after acute exposure are available.

Acute intoxication by ingestion may cause retrosternal pain (caused by esophageal irritation), nausea, vomiting, abdominal cramps, and diarrhea. Shock may be observed, which can be caused by fluid loss or cardiovascular depression or both. Ingestion of more than 150 g should be considered life threatening [18, 19].

Chronic Exposure

Cortona and colleagues [20] measured respiratory function parameters (forced expiratory volume, forced vital capacity, residual volume, and carbon monoxide diffusion) in 69 smoking and nonsmoking male subjects exposed for years to concentrations of 0.008–1.53 mg/m^3 of cadmium fumes in a factory producing cadmium alloys. In exposed workers, residual volume was more than 8% higher than in unexposed workers. In severely exposed workers, residual volume was increased by more than 10%.

Lung cancer risk also may be increased after long-term inhalational cadmium exposure. Stayner and coworkers [21] calculated that chronic exposure to 0.10 mg/m³ cadmium oxide dust or fume 7 days/week and 8 h/day may cause 50–111 excess lung cancer deaths per 1000 workers.

Eating or inhaling lower levels of cadmium for a long period may cause a high cadmium body burden, which may result in renal damage. The kidney is the main target organ of cadmium toxicity, particularly the proximal tubules. Although intracellular metallothionein is induced by cadmium, offering partial protection, nephrotoxicity may occur at times when this protection is insufficient. Cadmium not bound to metallothionein presumably is responsible for the cadmium-related tissue injury. The mechanism of kidney damage is not fully understood. The role of zinc transporters, calcium transporters, divalent metal-ion transporter-1, and metallothioneins in the accumulation of cadmium in the kidney cell is nicely reviewed by Yang and Shu [22]. The early stages of cadmium-induced proximal tubule injury may involve specific changes in cell-cell adhesion, cellular signaling pathways, and autophagic responses, which occur before the onset of necrosis and apoptosis [23]. The lowest observed adverse effect level for chronic inhalational exposure causing renal effects in humans has been reported to be 0.05–0.1 mg/m³, and the no-effect level is 0.02–0.05 mg/m³ [24–27]. Proteinuria has been reported at inhalational exposure levels of 0.067 or 0.0379 mg/m³ [28, 29].

There is no convincing evidence that cadmium causes hypertension. There is weak support that increased cadmium body burden may alter central nervous system function as evaluated by neuropsychologic tests [30]. A modest difference was found between cadmium-exposed and nonexposed workers in attention, psychomotor speed, and memory tests.

Cadmium exposure has been shown to alter zinc, iron, and copper metabolism, causing deficiencies of these trace elements [31]. Cadmium also influences selenium metabolism, inducing reduction in the activity of the selenoenzyme glutathione peroxidase [32].

Cadmium affects calcium metabolism. Painful bone disorders, including osteomalacia, osteoporosis, and spontaneous bone fractures, have been reported in persons chronically exposed to cadmium in food (e.g., itai-itai disease) [33, 34]. Dietary deficiencies of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects after cadmium exposure [35]. Cadmium-exposed people exhibit a progressive disturbance in renal metabolism of vitamin D to its biologically active form [16, 36, 37]. Cadmium exposure is associated with risk of renal stones [38, 39]. Mason and associates [40] reported decreased renal reabsorption of calcium among cadmium alloy workers. This decreased calcium reabsorption is presumably responsible for the higher risk of renal stones in cadmium-exposed persons.

Diagnosis

Cadmium can be measured in blood, urine, hair, and nails. The blood concentration of cadmium is the best indicator of recent exposure [41, 42]. Urinary excretion of cadmium correlates with body burden and renal damage [41, 42]. Cadmium-exposed persons with proteinuria generally have increased cadmium excretion. The urine cadmium excretion may decrease, however, if renal damage is severe [15]. Hair and nails are less reliable because they can be contaminated easily. Within 1 day after exposure, the cadmium in blood is contained mainly in the red blood cells, and the plasma concentration may be low [43]. Whole-blood cadmium concentrations normally range from 0.4 to 1 µg/L (approximately 4–9 nmol/L) for nonsmokers and 1.4–4 µg/L (approximately 13–36 nmol/L) for smokers [13]. Whole-blood cadmium concentrations of 10 µg/L (approximately 89 nmol/L) are considered acceptable for occupational exposures [44]. The urine cadmium concentration is normally less than 1 µg/g of creatinine (approximately 1 nmol/mmol of creatinine) [13]. The average urine cadmium concentration is 0.35 µg/g of creatinine (approximately 0.35 nmol/mmol of creatinine) in nonsmokers; levels greater than 2 µg/g of creatinine (approximately 2 nmol/mmol of creatinine) are rare.

Proximal renal tubular damage can be diagnosed by increased concentrations of low-molecular-weight proteins in the urine. The leakage of these proteins is not specific for cadmium toxicity but is a marker of proximal tubular damage. These proteins, such as β_2 -microglobulin, light-chain immunoglobulins, retinol-binding protein, lysosomal enzyme *N*-acetyl- β -D-glucosaminidase (NAG), and ribonuclease, are filtered by the glomerulus and normally reabsorbed in the proximal tubules of the kidney. When kidney injury is present, the reabsorption of these low-molecular-weight proteins is hampered. NAG and β_2 -microglobulin are the most commonly used biomarkers of cadmium-induced proximal tubule injury. Of these, NAG is more sensitive. A novel marker that has shown promise in preclinical studies is kidney injury molecule-1 (KIM-1). KIM-1 is a transmembrane protein that is not detectable in normal kidney but is expressed at high levels in the proximal tubule after ischemic or toxic injury. Urinary KIM-1 serves as an earlier diagnostic indicator of kidney injury when compared with any of the conventional biomarkers [45]. In severe kidney damage, high-molecular-weight proteins, such as albumin, also can be detected in urine. Decreased reabsorption of amino acids or glucose may be more sensitive for tubular dysfunction than the leakage of low-molecular-weight proteins.

Treatment

Acute Exposure

Therapy should begin by removal of the subject from the exposure. There is inadequate documentation on the usefulness of gastrointestinal decontamination in the case of ingestion of cadmium. Activated charcoal has no proven benefit after cadmium exposure. Hemodialysis and hemoperfusion are not useful in the treatment of cadmium intoxication. In cases of severe renal damage, hemodialysis is useful to replace kidney function.

In acute cadmium poisoning, chelation efficacy depends on the chelating agent used, the molar ratio between the chelator and cadmium

(Cd^{2+}), the route of exposure, and the time elapsed between exposure and the initiation of therapy. Sodium calcium edetate (EDTA), penicillamine, and British antilewisite have been used, but these seem to be of limited value and may increase kidney burden and damage [46]. Andersen [47, 48] reported that 2,3-dimercaptosuccinic acid (DMSA) was effective in acute cadmium poisoning in mice. DMSA and 2,3-dimercapto-1-propane sulfonate (DMPS) were effective in reducing mortality and reducing cadmium burden in liver and kidneys in cadmium-intoxicated mice [49, 50]. DMPS is also active intracellularly; DMSA is not. Chelation therapy for acute cadmium exposure may be useful, but this needs to be confirmed in human clinical practice. Doses of DMSA or DMPS normally used during the chelation of other heavy metals should be used (see ► Chaps. 165, “Succimer,” and ► 168, “Unithiol”, respectively, for a further discussion of these agents).

Indications for ICU Admission in Cadmium Poisoning

- Acute inhalational exposure with respiratory failure due to pneumonitis, pulmonary edema, or both
- Severe metabolic disturbances due to renal failure from chronic exposures

Chronic Exposure

The treatment of chronic cadmium poisonings is complicated by the difficulty in evaluating the body burden and the lack of data regarding chelating agents in this setting [51]. At present, chelation generally is not advised for chronic cadmium exposure. DMPS and DMSA may decrease cadmium body burden effectively. It has not been established, however, whether this therapy would decrease cadmium-induced end-organ toxicity and advice should be sought from a medical toxicologist on a case-by-case basis.

In chronic cadmium exposure, removal from exposure is of fundamental importance. Adequate

occupational hygiene, environmental monitoring, and worker surveillance are important to limit occupational vapor exposure.

Criteria for ICU Discharge in Cadmium

Poisoning

- Patient weaned from the mechanical ventilator
- Metabolic disorder mainly corrected

Key Points in Cadmium Poisoning

1. Cadmium accumulates in the body.
2. The kidney is the main target organ.
3. Measure whole-blood cadmium concentration to validate acute exposure.
4. Measure urine cadmium concentration to validate chronic exposure and increased body burden.
5. Treatment is primarily supportive.
6. The efficacy of chelation therapy is not proven.
7. In chronic cadmium exposure, be aware of osteomalacia and osteoporosis (itai-itai disease).
8. Chronic cadmium exposure is associated with risk of renal stones.

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Lead poisoning is one of the oldest intoxications known to medicine. The ancient Greek physician Galen warned that consumption of water transported through lead pipes rendered individuals “subject to disorders in the intestines” [1]. In 200 BC, Nikander of Colophon wrote that exposure to the lead oxide litharge could cause “deadly disturbances of the bowels, which, attacking with pains unexpected, overpower mankind” [2]. More than two millennia later, lead poisoning continues to be a major issue in environmental and occupational health. Although reductions in high-dose exposure have shifted the focus of public health concern to the effects of chronic low-dose exposure, overt, symptomatic lead intoxication continues to arise in a diversity of settings. In industry, it occurs predominantly in tasks associated with high-level exposure to lead dust or fume, such as welding or torch cutting of painted metal during construction or demolition, grinding or sandblasting of lead-coated surfaces, lead ore or zinc ore mining, smelting or refining of lead ores or scrap metal, repair of automotive radiators, use of powdered lead additives in fabrication of plastic, and manufacturing or recycling of lead storage batteries [3, 4]. In environmental settings, high-dose lead exposure may result from use of oral folk remedies or tonics that contain large amounts of lead (e.g., azarcon, greta, paylooah), consumption of illicitly distilled alcohol (moonshine), pica ingestion by children of lead-contaminated paint chips or lead objects, residential remodeling or repainting, and consumption of food or beverages prepared or stored in lead-glazed ceramics or lead-containing vessels. Fatal lead encephalopathy has resulted from the partial dissolution of retained lead bullets or shotgun pellets [5]. This process occurs primarily when the bullet, pellet, or lead fragment has lodged in or migrated to or is adjacent to a joint space or pseudocyst.

Chemistry and Pharmacokinetics

Lead is a soft, ductile, heavy metal that is obtained from the primary smelting of lead-containing ores, such as galena (lead sulfide) or cerussite (PbCO_3), or from the secondary smelting of

recycled lead scrap. The potential for lead intoxication is highest after inhalation or ingestion of lead that is in a soluble and readily absorbable form. These forms include fume, particulate, and glaze composed of lead oxides (litharge, red lead [Pb_3O_4]); dust or particulate composed of basic lead carbonate (white lead [$\text{Pb}(\text{OH})_2 \cdot 2\text{PbCO}_3$]), lead sulfate, or lead acetate; and solutions containing dissolved lead cations. Lead products of lower solubility, such as elemental lead, lead chromate, or lead sulfide, pose less acute risk but still may result in toxicity if the absorbed dose is high or if factors such as fine particle size, prolonged gut retention, or intraarticular contact promote in vivo dissolution. Organolead compounds, such as the oily liquid, tetraethyl lead, still used as an additive in certain aviation gasolines, are slightly soluble in water but are well absorbed by dermal, oral, and inhalational routes.

Pharmacokinetics of Inorganic Lead Volume of Distribution

Because of the affinity of lead for proteins in the erythrocyte, the initial volume of distribution of lead is low. After intravenous injection of a lead isotope to human volunteers, approximately 70–80% of the dose is present in whole blood at 7 h, and approximately 24% remains in whole blood at 20 days [6–8]. This time-dependent intravascular retention corresponds to a volume of distribution of 0.1–0.2 L/kg. With the passage of time, lead that is not excreted is redistributed predominantly to bone. Toxicokinetic studies in humans consuming stable lead isotopes over a period of months indicated that approximately 1% of lead is found in blood [9], which is consistent with a final volume of distribution of approximately 7 L/kg.

Protein Binding

At low-to-moderate concentrations of lead in whole blood, >99% of the lead is associated with the erythrocyte. The fraction of lead in the plasma increases nonlinearly with dose and may reach a few percentage points as whole-

(continued)

blood lead concentrations become $>80\text{--}100\text{ }\mu\text{g/dL}$ ($>3.9\text{--}4.8\text{ }\mu\text{mol/L}$) [10, 11]. The polymorphic enzyme δ -aminolevulinic acid dehydratase is the principal binding site for erythrocyte lead [11], and genetic polymorphisms in δ -aminolevulinic acid dehydratase seem to influence the toxicokinetics of lead and susceptibility to its toxic effects [12, 13]. Most plasma lead is protein bound, and only approximately 15% of the plasma lead is ultrafilterable [14].

Mechanisms of Clearance

Approximately 70% of total lead clearance occurs through the urine, with the balance excreted mostly in the feces and to a minor extent in sweat, hair, and nails [9, 14, 15]. Clearance from the blood is greater after acute exposure than with chronic exposure; in both cases, clearance increases exponentially with increasing blood lead concentration. After chronic exposure, urinary clearance of lead from the blood of adults has ranged from approximately 0.08 L/day at low blood lead concentrations to 0.3 L/day at high blood lead concentrations [14]. The overall temporal pattern of decline in blood lead concentration after removal from chronic lead exposure may be characterized by a multicompartiment kinetic model, composed predominantly of a fast compartment in the blood and soft tissues (half-time 1–2 months) and slower compartments in the skeleton (half-times of years to decades).

Active Metabolites

There are no known active metabolites.

Methods to Enhance Clearance

In lead-poisoned patients, chelation with chelating agents such as calcium EDTA or succimer initially may increase the rate of daily urinary lead excretion by 10-fold to 50-fold [16–23]. There is no role for enhancement of clearance by extracorporeal methods in patients with intact renal function. In patients with severe renal insufficiency, clearance may be increased by calcium EDTA chelation combined with hemofiltration or dialysis (see text).

Pathophysiology

Lead exerts a wide range of toxic effects involving multiple organ systems. The expression of lead toxicity is influenced by several factors, including the tempo and magnitude of the dose; the target organ; and the nutritional, genetic, and developmental characteristics of the host. On a biochemical level, many of the key effects of lead are mediated by interference with essential cations, particularly calcium, and interaction with enzymes and other proteins. Lead mimics or inhibits multiple cellular actions of calcium and alters calcium flux across membranes, ultimately increasing levels of cytoplasmic calcium in many cell types [24, 25]. Increases in intracellular calcium in cerebrovascular endothelium may disturb microfilaments or other cellular components responsible for the integrity of tight junctions and contribute to cerebral edema [26]. Damage to brain capillaries and interstitial edema of white matter, particularly in the cerebellum, are a histopathologic feature of lead encephalopathy [27, 28]. The increased susceptibility of juvenile animals to lead encephalopathy may be in part a consequence of the diminished ability of immature brain astrocytes to sequester lead [29].

Lead's interaction with calcium flux seems partly responsible for its myriad effects on central and peripheral neurotransmission [24]. Alterations in synaptic transmission at the neuromuscular junction of visceral smooth muscle may underlie the disordered intestinal motility and tone that occurs during lead colic [30, 31]. At low concentrations, lead can substitute for calcium in the activation of protein kinase C, which contributes to lead's amplification of glutamate-induced oxidative stress in the brain and other tissues [32]. In some neuronal cells, lead interacts with calcium-sensitive mitochondrial permeability transition pores, which results in mitochondrial depolarization and the initiation of the cytochrome-*c*–caspase cascade of apoptosis [33].

Lead's disruption of mitochondrial membranes also may contribute to the diminished incorporation of iron into protoporphyrin IX, which is a feature of lead-induced anemia. Lead interferes

with the action of enzymes and other proteins through its affinity for diverse biochemical ligands, including sulfhydryl, phosphate, and carboxyl groups. It may alter the conformation of the zinc finger motifs that are integral to the function of many DNA binding proteins, enzymes, and receptors [34]. Lead avidly binds to and inhibits the heme synthesis enzyme δ -aminolevulinic acid dehydratase. This action not only contributes to deficits in heme synthesis but also results in accumulation of heme precursors, such as aminolevulinic acid, that may have direct or indirect neurotoxic properties [35]. Lead's ability to be a potent agonist of calcium in its activation of calmodulin and protein kinase C affects multiple aspects of signal transduction. The potential for numerous additional biochemical modes of action has been documented and is the subject of ongoing research investigations. The complex interplay of these effects, which range from subtle alterations in cell signaling to overt cytotoxicity, are paralleled by the diverse manifestations of human lead intoxication.

Clinical Presentation and Life-Threatening Complications

The adverse health effects of lead include a broad spectrum of multisystemic effects, ranging from subclinical impacts on cognitive and cardiovascular function to overt, life-threatening clinical presentations. This chapter focuses on the manifestations of lead poisoning that always require acute, inpatient medical care: *lead encephalopathy* and *lead colic*. These conditions are associated with high-dose lead exposure and blood lead concentrations that usually are greater than 80–100 $\mu\text{g/dL}$ (>3.9 – 4.8 $\mu\text{mol/L}$). As a result of preventive public health measures, these severe effects are now a relatively rare presentation of lead intoxication in North America and Europe, but there continue to be outbreaks of severe lead poisoning in other areas of the world [36, 37].

Lead Encephalopathy

Lead encephalopathy is a potentially life-threatening disturbance of central nervous system function associated with an altered sensorium, ataxia or incoordination, seizures, and coma. Because lead encephalopathy usually occurs in the context of recurrent lead exposure and a progressive increase in blood lead concentration, it often is preceded by several weeks or more of prodromal neurologic and constitutional symptoms, including severe headache, fatigue, sleep disturbance, anorexia, irritability, or loss of libido. Although rare, lead encephalopathy may occur after a single high-dose lead exposure [38]. An altered level of consciousness, which is expressed variably as delirium, hallucinations, lethargy, or stupor, may follow abruptly the prodromal symptoms. Isolated or recurrent seizures are common, affecting three quarters of the subjects in one survey [39]. Generalized seizures are most typical, but focal motor seizures also may occur. In some cases, convulsions may precede any evidence of an altered sensorium. Delirium, when it occurs, may persist or intensify over days to a week, even after the patient has been removed from lead exposure. Rarely the encephalopathic patient may lapse into a coma, and death may occur in the setting of progressive cerebral edema and increased intracranial pressure.

In children exposed acutely or recurrently to large doses of lead, the appearance of lead encephalopathy usually is preceded by 1 or more weeks of antecedent symptoms, which may include headache, lethargy, anorexia, vomiting, clumsiness, ataxia, and gait disturbance. In incipient cases, there may be evidence of a recent decline in visual acuity, and reversible blindness has rarely occurred in children and adults [40, 41]. In all age groups, the classic lead-related gastrointestinal effects of colic (see later) and constipation do not always precede or accompany the emergence of even florid encephalopathy [42, 43].

The neurologic examination in lead encephalopathy is variable. Despite presentation with an altered sensorium or a history of recent

convulsions, the patient may have no apparent neurologic deficits at the time of examination. In other cases, a wide variety of positive findings may be present. Reports have noted hyporeflexia and flaccidity [44, 45] and hyperreflexia and hypertonia [46–48]. When present, ataxia frequently has been characterized as central or truncal, and an unsteady gait occasionally may be a prominent feature [49, 50]. In a few cases, there may be lateralizing findings, such as hemiparesis [39, 51–54]. There may be recent-onset strabismus, and cranial nerve palsies affecting the third or sixth cranial nerves have been noted, usually in conjunction with evidence of increased intracranial pressure [43, 44, 46, 53, 55]. Facial nerve (cranial nerve VII) palsy also may occur [44, 54, 56]. Papilledema, with or without retinal hemorrhages, was a rare finding in a series of adults with lead encephalopathy, most of whom survived [39]. Papilledema was more common with fatal lead encephalopathy in children [51], but it is a finding with low sensitivity and negative predictive value. Bulging and tense anterior fontanelles may be present on physical examination of infants with lead-induced cerebral edema and elevated intracranial pressure.

Lead Colic

Although lead colic is not life-threatening, it manifests as severe abdominal pain and usually warrants intensive care for prompt parenteral chelation, pain control, and monitoring for the possible development of lead encephalopathy. Painful lead colic generally emerges in patients with blood lead concentrations greater than 80 µg/dL (>3.9 µmol/L). Milder, nonspecific gastrointestinal discomfort and constipation may appear at blood lead concentrations greater than 60 µg/dL (>2.9 µmol/L) in some individuals. The clinical presentation of lead colic was described extensively by Tanquerel des Planches and Dana [57], who attended to 1217 cases of this disorder over 8 years. More than a century and half since its

publication, Tanquerel des Planches' classic treatise on lead diseases remains unparalleled for the detail of its bedside observations and the extent of the case material. Tanquerel des Planches [57] observed the following:

This colic pain generally consists of a violent twisting sensation. In other cases less numerous it is an acute feeling of dilacerations, tearing out, pricking, burning, boring. Sometimes this increase of sensibility is compared by the patient to a simple constriction, or rather compression, produced by a weight upon the abdomen. In this last case the abdominal pains are generally obtuse, and their progress continues to be nearly uniform. In all other cases the pain is so intense that it throws the patient into the greatest agitation, but then it is not always the same; it becomes more severe by fits, either by day or by night.

As noted further by Tanquerel des Planches [57] and other experienced observers [58], the paroxysms of pain last minutes to hours and may recur at widely variable intervals, ranging from minutes to days. The pain typically is midline but may shift superiorly or inferiorly between bouts. Obstinate constipation is almost always present ($>90\%$ of cases), often resulting in a cessation of bowel movements for several days. Rarely a patient either may maintain a normal bowel pattern or may experience diarrhea. As observed by Tanquerel des Planches [57], the abdomen is retracted in approximately half of cases of active colic, and in approximately two thirds of affected patients the pain is diminished by application of external pressure or palpation. Patients frequently press on their abdomens with both hands or shift to a prone position in a restless attempt to obtain relief. Abdominal tenderness to palpation occurs but is rare. Borborygmus was noted in three fourths of Tanquerel des Planches' cases, and vomiting occurred in one third. Despite the pain, the pulse is notably slow. The heart rate ranged from 30 to 60 beats/min in approximately 55% of the painful episodes observed by Tanquerel des Planches [57]. Blood pressure may be increased. Fever usually is absent. Although patients may be distraught and distracted by the intense pain, their sensorium usually is intact.

Other Clinical Features in Overt Lead Intoxication

Additional lead-induced medical problems may complicate the clinical presentation of lead encephalopathy or lead colic but seldom are the sole basis for inpatient medical attention. High-dose lead exposure that is chronic, but occasionally acute, may result in a predominantly *motor* polyneuropathy. Overtly affected individuals usually have blood lead concentrations greater than 80–100 µg/dL (>3.9 – 4.8 µmol/L). The classic presentation begins with weakness of the extensors of the fingers and wrists (wristdrop), but variants that primarily involve the extensors of the toes and feet or the shoulder girdle also may occur [58–60]. In chronic cases, there may be antecedent tremor. Patients with advanced neuropathy may note decreased sensation, but painful dysesthesias are absent. Patients with months to years of blood lead concentrations greater than 80–100 µg/dL (>3.9 – 4.8 µmol/L) may become emaciated and cachectic.

Rarely, jaundice may develop after acute or subacute high-dose exposure [58, 61–63], usually in association with hemolysis and indirect hyperbilirubinemia. Tanquerel des Planches [57] described the jaundice caused by heavy lead exposure to be an “earthy yellow” that was less green and bright than “common jaundice,” which he presumably associated with infectious hepatitis.

In patients with poor oral hygiene, hydrogen sulfide released by the action of oral microbes present in the gingival sulcus may react with lead in the gingival circulation to form lead sulfide [64]. This precipitate may appear as a darkly pigmented blue-gray line a few millimeters wide at the gingival margins. Although the presence of a gingival “lead line” sometimes may provide a useful clue to the presence of lead poisoning, it has low sensitivity as a diagnostic finding, as it may be absent in individuals with good oral hygiene or brief exposure [58].

Patients with chronic elevation of blood lead concentrations greater than 40–50 µg/dL (>1.9 – 2.4 µmol/L) may complain of prominent arthralgia and myalgia without evidence of localized synovitis or tenderness [65, 66]. Lead-

induced chronic renal insufficiency is associated with an increased risk of gout and gouty arthritis, a consequence of decreased renal clearance of uric acid [67–69]. As noted further subsequently, laboratory tests in a patient with overt lead poisoning frequently reveal hematologic abnormalities and less commonly renal dysfunction. Problems associated with lower-dose lead exposure, such as a history of hypertension, neuropsychologic dysfunction, developmental delay, and adverse reproductive outcome, also may be present in a patient who presents with lead colic or lead encephalopathy.

Diagnosis

Rapid, Nonspecific Diagnostic Tests

Several readily available laboratory and radiographic tests can assist in the diagnosis of overt lead intoxication. Patients with lead encephalopathy or lead colic usually have evidence of anemia on the complete blood count. The anemia may be a consequence of hemolysis associated with acute or subacute high-dose exposure [61, 63], but more commonly there is the gradual onset of a hypochromic anemia with normocytic or microcytic indices. The microcytosis often may be related to coexistent iron deficiency [70]. Iron deficiency acts synergistically with lead in depressing heme synthesis [71], and it may increase the risk of lead intoxication by enhancing gastrointestinal lead absorption [72]. Examination of the peripheral blood smear may reveal erythrocytes with basophilic stippling. The stippling is due to aggregation of ribosomal fragments in the maturing erythrocyte, possibly as a consequence of lead-induced inhibition of ribonuclease activity [73]. Basophilic stippling has been found within 3–4 days of acute, high-dose lead exposure [74, 75], and it may precede the appearance of anemia [38, 76]. The number of stippled cells sometimes increases steeply within 1–3 days after the onset of lead colic [76]. Although basophilic stippling of erythrocytes may serve as an important diagnostic clue to the presence of lead intoxication, it is neither a sensitive nor a specific finding. It also

can occur in other illnesses associated with hematologic effects, including arsenic poisoning, benzene exposure, thalassemia, and certain types of cancer.

Reticulocytosis is another hematologic finding that frequently but not invariably is present in patients with lead-induced anemia. Bone marrow examination may reveal either erythroid hyperplasia or hypoplasia, depending on whether the predominant hematologic impact has been hemolysis or suppression of erythropoiesis [77]. An increase in marrow ringed sideroblasts also may be observed. In adults, anemia due to lead exposure generally emerges at blood lead concentrations greater than 50–60 $\mu\text{g/dL}$ (>2.4 – 2.9 $\mu\text{mol/L}$), but in children an increased prevalence of anemia has been found with blood lead concentrations greater than 25 $\mu\text{g/dL}$ (>1.2 $\mu\text{mol/L}$) [78, 79].

Other common, rapidly available laboratory tests are affected less consistently by overt lead intoxication. Transitory azotemia, possibly a consequence of intrarenal vasoconstriction, may accompany lead colic [63, 80]. This condition causes moderate increases in blood urea nitrogen and serum creatinine that typically resolve within 1 month or less. The urine might transiently reveal increased cellularity on urinalysis [74, 80], but it is often entirely normal [81]. Children with high-dose lead exposure may develop a reversible Fanconi syndrome characterized by aminoaciduria, glycosuria, and hypophosphatemia with relative hyperphosphaturia [82]. However, this tubular effect usually is not accompanied by diminished glomerular filtration rate or overt renal insufficiency. The reversible renal abnormalities of acute or subacute lead intoxication should be distinguished from the irreversible interstitial and peritubular fibrosis of chronic lead nephropathy, a relatively rare condition that may appear after years of high-dose lead exposure (i.e., blood lead concentrations >80 $\mu\text{g/dL}$ [>3.9 $\mu\text{mol/L}$]) [83].

Liver function tests in severe lead intoxication may be notable for mild-to-moderate elevations in serum transaminases [63, 73, 84]. The rare elevation in total bilirubin is usually a result of hemolysis, in which case the indirect (unconjugated) bilirubin fraction predominates.

The characteristic features of lumbar puncture in patients with lead encephalopathy are an elevated opening pressure, often greater than 300 mm H_2O , and an increased cerebrospinal fluid (CSF) protein count [39, 55]. The CSF white blood cell count may be normal or slightly elevated (usually <30 white blood cells/high-power field), resulting in a mild albuminocytologic dissociation.

Several radiologic studies may be helpful in the diagnosis and management of overt lead intoxication. In patients with lead encephalopathy, computed tomography or magnetic resonance imaging of the brain frequently shows evidence of diffuse cerebral edema (e.g., effacement of the cerebral gyri or symmetrically narrowed ventricles). Other, less common findings include focal cerebellar edema [45], which may cause compression of the fourth ventricle, and obstructive hydrocephalus [46, 48]. Asymmetric compression of a lateral ventricle has also been shown [85].

In children with a history of severe lead intoxication, plain radiographs of the skeleton may reveal dense, thick, transverse opacities at the metaphyseal ends of the bones. Commonly referred to as *radiographic lead lines*, these usually are best visualized at the ends of long bones, such as the tibia, fibula, femur, humerus, radius, or ulna. Lead lines also may be apparent at the iliac crests or the tips of the scapulae [86]. The opacities are not collections of “lead” but rather are bands of increased calcium deposition associated with lead-induced inhibition of calcified cartilage resorption. Although predominantly observed in children 2–6 years old [87], radiographic lead lines also may be visible in neonates and infants [48, 88]. Discrete lead lines migrate toward the diaphysis and eventually disappear as the child grows. They are not useful as markers of lead exposure in older children or adults. In one survey of 104 lead-poisoned children and 18 age-matched controls, the mean blood lead concentration of the children with lead lines was 49 ± 17.3 $\mu\text{g/dL}$ (2.4 ± 0.8 $\mu\text{mol/L}$) [89]. The authors of the survey suggested that the presence of a dense opacity in the proximal fibula may be helpful in distinguishing lead lines from bands that occur in physiologic sclerosis, particularly in children older than 3 years of age. Lead lines may be absent

in patients with severe childhood lead intoxication, particularly in the setting of recent, acute exposure. In addition, lead lines do not form at low levels of lead exposure that nonetheless may be of public health concern. Accordingly, radiographic lead lines should not be used to screen for or rule out childhood lead poisoning. Nevertheless, lead lines should increase the index of suspicion for lead poisoning in a child with consistent signs and symptoms and should prompt an investigation for potential lead exposure whenever they are observed as an incidental finding.

Plain radiographs of the abdomen may reveal flecks of a radiopaque substance or discrete lead-containing foreign bodies (e.g., fishing weights), in the gastrointestinal tract of children or adults who recently have ingested substantial amounts of lead [75, 86, 90]. Because finely suspended or highly soluble lead formulations may be poorly visualized, however, or because the nonabsorbed portion of the ingested lead may have been evacuated by the time of the examination, the absence of suspicious radiopacities on abdominal radiographs does not rule out a significant recent ingestion. In patients with acute lead colic, abdominal X-rays may reveal focal intestinal dilation [31, 91].

Blood Lead Concentration

The blood lead concentration is the most specific and useful diagnostic test for lead intoxication. Because greater than 95% of the lead in blood occurs in the erythrocyte, the measurement is conducted on whole blood rather than serum or plasma. Blood intended for clinical evaluation of potential lead intoxication should be collected in a special trace metal evacuated tube (e.g., royal blue top in the United States) containing a small amount of ethylenediaminetetraacetic acid (EDTA) or heparin as an anticoagulant. In situations in which such a tube is unavailable, blood collected in a standard complete blood count tube (e.g., lavender top in the United States) still may yield useful information. A commercially available point-of-care blood lead testing analyzer (LeadCare II), sometimes fielded in resource limited environments, quantifies blood lead

concentrations up to a maximum of 65 $\mu\text{g/dL}$ (3.1 $\mu\text{mol/L}$) and displays a reading of “HI” (high) for more elevated samples. A technique that dilutes such “high” blood samples with uncontaminated low level blood lead obtained from unexposed donors has recently enabled the LeadCare II instrument to be used in the quantitation of blood samples containing up to approximately 400 $\mu\text{g/dL}$ (19.3 $\mu\text{mol/L}$) lead [92]. In adults, the blood lead concentration in lead encephalopathy almost always is greater than 100 $\mu\text{g/dL}$ (>4.8 $\mu\text{mol/L}$), and it is common for such cases to present first with levels greater than 150 $\mu\text{g/dL}$ (>7.2 $\mu\text{mol/L}$). Children are more vulnerable to the central nervous system toxicity of lead, and blood lead concentrations greater than 70 $\mu\text{g/dL}$ (>3.3 $\mu\text{mol/L}$) are considered to pose a risk of encephalopathy [93]. The mean blood lead concentration was 330 $\mu\text{g/dL}$ (15.9 $\mu\text{mol/L}$) among a large series of children treated for lead encephalopathy in Baltimore between 1931 and 1970 (approximate range 90–800 $\mu\text{g/dL}$ [4.3–38.6 $\mu\text{mol/L}$]) [94, 95]. The mean blood lead concentration of children who died as a result of lead poisoning in that series was similar (327 $\mu\text{g/dL}$ [15.6 $\mu\text{mol/L}$]). Among a large cohort of rural Nigerian children with elevated blood lead concentrations ($n = 972$), the odds ratio for severe neurological findings consistent with lead encephalopathy was 7.35 (95% CI 2.02–26.79) at a blood lead concentration of 100–119 $\mu\text{g/dL}$ compared to 45–64 $\mu\text{g/dL}$ and 23.96 (95% CI 7.33–78.31) at a blood lead concentration ≥ 120 $\mu\text{g/dL}$ [96]. Lead colic in adults usually occurs at blood lead concentrations greater than 80 $\mu\text{g/dL}$ (>3.9 $\mu\text{mol/L}$).

The time interval between the acquisition of an elevated blood lead concentration and the manifestation of overt symptoms is highly variable and depends in part on the tempo and intensity of the exposure and individual host factors. Exposure to massive doses of lead, which may occur with intentional oral overdose [74, 97, 98] or parenteral injection [99], may produce overt gastrointestinal or neurologic symptoms in a few hours. Individuals with acute, high-dose inhalational exposure to lead fume or dust have developed symptoms within a few days to a week [38, 61]. In one individual who ingested multiple metallic objects,

there was a documented lag time of at least 8 days between a blood lead concentration of 436 $\mu\text{g}/\text{dL}$ (21.1 $\mu\text{mol}/\text{L}$) and the development of lead encephalopathy [59]. In most cases, a patient with severe lead intoxication has been exposed to lead repeatedly over weeks to months or longer. Accordingly, most of the data linking a given blood lead concentration to a particular constellation of signs and symptoms have been derived from studies or cases in which the presumed exposure occurred in a chronic, subacute, or acute-on-chronic pattern.

The geometric mean blood lead concentration in the United States from 2011 to 2012 was estimated to be 0.973 $\mu\text{g}/\text{dL}$ (95% confidence interval 0.916–1.04 $\mu\text{g}/\text{dL}$) [100]. This represents an approximately 92% decline from the late 1970s, when the corresponding value was 12.8 $\mu\text{g}/\text{dL}$ (0.6 $\mu\text{mol}/\text{L}$) [101]. In 2012, the US Centers for Disease Control and Prevention recommended that a “reference value” blood lead concentration corresponding to the 97.5 percentile of US children age 1–5 years old assessed in the semi-annually updated National Report on Human Exposure to Environmental Chemicals be used to identify children with an elevated blood lead concentration. Blood lead concentrations across the range of 1–10 $\mu\text{g}/\text{dL}$, with no demonstrable no-effect threshold, have been associated with subclinical neurocognitive deficits in children [102, 103]. Children with a blood lead concentration equal to or greater than the reference value, which was 5 $\mu\text{g}/\text{dL}$ in 2012, should receive follow-up blood lead monitoring and investigation [104].

In all age groups, the magnitude of lead exposure and the concentration of lead in blood associated with the onset of symptomatic lead intoxication are characterized by a wide range of interindividual variability. The clinical presentation of a symptomatic patient with a high blood lead concentration is highly variable; some patients exhibit severe lead colic without any evidence of encephalopathy, whereas others with comparable blood lead levels may present with delirium and seizures without any history of gastrointestinal symptoms. Some adult or pediatric patients may be asymptomatic despite

blood lead concentrations greater than 100 $\mu\text{g}/\text{dL}$ ($>4.8 \mu\text{mol}/\text{L}$) [95]. In the recent Nigerian childhood lead poisoning epidemic associated with artisanal gold mining, 40 of 100 children with blood lead concentration at initial screening $\geq 120 \mu\text{g}/\text{dL}$ displayed no neurological features. The 97.5th percentile among the asymptomatic subset ($n = 885$ of 972 children all with blood lead concentration $\geq 45 \mu\text{g}/\text{dL}$ (2.2 $\mu\text{mol}/\text{L}$)) was 146 $\mu\text{g}/\text{dL}$ (5.8 $\mu\text{mol}/\text{L}$) [96]. This wide interindividual variability applies to the entire scope of lead-related pathology, including constitutional, neuropsychologic, and cardiovascular effects that may occur at lower exposure levels. The biologic basis for the variability in response is poorly understood but might relate in part to polymorphisms in endogenous lead binding proteins and other genetic factors [12].

Zinc Protoporphyrin and Other Indices of Lead Exposure

Lead inhibits the formation of heme by several mechanisms, including interference with the incorporation of reduced (ferrous) iron into protoporphyrin IX [105]. Zinc becomes incorporated into this precursor molecule instead, resulting in an accumulation of zinc protoporphyrin (ZPP) in developing erythrocytes. As erythrocytes with a normal concentration of heme disappear through senescence or hemolysis, there is a progressive increase in the blood concentration of ZPP or the ratio of ZPP to erythrocyte heme. In general, an elevation in ZPP greater than background levels becomes detectable within 2–6 weeks after the blood lead concentration becomes greater than 30 $\mu\text{g}/\text{dL}$ ($>1.4 \mu\text{mol}/\text{L}$). This lag time may provide information on the likely time course of a patient’s lead exposure. A high blood lead concentration in the presence of a normal ZPP suggests that the lead exposure began recently. Conversely, a high blood lead concentration with an elevated ZPP suggests that the lead exposure began more than 2 weeks ago, provided that the patient does not have another medical condition (e.g., iron deficiency or anemia of chronic disease) that also can elevate ZPP.

Measurement of the amount of lead excreted in the urine in the first 24 h after initiation of chelation may provide reassurance that a significant amount of lead has been mobilized, but as a practical matter diagnostic and management decisions should be guided primarily by the blood lead concentration. A qualitative urine “heavy metal screen” offered by some laboratories frequently is subject to false-negative results and should never be relied on to rule out lead poisoning [5]. Chelation challenge or provocation tests that measure the urinary excretion of lead after a single dose of a chelating agent, such as calcium EDTA, do not reliably reflect the major body burden of lead found in the skeleton or a patient’s long-term cumulative lead exposure [106–108]. At present, chelation challenge tests have not been validated as a means to identify patients who might derive therapeutic benefit from chelation, and their use for this purpose has been criticized [109]. Measurement of lead in bone by noninvasive x-ray fluorescence may be a useful biomarker of a patient’s long-term lead exposure, but it is not a tool for acute assessment.

Key Diagnostic Features and Differential Diagnosis

Lead encephalopathy should be considered in the differential diagnosis of patients who present with delirium or seizures and anemia. The coexistence of abdominal pain, constipation, and anemia should suggest the potential presence of lead colic. For both conditions, a history of antecedent constitutional or neurobehavioral symptoms (e.g., fatigue, lethargy, anorexia, irritability, myalgia, or headache) should increase the index of suspicion. Less commonly, there may be a concurrent history of ataxia, motor neuropathy, developmental delay (in children), or renal insufficiency or gout (in adults). Basophilic stippling of erythrocytes, a gingival lead line, and (in children) the presence of radiographic lead lines on the long bones are relatively specific clues; however, they are

insensitive findings and often are absent. Obtaining a careful environmental and occupational history is always indicated because it is likely to identify a potential source of lead exposure in many, albeit not all, cases. The ultimate diagnosis of lead poisoning should be confirmed by a sufficient elevation in blood lead concentration, but treatment for severe intoxication (see later) should not be withheld pending return of blood lead test results, which may take one or more days in many locations.

The differential diagnosis of lead encephalopathy includes a variety of infections of the central nervous system, particularly encephalitis, but also subacute meningitis and intracranial abscess. Similar to lead encephalopathy, these conditions can present with a history of headache, delirium, and seizures and can be accompanied by signs of increased intracranial pressure. Fever is often prominent in central nervous system infections but is relatively rare in lead encephalopathy. Lead encephalopathy is not associated with the CSF pleocytosis that is a feature of many central nervous system infections. Although some viral processes that cause encephalitis also may cause bone marrow depression, anemia is apt to be more common in patients with lead encephalopathy.

Patients in alcohol withdrawal can present with delirium and seizures and may have laboratory evidence of anemia and elevations in transaminases and serum bilirubin. Alcohol withdrawal generally does not cause cerebral edema, however, and patients in withdrawal usually display a hyperadrenergic state that is not a feature of lead encephalopathy. In contrast to the normocytic or microcytic anemia of lead poisoning, the anemia common in chronic alcoholism tends to be macrocytic. In certain cases, prominent cerebellar edema in lead encephalopathy can mimic a midline cerebellar tumor, and both conditions can present with signs of altered mental status and obstructive hydrocephalus. Lead encephalopathy sometimes causes lateralizing neurologic signs that resemble presentations of

subdural hematoma or focal brain edema from intracranial masses. These central nervous system lesions are not likely, however, to be accompanied by the anemia that often is found in patients with lead encephalopathy. Reye's syndrome is an encephalopathic process associated with vomiting, cerebral edema, and an acellular CSF. With rare exceptions [110], the hyperammonemia and severe liver dysfunction of Reye's syndrome are not features of lead encephalopathy. In contrast to Reye's syndrome, laboratory findings in lead encephalopathy include elevated CSF protein and anemia. Carbon monoxide poisoning can present with a history of headache, nausea, and vomiting progressing to altered mental status and convulsions, but the cerebral edema and anemia common to patients with lead encephalopathy are absent.

The differential diagnosis of lead colic includes other causes of severe abdominal pain, such as appendicitis, pelvic inflammatory disease, biliary colic, renal colic, intestinal obstruction, pancreatitis, and peptic ulcer. Gastrointestinal neoplasms can be associated with anemia, weight loss, and abdominal pain, although the pain generally is less severe and paroxysmal than that associated with lead colic. Attacks of acute intermittent porphyria and an even rarer condition, δ -aminolevulinic acid dehydratase deficiency porphyria, can share many of the features of severe acute lead intoxication, including colicky abdominal pain, constipation, nausea, and vomiting. In some cases, the gastrointestinal symptoms of porphyria are accompanied by neurologic derangements, including altered mental status, seizures, and motor neuropathy. However, severe lead intoxication is usually associated with a more profound anemia. The attacks of abdominal pain in lead colic often are accompanied by a slowing of the pulse rate, in contrast to the tachycardia of acute intermittent porphyria. A patient with sickle cell disease suffering a vaso-occlusive crisis may present with abdominal pain, joint pain, and anemia as well as altered mental status if acute CNS

vaso-occlusion is present. Although examination of the peripheral blood smear for characteristic sickle cells may facilitate the rapid diagnosis of sickle cell disease, care should be taken not to overlook the possible co-occurrence of severe lead intoxication in sickle cell disease patients [111]. CNS vaso-occlusive episodes are also more likely than lead encephalopathy to present with lateralizing neurological signs.

Treatment

Effective treatment of lead intoxication requires attention to decontamination, supportive care, and use of specific chelating drugs.

Decontamination

Ingestion of lead-containing material (e.g., paint chips, small lead weights or pellets, or lead-contaminated folk remedies or food) has been a common cause of severe lead poisoning in children and occasionally is the source of lead poisoning in adults. What visibly might appear to be a small quantity (e.g., a single paint chip, a sip of a lead-containing glaze, or a small lead fishing weight) may contain hundreds of milligrams of lead. Ingestion of lead pellets [112] and lead-based ceramic glaze [75, 113] has been associated with substantial increases in blood lead concentration within several hours. Partial dissolution of solid lead objects retained in the gastrointestinal tract has resulted in death within weeks [90, 114]. As noted earlier, radiopacities on abdominal X-rays may suggest the presence of retained gastrointestinal lead, but a negative radiograph does not rule it out. The possible presence of lead in the gastrointestinal tract should be considered in all children and many adults who present with symptomatic lead intoxication, and an aggressive approach to decontamination is indicated when there are positive radiographs or when recent ingestion is otherwise suspected.

Indications for ICU Admission in Lead Poisoning Suspected or Confirmed Lead Encephalopathy

History of potential lead exposure
 Altered level of consciousness (delirium, hallucinations, lethargy, stupor, coma)
 Seizure – focal or generalized
 Ataxia or gait disturbance (often absent)
 Prodromal symptoms of increasing headaches, lethargy, anorexia, vomiting, clumsiness, irritability, sleep disturbance; fever is uncommon

Neurologic examination findings consistent with increased intracranial pressure (often absent) – papilledema, cranial nerve palsies (especially cranial nerves III and VI), recent-onset strabismus, or decrease in visual acuity

Gingival lead line (helpful but often absent)

Neuroimaging consistent with increased intracranial pressure

Laboratory findings – anemia (common), basophilic stippling, indirect hyperbilirubinemia (rare), radiographic lead line (children only; helpful but insensitive), cerebrospinal fluid with elevated protein and relative acellularity

Blood lead concentration (whole blood) – usually $>100 \mu\text{g/dL}$ ($>4.8 \mu\text{mol/L}$) in adults, $>70 \mu\text{g/dL}$ ($>3.4 \mu\text{mol/L}$) in children

Lead Colic (Predominantly in Adults)

Severe, paroxysmal abdominal pain, often diminished by palpation, often with retraction of abdominal wall

History of severe constipation (common) or diarrhea (rare); nausea or vomiting

Slow or normal heart rate during episodes of abdominal pain

Blood concentration (whole blood) – usually $>80 \mu\text{g/dL}$ ($>3.9 \mu\text{mol/L}$)

Patients with lead encephalopathy or lead colic may present with other features of lead poisoning. In adults, these features may include motor predominant peripheral neuropathy, tremor, gout, hypertension, acute or chronic renal insufficiency, neuropsychologic

dysfunction (cognitive and behavioral), and history of adverse reproductive outcomes. In children, this may include developmental delay (neurocognitive, physical growth) and Fanconi-like renal syndrome. Because of the risk of incipient lead encephalopathy, intensive care unit admission should be considered for asymptomatic patients with extremely high blood lead concentrations ($>150 \mu\text{g/dL}$ [$>7.2 \mu\text{mol/L}$]).

Activated charcoal has relatively low affinity for many metal ions, and its potential value in reducing gastrointestinal absorption of inorganic lead is doubtful but unknown. Case reports suggest that whole-bowel irrigation may accelerate the elimination of gastrointestinal lead and diminish further absorption [115–117]. This process requires the administration of commercially available solutions of polyethylene glycol and electrolytes by mouth or per nasogastric tube at a rate of 20–30 mL/kg/h until a clear rectal effluent is achieved.

Although gastrointestinal decontamination may be desirable, many patients with symptomatic lead poisoning, particularly lead colic, have severe constipation that may limit the potential effectiveness of whole-bowel irrigation or cathartics. Suspected lead foreign bodies that exhibit prolonged radiographic retention in the gastrointestinal tract (i.e., >48 h), such as large intragastric objects or pellets lodged in the appendix, may require endoscopic or surgical removal [118–120].

Retention of lead-containing bullets, shotgun pellets, or other metallic projectiles poses a well-documented risk of severe lead poisoning when the location of the foreign body results in dissolution and systemic distribution of lead [5, 121]. The risk is greatest when the foreign body lodges or migrates into a joint space, where synovial fluid and mechanical factors accelerate breakdown of the object and dissolution of the lead [122, 123]. Severe lead poisoning also has been

reported when lead fragments have come in direct contact with bone or with fluid-filled spaces, such as paravertebral pseudocysts or a subscapular bursa [5, 124]. An isolated lead bullet fragment embedded in muscle or other soft tissue often becomes encased in fibrous tissue that permanently minimizes systemic lead exposure. Patients with retained lead bullets or projectiles who present with signs or symptoms of lead poisoning, or with high blood lead concentrations in the absence of clinical effects, should receive prompt supportive care and chelation to stabilize their condition and lower blood concentrations (see later). If radiographic evaluation determines that the retained objects are in or adjacent to a joint space, bursa, or pseudocyst or in direct contact with bone, surgical removal should be strongly considered. Successful arthroscopic extraction of a lead shotgun pellet from the knee joint has been reported [125]. Patients with retained lead foreign bodies without end organ effects and who have negligible or mild elevations in their blood lead concentrations require periodic monitoring for particle migration and blood lead elevation for at least the first year and possibly longer. Patient education and lifetime vigilance are warranted in all such cases because lead intoxication often insidiously or abruptly has emerged years to decades after the initial injury.

Health professionals involved in the diagnosis or care of a patient with lead poisoning should endeavor to have the source(s) of their patient's lead exposure investigated and controlled. Because overexposure to lead may be unrecognized or misdiagnosed, it is possible that a patient with confirmed lead intoxication may represent an "index case" indicative of unrecognized or ongoing overexposure to lead among family members, co-workers, neighbors, or other individuals in contact with the same or similar lead source(s). Employers and occupational and environmental public health agencies at the federal, state, or local level, including some with specific lead poisoning prevention programs, may be able to assist with exposure investigation and case management [126, 127].

Supportive Care

Lead encephalopathy is a medical emergency that requires management in an intensive care unit. Supportive care is targeted to three key objectives: (1) diminution or normalization of increased intracranial pressure, (2) maintenance of a urine output that permits adequate urinary lead excretion, and (3) control of seizures with anticonvulsants. Critical elevations in intracranial pressure may be signaled on examination by a progressive decline in level of consciousness, papilledema, cranial nerve dysfunction, abnormal pupillary responses, or focal neurologic deficits. Elevated intracranial pressure may be confirmed by neuroimaging or direct intracranial pressure measurement. Emergent treatment should include hyperosmolar agents (e.g., intravenous mannitol 0.25–1.0 g/kg as a 20–25% solution or hypertonic saline) as well as intubation and short-term hyperventilation initially targeted to a PaCO₂ of 30–35 mmHg [128, 129]. Because the pathophysiology of cerebral edema in lead encephalopathy involves altered permeability of the brain microvasculature, there is theoretical benefit to the use of glucocorticoids, such as dexamethasone. However, the evidence supporting their use is very limited. If seizures occur, benzodiazepines, such as diazepam or lorazepam, are the anticonvulsants of choice, with recourse to supplemental propofol, phenobarbital, or general anesthesia in recalcitrant cases. The use of phenothiazines for sedation or treatment of delirium should be avoided because they may lower the seizure threshold.

Lead is excreted predominantly through the kidney, and elimination is optimized when urine output is maintained at 1–2 mL/kg/h (Grade III recommendation). Patients with lead encephalopathy are often volume depleted due to vomiting or decreased oral intake, requiring intravenous fluid to achieve this goal. Fluid supplementation must be managed carefully to avoid volume overload and exacerbation of cerebral edema. In critically ill encephalopathic patients, optimization of fluid status may require invasive hemodynamic monitoring and intracranial pressure monitoring. In

patients without intravascular volume depletion, fluids should be minimized, and urine output should be augmented as needed with loop diuretics or by the secondary diuretic effects of mannitol administered for treatment of cerebral edema.

Transfusion of packed red blood cells may be of potential therapeutic benefit in the severely symptomatic patient with a hematocrit less than 30 and a blood lead concentration greater than 100 µg/dL (>4.8 µmol/L). The fraction of blood lead found in plasma (normally $<1\%$) increases at a supralinear rate in the presence of high blood lead concentrations or low hematocrits [10, 130]. Plasma lead has a greater capacity than erythrocyte-associated lead to cross endothelial barriers or cell membranes and partition into critical target organs, particularly the brain [131, 132]. A high blood lead concentration in the presence of severe anemia is of even greater toxicologic concern than the same level in the presence of a normal hematocrit. Transfusion of packed red blood cells in an anemic, encephalopathic patient with a high blood lead level may be of benefit by lowering the plasma fraction of lead in the blood. Anecdotal experience suggests that this intervention is of clinical value, but it has not undergone systematic study.

Before the more widespread use of chelating agents in the 1960s, adults with acute lead colic frequently were treated with intravenous injection of calcium salts, which was observed to provide rapid, dramatic relief from the abdominal pain. Hunter [133] noted, "In severe cases, it is possible, by the slow intravenous injection of 15 mL of a 20% solution of calcium gluconate, or of 10 mL of a 5% solution of calcium chloride, to relieve the pain by the time the injection is over." Hamilton and Hardy [58] commented, "So dramatic is the effect of calcium that there is no need to use morphine or atropine." Soon after the introduction of the chelating agent calcium EDTA in the early 1950s, Belknap and Perry [134] described the sequential use of calcium gluconate and calcium edetate in patients with acute lead colic, a regimen they believe combined the rapid pain relief of the former with the lead-mobilizing effect of the latter. These investigators noted the following:

Intravenous treatment with edathamil calcium disodium ($\text{CaNa}_2\text{-EDTA}$) does not give the prompt relief of lead colic which we expect within one-half hour with intravenously administered calcium gluconate. Therefore, a combination of intravenously administered calcium gluconate in alternate doses with intravenously administered edathamil calcium disodium is calculated to give immediate pain relief, combined with a sharp reduction of circulating, and therefore potentially dangerous lead.

By the mid-1960s, chelation alone supplanted the use of calcium salts in the treatment of the progressively rarer adult patient with acute lead colic. Aside from the observations of Belknap and Perry [134], there seems to be scant discussion in the literature regarding clinical experience with calcium salts or opioids as adjuncts to chelation in the treatment of this condition. Slow intravenous administration of calcium gluconate (e.g., 30 mL of a 10% solution over 20 min in an adult) could be considered as an adjunctive measure in patients with lead colic that does not promptly respond to continuous infusion of calcium EDTA.

Chelation

Several pharmaceuticals, known as *chelating agents* or *chelators*, are available for the treatment of lead intoxication. The principal agents are sodium calcium edetate (edetate calcium disodium or calcium EDTA) and the three dimercapto compounds – dimercaprol (dimercaptopropanol, British antilewisite), succimer (*meso* 2,3-dimercaptosuccinic acid, DMSA [Chemet]), and unithiol (dimercaptopropanesulfonic acid, DMPS [Dimaval]). Calcium EDTA and, in the case of the dimercapto agents, either the parent compound or the biotransformation products are thought to form relatively stable complexes with the lead atoms in vivo, enhancing lead mobilization and diminishing interaction with cellular proteins. Administration of each of the chelating agents results in reductions in blood lead concentrations and large increases in urinary lead excretion. There are no randomized clinical trials, however, that establish the ability of chelation to improve clinical outcome in lead-poisoned patients. There was no

apparent benefit of chelation on survival in one of the few controlled animal studies that examined chelation treatment of acute high-dose lead poisoning [135]. A randomized, placebo-controlled, double-blind study of chelation with succimer in children with blood lead concentrations of 25–44 $\mu\text{g/dL}$ (1.2–2.1 $\mu\text{mol/L}$) found no benefit in neuropsychologic outcome or long-term blood lead reduction [136]. For children with lead encephalopathy, the benefit of chelation has been suggested by the sharp decline in the case mortality rate since this treatment was introduced. In the 1940s, before the availability of chelating drugs, the case mortality rate for severe pediatric lead encephalopathy was approximately 65%, but it decreased to less than 5% among similar cases treated with chelation in the 1960s [55, 137, 138]. In nonencephalopathic patients with high blood lead concentrations, chelation has been advocated as a means to decrease blood lead concentration rapidly and avert possible progression to encephalopathy, a condition that potentially can result in death or permanent neurologic sequelae [49].

Various chelation regimens have been proposed over the years (Table 1). Dimercaprol was investigated as a chelating agent for lead intoxication soon after its introduction as an arsenic antidote in the mid-1940s. In contrast to its beneficial effect in acute arsenic poisoning, dimercaprol did not prolong survival in animals challenged with lethal doses of lead acetate, despite increasing urinary lead excretion [139, 140]. In these animal experiments, dimercaprol actually increased the toxicity of lead. In early human case series, dimercaprol was thought to be of possible value in severe pediatric lead encephalopathy [137], but it was considered to be less useful in adult cases, particularly patients with lead colic [141, 142]. Calcium EDTA, introduced in the early 1950s, generated far more enthusiasm for its perceived therapeutic benefit [16, 143]. Calcium EDTA replaced dimercaprol as a single agent in the treatment of lead intoxication after several pediatric case series associated it with better neurologic outcome among survivors and a higher therapeutic index [51, 144].

In a small randomized clinical trial conducted in the 1960s, Chisolm [138] observed that a

two-drug regimen consisting of dimercaprol and calcium EDTA resulted in a more rapid decline in blood lead concentration and greater urinary lead excretion than those achieved with calcium EDTA alone. By administering the highest tolerable dose of two distinct types of agents, it was thought that the overall delivery of chelating moieties could be maximized. It also was suggested that the relatively higher lipophilicity of dimercaprol mobilized lead from intracellular sites and then shifted it extracellularly, where a more stable lead-EDTA chelate could be formed [145]. In a common two-drug regimen developed for pediatric lead encephalopathy [146], treatment is begun with a priming dose of dimercaprol, 75 mg/m^2 intramuscularly, which is repeated every 4 h for a total daily dose of 450 $\text{mg/m}^2/\text{day}$. Four hours after the initial dimercaprol dose, calcium EDTA, 1500 $\text{mg/m}^2/\text{day}$, is begun by slow, continuous intravenous infusion. Calcium EDTA (Calcium Disodium Versenate) is supplied in 5-mL ampoules (200 mg/mL), which should be diluted to 2–4 mg/mL in saline or 5% dextrose for intravenous infusion. Although intramuscular injection of undiluted calcium EDTA (combined with lidocaine for local analgesia) sometimes has been advocated to minimize fluid load in encephalopathic patients with cerebral edema, the small amount of fluid required for intravenous infusion carries minimal risk and ensures efficient systemic delivery. The combined regimen of dimercaprol and calcium EDTA is continued for 5 days, although in some cases dimercaprol is discontinued after 3 days if the blood lead concentration has decreased to less than 50 $\mu\text{g/dL}$ (<2.4 $\mu\text{mol/L}$). Other two-drug regimens have used a dimercaprol dose of 4 mg/kg intramuscularly every 4 h (slightly higher than 5 mg/m^2 in an average-size child) [138]. Alternative calcium EDTA doses have included 1000 $\text{mg/m}^2/\text{day}$ (approximately 40 mg/kg/day in an average-size child) [147] or 50 mg/kg/day [148].

Dimercaprol is supplied dissolved in peanut oil in 3-mL ampoules (100 mg/mL) for deep intramuscular injection. Dimercaprol is associated with a high incidence of adverse side effects, including nausea and vomiting, hypertension, prolongation of the partial thromboplastin time, fever (particularly in children), and pain at the

Table 1 Venous blood lead level after an initial course of chelation as a percentage of pre-course value (ECP)

Study	Drug	Dose regimen	Drug administration method	Number of treatment courses	Mean pre-course VBLL ($\mu\text{g}/\text{dl}$)	ECP
Chisolm [138]	CaNa_2EDTA (i.m.) + dimercaprol (i.m.)	$12.5 \text{ mg/kg q } 4 \text{ h} \times 72 \text{ h}$ and $4 \text{ mg/kg q } 4 \text{ h} \times 72 \text{ h}$	In patient	8	272	19%
Chisolm [138]	CaNa_2EDTA (i.m.)	$12.5 \text{ mg/kg q } 4 \text{ h} \times 72 \text{ h}$	In patient	7	163	47%
Chisolm [161]	CaNa_2EDTA (i.m.)	$500 \text{ mg/m}^2 \text{ BD} \times 5 \text{ days}$	In patient	18	55	60%
Graziano et al. [160]	CaNa_2EDTA (IV)	$500 \text{ mg/m}^2 \text{ BD} \times 5 \text{ days}$	In patient	4	54	55%
Graziano et al. [160]	DMSA (po)	$350 \text{ mg/m}^2 \text{ TDS} \times 5 \text{ days} + 350 \text{ mg/m}^2 \times 15 \text{ days}$	Inpatient (5 days) then outpatient (15 days, no DOT)	6	52	50%
Liebelt et al. [220]	DMSA (po)	$10 \text{ mg/kg TDS} \times 5 \text{ days} + 20 \text{ mg/kg BD} \times 14 \text{ days}$	Outpatient (no DOT)	7	51	42%
Liebelt et al. [220]	DMSA (po)	$10 \text{ mg/kg TDS} \times 5 \text{ days} + 20 \text{ mg/kg BD} \times 14 \text{ days}$	Outpatient (no DOT)	23	31	40%
Chisolm [221]	DMSA (po)	$350 \text{ mg/m}^2 \text{ TDS} \times 5 \text{ days} + 350 \text{ mg/m}^2 \text{ BD} \times 21\text{--}23 \text{ days}$	Inpatient and outpatient	66	37	35%
TLC Trial Group [222, 223]	DMSA (po)	$350 \text{ mg/m}^2 \text{ TDS} \times 7 \text{ days} + 350 \text{ mg/m}^2 \text{ BD} \times 19 \text{ days}$	Outpatient (no DOT)	396	26	57%
Thurtle et al. [162]	DMSA (po)	$10 \text{ mg/kg TDS} \times 19 \text{ days}$; or $10 \text{ mg/kg} \times 7 \text{ days} + 10 \text{ mg/kg BD} \times 12 \text{ days}$; or $10 \text{ mg/kg BD} \times 28 \text{ days}$	Inpatient (>95% course as inpatient)	159	101	48%
Thurtle et al. [162]	DMSA (po)	$10 \text{ mg/kg TDS} \times 19 \text{ days}$; or $10 \text{ mg/kg TDS} \times 7 \text{ days} + 10 \text{ mg/kg BD} \times 12 \text{ days}$; or $10 \text{ mg/kg TDS} \times 5 \text{ days} + 10 \text{ mg/kg BD} \times 14 \text{ days}$	Outpatient (>80% as outpatient) with alternate-day DOT	2,285	62	79%

po, per os (orally); i.m., intramuscular; q, every
DOT = directly observed therapy
TDS = three times daily
BD = twice daily
VBLL = venous blood lead level
ECP = (end-course VBLL/pre-course VBLL) \times 100
Adapted from Thurtle et al. [162]

injection site. Sterile or pyogenic abscesses at the injection sites also may occur. Because it is supplied in a peanut oil vehicle, it should not be used in patients who have an allergy to peanuts. Although combined therapy with dimercaprol and calcium EDTA accelerated the decline in blood lead concentration, there is little evidence that the addition of dimercaprol to calcium EDTA monotherapy measurably improves clinical outcome [86, 138]. In 1992, a retrospective study of the treatment of hospitalized, nonencephalopathic children with blood lead concentrations of 50–60 µg/dL (2.4–2.9 µmol/L) found that treatment with calcium EDTA alone produced a greater short-term reduction in blood lead than did combined treatment with dimercaprol and calcium EDTA [149]. Patients not treated with dimercaprol displayed fewer adverse side effects. Because of dimercaprol's side-effect profile and the limited nature of the data supporting its added value, some clinicians omit it from chelation regimens of severely lead-poisoned patients, particularly adults. In encephalopathic adults with massively elevated blood lead concentrations (>400 µg/dL [>19.3 µmol/L]), treatment has been initiated with calcium EDTA alone without complications [59, 150, 151]. The dosage of calcium EDTA used in adults with lead encephalopathy or lead colic is usually 2–4 g/24 h, or approximately 30–50 mg/kg/day, administered as a continuous intravenous infusion. Although formal dose–response studies have not been conducted, limited evidence suggests that higher doses are not associated with substantive increases in urinary lead excretion [152].

Courses of treatment with calcium EDTA are limited to 5 consecutive days to diminish the risk of nephrotoxicity reported with prolonged high doses [153–155]. In patients with acute lead intoxication who receive chelation therapy soon after their lead exposure ends, the peak urinary lead excretion usually occurs within the first 2 days [51, 138, 152]. A report that an initial dose of calcium EDTA redistributed lead to the brain of rats [156] was not replicated in a more recent investigation conducted with sensitive measurement of a stable lead isotope tracer [157].

Based on clinical trials conducted in nonencephalopathic patients with blood lead concentrations less than 100 µg/dL (<4.8 µmol/L), oral succimer, a water-soluble analogue of dimercaprol, seems equivalent or slightly more effective than parenteral calcium EDTA in lowering blood lead concentrations [17, 158–160]. Oral succimer is nearly comparable to parenteral calcium EDTA in mobilizing lead into the urine [160, 161]. These clinical trials and other experimental studies and clinical reports reviewed in detail by Bradberry and Vale [23] have not established the overall clinical superiority of either drug in the treatment of lead poisoning. Accordingly, for many years succimer has been considered an acceptable alternative to calcium EDTA, or dimercaprol/calcium EDTA combination therapy, in nonencephalopathic lead-poisoned patients who are able to tolerate an oral medication.

Recent clinical experience with a large cohort of lead-poisoned children in rural Nigeria exposed to lead contaminated dust and soil as a consequence of artisanal gold mining of lead-laden ore established that oral succimer was pharmacologically effective in decreasing blood lead concentration in patients with lead encephalopathy [162]. In a subset of hospitalized children with a geometric mean pretreatment blood lead concentration of 106 µg/dL (5.1 µmol/L), the blood lead concentration had declined an average of 55% at the end of a 19 or 28 day in-patient course of oral succimer. Declines in blood lead of a similar magnitude have been observed in children in the United States chelated with either succimer or calcium EDTA ([162], Table 8).

There is some evidence that the chelating effect of succimer in humans requires *in vivo* biotransformation to form succimer-cysteine adducts [163, 164]. The possible impact of very high blood lead concentrations on this biotransformation is unknown. In a case report, oral succimer was added to a regimen that included calcium EDTA and dimercaprol for treatment of an encephalopathic child with a blood lead concentration of 550 µg/dL (26.6 µmol/L) [116]. In that case, blood lead concentrations rebounded upward when the parenteral chelators were stopped, even though succimer was continued. A

controlled retrospective study in nonencephalopathic pediatric patients with mean blood lead concentrations of 50–60 $\mu\text{g/dL}$ (2.4–2.9 $\mu\text{mol/L}$) found that two-drug therapy with succimer and calcium EDTA was equivalent to two-drug therapy with dimercaprol and calcium EDTA in lowering blood lead concentration but resulted in fewer adverse side effects [165]. A direct comparison of two-drug therapy with monotherapy was not conducted.

Succimer is supplied as 100 mg capsules (Chemet[®] in North America) or 200 mg capsules (Succicapital[®] in Europe) for oral administration. The small size of the 100 mg capsules reflects the drug's US Food and Drug Administration–approved indication as a treatment for lead poisoning in children. The medication is equally effective in adults, however. A commonly used treatment regimen consists of 10 mg/kg orally (in children, 350 mg/m²) every 8 h for 5 days, decreasing to every 12 h for the next 14 days [166]. Succimer generally is well tolerated, although adverse effects, including gastrointestinal distress, allergic skin rashes, mild reversible elevations in liver transaminases, and mild-to-moderate neutropenia, occasionally have been noted. A study conducted in primates found that oral treatment with succimer does not increase absorption of lead that may be present in the gastrointestinal tract [167]. Nonetheless, the whole bowel irrigation that is indicated in some cases of recent lead ingestion with radiographic signs of lead particles in the gastrointestinal tract (see earlier) prevents initiation of oral chelation until the decontamination process is completed. The clinical pharmacology of succimer is discussed in ► Chap. 165, “Succimer.”

The initial use of an oral medication may also be problematic in encephalopathic patients, who may have nausea, vomiting, or obtundation, or in patients with severe lead colic, in whom gastrointestinal motility often is compromised. However, in the recent pediatric lead poisoning epidemic in rural Nigeria mentioned above, 26 unintubated obtunded patients with lead encephalopathy were initially administered succimer via nasogastric tube in the resource-limited field hospital. Three of the patients died from severe lead

encephalopathy early in treatment; one developed pneumonia of uncertain etiology and recovered; the others tolerated the nasogastric administration without complication [162]. In fully resourced critical care settings, an unconscious encephalopathic patient would be intubated for airway protection prior to nasogastric administration of succimer or other medication. The sodium salt of succimer, sodium dimercaptosuccinate, has been used in the intravenous treatment of lead poisoning in the People's Republic of China, but at present this formulation is not available elsewhere. In a small study, intravenous succimer at a dose of 1–2 g/day was found to be equivalent to intravenous calcium EDTA in increasing urinary lead excretion in adults [23, 168, 169] (Grade I evidence).

Unithiol, another water-soluble analogue of dimercaprol, is similar to succimer in its capacity to decrease tissue levels of lead in experimental animals [170]. Treatment with oral unithiol has resulted in a decline in blood lead concentration and an increase in renal lead excretion in the relatively few reports of its use in the treatment of human lead intoxication [18, 171]. No published reports are available regarding the use of unithiol in the treatment of patients with lead encephalopathy or patients with extremely high blood lead concentrations (>150 $\mu\text{g/dL}$ [$>7.2 \mu\text{mol/L}$]). Unithiol is available in oral and parenteral formulations. It has been sold as a registered pharmaceutical in Germany and Russia for many years, but it only more recently became available in the United States for dispensation through compounding pharmacies [172]. Unithiol generally is well tolerated, although rare allergic cutaneous reactions and isolated cases of mild reversible transaminase elevation or leukopenia have been observed [173]. D-Penicillamine has been used for oral lead chelation but is inferior to succimer in lead mobilization [174] and is associated with a higher incidence of adverse effects [175–177]. The clinical pharmacology of these two agents is discussed in detail in their respective chapters.

The selection of a chelation regimen in a patient with symptomatic lead intoxication is influenced by the nature and severity of the clinical presentation. In patients with lead

encephalopathy or severe lead colic, intravenous calcium EDTA remains the current treatment of choice. As discussed earlier, some clinicians have advocated a combined regimen of dimercaprol and calcium EDTA, particularly in children. After 5 days, or possibly sooner if the patient is alert and able to tolerate an oral medication, the parenteral chelation agent may be replaced by an oral chelation agent, such as succimer or possibly unithiol if succimer is not available. Measurement of blood lead concentration immediately before initiation or alteration of any chelation regimen and repeat measurements 24–48 h later are indicated to confirm that blood lead levels are declining. Measurement of urinary lead during the first 24 h of chelation therapy may provide further assurance of substantive lead excretion, which can exceed several milligrams in the initial days of therapy [16, 19, 20, 22, 23]. If blood lead concentration increases after replacement of calcium EDTA with an oral chelator or if it remains greater than 100 µg/dL (>4.8 µmol/L), a second course of calcium EDTA is indicated. Each 5-day course of calcium EDTA should be separated, however, by a 2-day interval in which that drug is withheld. Further research is warranted to assess the clinical value of regimens that combine calcium EDTA with succimer or unithiol.

In adults who have symptomatic lead intoxication without evidence of encephalopathy or lead colic (usually at blood lead concentrations >60 – 80 µg/dL [>2.9 – 3.9 µmol/L]) and in children with blood lead concentrations greater than 45 µg/dL (>2.2 µmol/L) who likewise do not have encephalopathy or colic, chelation treatment may be initiated with oral succimer. Oral unithiol also may be appropriate in this setting. Because of limited experience regarding the use of succimer or unithiol as the sole chelating agent in patients with extremely high blood lead concentrations (>150 µg/dL [>7.2 µmol/L]), it is prudent to monitor the initial clinical progress and blood lead trend of such patients in an inpatient setting.

To avert potential progression to encephalopathy, which sometimes evolves abruptly after a symptom-free latent period [59], chelation is warranted for asymptomatic adults with blood

lead concentrations greater than 100 µg/dL (>4.8 µmol/L). Similarly, chelation has been recommended for all children with blood lead concentrations greater than 45 µg/dL (>2.2 µmol/L), even in the absence of symptoms [93, 148] (Grade III recommendation). Studies have observed that the urinary excretion of lead after succimer administration is influenced by at least two genetic polymorphisms [13]. Occasionally, some individuals who excrete large quantities of lead after calcium EDTA excrete considerably lesser amounts after succimer [19]. A small study of the pharmacokinetics of succimer found that clearance of the drug and its metabolites may be prolonged in lead-poisoned children relative to lead-poisoned adults [178], and another investigation observed that the half-life of succimer elimination was prolonged at elevated blood lead concentrations [179]. Although further study of these factors is necessary, the clinician should be alert to the possibility that an occasional patient may not respond to chelating agents with a substantial increase in urinary lead excretion or decline in blood lead concentration ($\geq 20\%$ by 48–96 h). Although genetic or medical factors in the patient may be responsible, the possibility of noncompliance, ongoing occult exposure, or retention of lead in the gastrointestinal tract or in a synovial cavity also should be considered.

After termination of lead exposure, the pattern of decline in blood lead concentration is approximated by a two-compartment model: a fast, initial decline reflecting clearance of lead in the soft tissues followed by a slow, second phase representing the major body burden of lead present in bone [180]. Chelating agents, which predominantly mobilize lead from the soft tissues, accelerate the initial rate of decline associated with the first compartment but exert a relatively modest impact on the second (skeletal) compartment. The ability of chelation to clear even the soft tissues of lead has limitations. In a study of juvenile primates, 77% of an injected lead isotope was retained in the body after 5 days of oral succimer, even though chelation was begun 15 min after the injection [181]. The amount of lead excreted in the urine during a course of

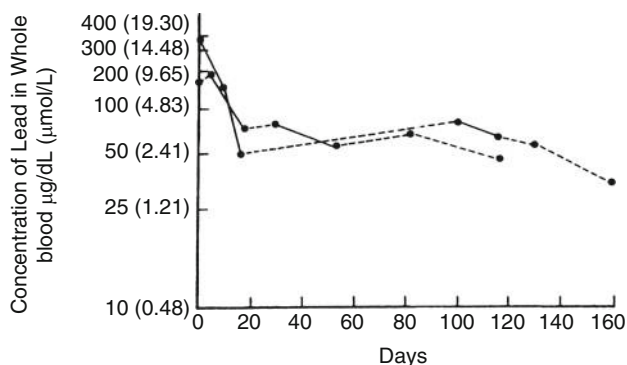


Fig. 1 Response of blood lead concentrations to brief courses of chelation therapy. Data were obtained in two patients. *Solid-line* segments show decrease in blood lead concentrations during and after therapy with calcium

disodium edetate (or dimercaprol and calcium disodium edetate), and *dashed-line* segments show trend in blood lead concentration without chelation therapy (From Moel et al. [182], with permission)

chelation, often on the order of 10 mg within 1 week in a symptomatic individual, is small relative to the hundreds of milligrams that may be present in the skeleton after chronic or recurrent high-dose exposure.

In patients with a pattern of chronic or acute-on-chronic, high-dose lead exposure, cessation of chelation typically is followed by an upward “rebound” in blood lead concentration over the next few weeks as lead in the skeleton reequilibrates with the circulation. In general, the first one or two courses of chelation have an appreciable and enduring capacity to reduce blood lead concentrations below the high values associated with major, overt symptoms. Because of postchelation rebound from bone lead stores, however, subsequent courses of chelation may have only a modest impact on the long-term pattern of decline in blood lead concentration (Fig. 1) [182]. The benefit of repeated courses of chelation in these settings has not been established [183]. A key component of successful clinical management is assurance that the patient is not discharged to an environment where hazardous lead exposure will continue and close collaboration with occupational or environmental public health agencies, social work services, outpatient case managers, or employers is important in this regard.

Prognosis

The long-term prognosis for complete recovery from severe lead intoxication in children is guarded. In a series of 425 children treated for lead intoxication published in 1966, Perlstein and Attala [49] observed neurologic sequelae in 168 cases (39%). Among a subset of 59 patients who survived lead encephalopathy, 54% were noted to have a persistent seizure disorder; 38% were described as having mental retardation (“generally of a profound type”); and 13% were said to have cerebral palsy, usually characterized by spastic hemiplegia. Although 18% were believed to have no sequelae, this and other early studies did not assess the long-term effects of childhood plumbism on subclinical neurocognitive or neurobehavioral outcome. More recent long-term prospective studies of asymptomatic children with mild-to-moderate elevations in lead exposure have found evidence of enduring subclinical deficits in cognitive function or educational performance [184–186].

The long-term outcome of adults with overt lead poisoning, including encephalopathy, has not been subject to formal prospective study, but in general these patients experience considerable improvement in symptoms after removal from

exposure and decline in blood lead concentration. Most patients experience complete recovery from gastrointestinal symptoms and anemia. Peripheral neuropathy also improves, although patients who sustained severe insults may have residual deficits. The prospect for recovery of clinical neurocognitive and neurobehavioral function is favorable, although the rate of improvement may lag behind the decline in blood lead concentration. Reduction in brain lead occurs more slowly than reduction in blood lead, particularly during chelation [28, 181]. A program of physical therapy and cognitive rehabilitation may foster improvement in neurologic function. Depending on the severity of intoxication, complete functional recovery in some patients may require 1 year or more, and occasional patients, particularly the elderly, may have persistent cognitive deficits. A study that used noninvasive X-ray fluorescence to measure lead in bone in former organolead workers found an association between past adult lead exposure and longitudinal decline in cognitive function [187].

Special Populations

Patients with Renal Insufficiency

Lead excretion in humans occurs predominantly via the kidney. In patients with lead poisoning, chelating agents initially can increase daily urinary lead excretion by 10-fold to 50-fold [17, 18, 20–23]. The effect of chelation on lead elimination in the presence of renal failure has been best characterized for calcium EDTA. In patients with moderate renal insufficiency but preserved urine output, calcium EDTA results in large increases in urinary lead excretion but at a slower rate than what occurs in patients with normal renal function [188, 189]. When treating these patients for symptomatic lead intoxication, it is advisable to decrease the administered dose of calcium EDTA by half (e.g., 1 g/24 h in an adult instead of 2 g/24 h) (Grade III recommendation).

A few case reports suggest that calcium EDTA can be combined with extracorporeal

techniques to increase lead elimination in patients with severe renal failure. A patient with chronic lead poisoning and end-stage renal failure received calcium EDTA, 500 mg intravenously, before peritoneal dialysis. The amount of lead removed in the dialysate increased 4.5-fold, resulting in elimination of 16.8 mg of lead in 20 h [190]. In another patient with chronic renal failure, calcium EDTA, 1.0 g intravenously, increased the amount of lead removed by peritoneal dialysis from a baseline of 16 µg/day to 1932 µg over 4 days [191]. Kessler and colleagues [192] used calcium EDTA, 1.0 g intravenously, 1 h before hemofiltration to increase lead removal in patients with end-stage renal failure. In like manner, administration of 1 g of calcium edetate in 250 cc normal saline intravenously over 1 h followed immediately by 4 h of hemodialysis using a high flux dialysis membrane, such as the F160, was followed by an accelerated decline in blood lead concentration [193].

Because effective lead mobilization by succimer may require biotransformation in the kidney to form a 1:2 dimercaptosuccinic acid–cysteine adduct [164, 179], there is reason to doubt its potential ability to increase lead elimination in patients with end-stage renal failure. In limited unpublished reports, succimer did not seem to increase lead clearance by hemodialysis [166].

Pregnant Patients

Lead undergoes transplacental transport, and at low-to-moderate blood lead concentrations, umbilical cord blood lead levels at delivery are approximately 85–90% of the maternal blood lead [194]. Factors that elevate the plasma fraction of maternal blood lead (e.g., high blood lead concentrations, anemia, or high maternal bone lead burden) [195] are likely to increase fetal lead exposure. High-dose lead exposure during pregnancy has been associated with an increased risk of spontaneous abortion and stillbirth. Lead has been used illicitly as an abortifacient [196], and

studies of reproductive outcome among women with relatively high occupational lead exposure in the late nineteenth and early twentieth centuries noted a high incidence of miscarriage and still-birth [197]. Contemporary epidemiologic studies generally have not detected an association between maternal blood lead concentrations less than 30 µg/dL (<1.4 µmol/L) and an increased risk of spontaneous abortion, although a nested case-control study found an odds ratio for spontaneous abortion of 1.8 (95% confidence interval 1.1–3.1) for every 5 µg/dL (0.24 µmol/L) increase in maternal blood lead over an approximate range of 5–20 µg/dL (0.24–1.0 µmol/L) [198].

Epidemiologic studies have yielded mixed results regarding a possible link between low-level lead exposure and preterm delivery or low birth weight [199–203]. Recently, two large studies of maternal–infant pairs in which the prenatal blood lead concentration was less than 10 µg/dL (0.5 µmol/L) found an inverse association between blood lead and birth weight [202, 203]. Most long-term prospective studies have found postnatal but not prenatal low-level lead exposure to be associated with subclinical decrements in cognitive function [102, 204]. However, long-term prospective studies in Yugoslavia [205] and Mexico City [206] have observed an enduring impact of prenatal lead exposure on the cognitive skills of school age children. Although high-dose lead exposure has been teratogenic in animal studies, there is no established link between in utero lead exposure and structural deformities in humans [94, 204].

Animal studies found that chelating agents may reduce the fetotoxic and teratogenic effects of lead. When administered to pregnant rats simultaneously with lead, equimolar doses of calcium EDTA greatly diminished lead-induced resorptions and malformations [207]. Although the calcium EDTA transiently increased transplacental lead transfer during a 64-min infusion, maternal lead clearance was enhanced, and fetal lead content was reduced greatly at 24 and 48 h after injection [208]. Oral succimer administered to lead-exposed pregnant rats prevented lead-induced decrements in the body weight of the

offspring assessed at the time of weaning and at 13 weeks of age [209]. Despite these beneficial effects, the use of chelating agents during pregnancy is tempered by the findings in animal studies that calcium EDTA was teratogenic at therapeutic doses [210] and that succimer was fetotoxic when administered at three times the standard therapeutic dose [211]. These findings may have been mediated by impacts on trace mineral metabolism, particularly zinc in the case of calcium EDTA [210] and copper in the case of succimer [212, 213]. Judicious trace mineral supplementation conceivably might mitigate adverse effects on the fetus in the event of chelation for maternal lead poisoning. Reports of lead during pregnancy are sparse. In two cases, calcium EDTA treatment of lead poisoning during the third trimester was followed soon by delivery of a normal infant [214, 215]. Although these cases and four out of five additional reports all described in a recent review noted similar seemingly favorable outcomes [216], the therapeutic impact of chelation on reproductive outcome in this setting remains uncertain. The same applies to assessment of rare instances of exchange transfusion followed by chelation undertaken for markedly elevated blood lead concentrations in the neonatal period [217–219].

Common Misconceptions About Lead Poisoning

1. The clinical presentation of *lead encephalopathy* sometimes is mistaken for a central nervous system infection or mass lesion.
2. The clinical presentation of *lead colic* sometimes is mistaken for appendicitis, pelvic inflammatory disease, biliary colic, renal colic, intestinal obstruction, pancreatitis, or peptic ulcer disease. Although useful, an occupational and environmental history often is omitted.
3. Basophilic stippling of erythrocytes, gastrointestinal radiopacities, gingival lead

(continued)

lines, and radiographic skeletal lead lines (in children) occasionally provide useful clues, but the absence of these insensitive findings should not exclude the diagnosis.

4. An elevation in blood lead concentration ultimately should confirm the diagnosis, but treatment for clinically suspected severe lead intoxication should not be withheld pending a laboratory delay of one or more days.

Key Points in Lead Poisoning

1. Lead encephalopathy should be suspected in patients with delirium or seizures and laboratory evidence of anemia.
2. Lead colic should be suspected in patients with abdominal pain, constipation, and anemia.
3. Blood lead concentration usually is $>100 \mu\text{g/dL}$ ($>4.8 \mu\text{mol/L}$) in adults with lead encephalopathy ($>70 \mu\text{g/dL}$ [$>3.4 \mu\text{mol/L}$] in children). In lead colic, blood lead concentration usually is $>80 \mu\text{g/dL}$ ($>3.9 \mu\text{mol/L}$).
4. Lead encephalopathy and lead colic may occur independently of each other, but other antecedent multisystemic findings almost always are present.
5. Effective treatment requires attention to decontamination, supportive care, and use of specific chelating agents. Intensive supportive care for lead encephalopathy may require hyperosmolar agents (e.g., mannitol or hypertonic saline), hyperventilation, corticosteroids for cerebral edema, and anti-convulsants for seizures.

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Mercury is a naturally occurring metal that exists in several physical and chemical forms. *Inorganic mercury* refers to compounds formed after the combining of mercury with elements such as chlorine, sulfur, or oxygen. After combining with carbon by covalent linkage, the compounds formed are called *organic mercury compounds* or *organomercurials*. The most common forms of mercury in the environment are elemental mercury, mercuric sulfide (cinnabar ore, from which elemental mercury is refined by heating), mercuric chloride, and the organic mercury compound methylmercury. In the environment, methylmercury is produced by the methylation of inorganic mercury by microorganisms. This form of mercury may enter and accumulate in the aquatic food chain [1]. Major methylmercury poisonings occurred in Minamata Bay, Japan, in the 1950s after the consumption of contaminated seafood following severe industrial mercury discharge into the bay. Another mass tragedy occurred in Iraq in 1971–1972 after the consumption of bread contaminated with methylmercury used as a fungicide on seed grain [2].

All forms of mercury have specific toxicity profiles to consider on exposure. The routes of exposure, toxicokinetics, target organs, and treatments differ to a great extent [3]. Acute toxicity usually is seen after inhalational exposure to elemental mercury vapors and ingestion of inorganic mercury compounds. Exposure to organic mercury most commonly occurs as a result of ingestion of seafood or other contaminated food products [4].

Exposures to elemental mercury without appreciable clinical relevance are the following. A frequently occurring exposure, especially in children, is the ingestion of small amounts of elemental mercury from a broken oral thermometer. After ingestion, elemental mercury is absorbed poorly from a normally functioning gastrointestinal tract. Because of this limited absorption and the small volume typically ingested, these elemental mercury exposures are considered nontoxic. If gastrointestinal function or anatomy is abnormal, however, elemental mercury may be absorbed into the blood or extravasate into the peritoneal space. The same is true of elemental

mercury in the rectum from a broken thermometer. Dermal exposure to elemental mercury vapor or liquid poses a minor occupational hazard compared with inhalational exposure because skin absorption is minimal [5]. Although there has been some concern about whether mercury vapors released from dental amalgam fillings pose health risks, there is no scientific evidence of toxic effects from these exposures [6, 7].

Mercury Compounds and Sources

Elemental Mercury

Synonyms for elemental mercury are metallic mercury (Hg^0), quicksilver, liquid silver, and hydrargyrum. Elemental mercury is a silvery, shining liquid at room temperature. It is a heavy metal with a high vapor pressure of 0.002 mmHg at 25 °C. Consequently, at room temperature, some mercury evaporates. These vapors are colorless and odorless; vaporization increases significantly when mercury is heated. After accidental spills, metallic mercury and its vapors are difficult to remove. Especially in enclosed rooms, significant concentrations may be reached. If decontamination is not carried out properly, this can result in prolonged exposure. Most intoxications arise from occupational exposures, mainly in mining and extracting processes, in industrial plants as chlor-alkali plants, in dental amalgam preparation, and in the manufacture and repair of instruments such as mercury thermometers, barometers, sphygmomanometers, batteries, electrical switches, and (compact) fluorescent lamp bulbs. Part of the mercury vapor originally inside a bulb converts to mercuric oxide. Elemental and inorganic mercury can be present in herbal preparations and used in religious and spiritual remedies.

Inorganic Mercury Salts

Synonyms for and examples of inorganic mercury salts are mercurous ion (Hg^+), mercuric ion (Hg^{2+}), mercurous chloride (HgCl , calomel), mercuric chloride (HgCl_2 , corrosive sublimate), and mercuric

oxide (HgO). Inorganic mercury exists primarily as a salt of monovalent (mercurous) or divalent (mercuric) forms. Concentrations of 1–5% of inorganic mercuric salts, such as mercuric chloride, already cause irritation, vesiculation, and corrosion of the skin. Corrosive damage will also occur after ingestion [8]. Mercuric chloride is a common salt. Inorganic mercury compounds have had many uses (e.g., as antibacterials, topical antiseptics, components of skin-lightening products, paints, tattoo dyes [red mercuric sulfide], diuretics, and cathartics). Currently, mercuric oxide still is used in batteries.

Organic Mercury

Organic mercury exists in three major forms: aryl, short-chain alkyl, and long-chain alkyl compounds. Methylmercury, a short-chain alkyl compound, is the predominant form of organic mercury found in the environment. In the short-chain alkyl compounds, there is a stable carbon–mercury bond. In the long-chain alkyl and aryl compounds, such as phenylmercury salts, the carbon–mercury bond is less stable, and the toxicity of these compounds may be due to the divalent mercury released after the carbon–mercury bond has been ruptured [2]. Organic mercury compounds have been used as biocides, as fungicides, as pesticides, as seed dressings, as antiseptics, as medicinal preservatives (thimerosal), and in paints.

Toxicokinetics

Elemental Mercury

The most important route of exposure is inhalation of mercury vapors. After inhalation, the lipid-soluble vapor rapidly diffuses across alveolar membranes, enters the blood, and partitions between plasma and red blood cells. Because of its high lipophilicity, mercury vapors are distributed throughout the body, including the central nervous system and fetus, if present. After absorption and distribution, most of the elemental mercury is oxidized intracellularly to inorganic

mercurous ions (and subsequently to mercuric ions) through the catalase–hydrogen peroxidase pathway. Mercuric mercury has a lower lipophilicity than unoxidized elemental mercury, which causes retention and accumulation of mercuric mercury in the brain, probably because of its presence as an insoluble selenium compound [9]. The further pattern of distribution changes toward that seen with inorganic mercury compounds, with accumulation primarily in the kidneys [2]. The overall retention of inhaled mercury vapor in human tissues is approximately 70–80% [10]. Elimination of elemental mercury occurs through expired air, urine, and feces [11]. Approximately 10% of an absorbed dose is exhaled in the first few days after exposure [12]. Urine and feces are the main excretory routes of mercury. In the first few days after acute exposure to high levels of mercury vapor, a large fraction of mercury can be found in the urine. Fecal excretion accounting for 50% of the total elimination was dominant after the first week [10, 11, 13]. In blood, there is an initial half-life of mercury of 2–16 days, followed by a half-life comparable to that observed in the kidneys of more than 1 month [10, 13]. The whole-body half-life of elemental mercury is about 60 days (range 35–90 days) [2].

Inorganic Mercury Salts

Approximately 10% of ingested mercuric chloride is absorbed. Disruption of the gastrointestinal mucosa may enhance mercury absorption. The monovalent mercurous salts are less soluble, and absorption is thought to depend on their oxidation to the divalent form [14]. Some mercuric compounds (e.g., HgS, HgSe) have such low solubility that they are regarded as nontoxic [15]. Cutaneous absorption of inorganic mercurials is possible, depending on the solubility of the vehicle. Although the mercuric ion's lipid solubility is low, with consequent poor penetration of the blood–brain barrier, chronic exposure, slow elimination, and the presence of a small amount of unoxidized elemental mercury (after reduction of inorganic mercuric ions) gradually result in accumulation of mercuric ions in the cerebellar and

cerebral cortices of the brain [16]. Mercuric ions do not readily cross the placenta [17]. In plasma, mercury is bound to protein. Most of the absorbed dose is accumulated in the kidneys [18]. Excretion of the circulating mercuric ion is mainly via the feces and urine. Elimination occurs by tubular secretion into the urine and by exfoliation of renal tubular cells [19]. Because renal excretion is inefficient, however, the mercury continues to accumulate in the kidney. Inorganic mercury can be secreted into bile. Small amounts of mercuric ions are reduced to elemental mercury vapor by reductase enzymes and oxygen dismutase and exhaled. The half-life of inorganic mercury is 30–60 days, with an average of approximately 40 days [2]. However, as for the half-life of inorganic mercury in the brain, current results from animal studies, human case studies including autopsy findings, and a few modeling studies indicate a half-life of several years to several decades [20].

Organic Mercury

Most organic mercury compounds are absorbed readily after ingestion. Gastrointestinal absorption of methylmercury (a short-chain alkyl compound) is about 90%. The absorption of aryl and long-chain alkyl compounds is less, but greater than 50% has been reported [17]. Dermal and inhalational absorption occur, although the extent is not known exactly. The exception is phenylmercury, which is not well absorbed after ingestion or dermal contact. After absorption, intracellular cleavage of the labile carbon–mercury bond of the aryl and long-chain organic mercurials causes rapid conversion to inorganic forms, resulting in kinetics and toxicity similar to those in inorganic mercury [11]. The short-chain alkyl mercurials are stable, and only a minor part is converted to inorganic forms. Because of their high lipophilicity, these short-chain alkyl compounds rapidly distribute throughout the body, with penetration of the blood–brain and placental barriers [11]. The brain-to-blood concentration ratio after completion of the initial distribution of methylmercury is about 10:1 [2]. Over the course of years,

conversion of methylmercury to inorganic mercury in the brain has been reported [21]. Accumulation of methylmercury in red blood cells results in a large red blood cell-to-plasma ratio (10:1) [17]. Accumulation of methylmercury is mainly in the kidneys and liver and to a lesser extent in brain tissues (although toxicity is expressed mostly in the brain) and hair [22]. Slow conversion of methylmercury to inorganic mercury also takes place in the kidneys. Elimination of methylmercury is predominantly fecal. Methylmercury binds to reduced glutathione and is secreted in bile [23]. The methylmercury–glutathione complex is degraded to cysteine complexes that are subject to reabsorption. The *N*-acetyl-homocysteine-methylmercury metabolite undergoes enterohepatic recirculation [11]. In the intestinal tract, a fraction of the methylmercury is converted to inorganic mercury and excreted in the feces [11]. The whole-body half-life of methylmercury is about 70 days [11, 24]. The half-life in blood is approximately 44 days [11, 24]. After the intravenous administration of methylmercury in volunteers, however, the half-lives were 44 days for the blood and whole body [24].

Pathophysiology of Toxic Effects

Elemental Mercury

Damage to the airways by elemental mercury vapor may be by direct-contact effects or may be indirect due to binding to sulfhydryl groups of enzymes and proteins. The vapor may cause an exudative alveolar and interstitial edema, with desquamation of the bronchiolar epithelium. The ensuing partial obstruction may result in alveolar dilation and the complications discussed subsequently in the section on “[Clinical Presentation](#)” [25]. After absorption and distribution, elemental mercury vapor is subject to oxidation (to mercuric ions) by the catalase–hydrogen peroxidase pathway. The oxidation process depends on the amounts of catalase and hydrogen peroxide in the cell, and inhibitors of catalase or competitive substrates can slow down the oxidation [2]. Mercuric cation can be reduced to elemental mercury

by processes involving reductase enzymes and oxygen dismutase [2]. At steady state, the oxidation–reduction reaction of absorbed elemental mercury favors the mercuric cation, however [26]. This conversion to inorganic mercury is responsible for mercury toxicity. Differences in the patterns of toxicity between inhaled mercury vapors and inorganic compounds are attributed to differences in lipophilicity and primary distribution and to specific characteristics of the inorganic compounds involved (e.g., corrosive features).

Inorganic Mercury Salts

The major mechanism of biologic activity of inorganic mercury *in vivo* is its reaction with sulfhydryl groups [2]. The covalent binding to sulfur replaces the hydrogen ion in the sulfhydryl group. This is an almost instantaneous reaction, causing a high-affinity binding of the divalent mercuric ion to thiol-containing molecules as proteins, cysteine, and glutathione [2]. Binding also occurs with phosphoryl, carboxyl, and amide groups [2]. Because of the binding to glutathione, inorganic mercury is secreted from liver cells into bile [2, 11]. The accumulation of the divalent cation in the kidneys induces the thiol-containing protein metallothionein [27]. This protein may play an important role in detoxification by forming a nontoxic Hg^{2+} -metallothionein compound. The divalent mercury cation also can give rise to oxidant free radicals that attack not only proteins but also DNA [2]. Through alterations in intracellular thiol status, mercury can promote oxidative stress, lipid peroxidation, and mitochondrial dysfunction. Widespread dysfunction of enzymes, transport mechanisms, membranes, and structural proteins results, leading to multiple organ dysfunction. Mercuric ions may directly injure the epithelial cells of the proximal renal tubules, causing renal tubular necrosis [28]. After the ingestion of corrosive mercuric salts, renal hypoperfusion due to shock also may cause renal tubular necrosis. An immune mechanism is attributed to the development of membranous glomerulonephritis. Type IV hypersensitivity reactions, which develop over 21–28

days after the exposure to mercury, underlie the formation of granulomas [29]. Granulomatous interstitial nephritis [29], granulomas forming after intravenous injection, and cutaneous mercury granulomas have resulted. Also, an idiosyncratic hypersensitivity reaction is often stated as the underlying pathophysiologic etiology for acrodynia, or “pink disease,” in children exposed to inorganic mercury. However, there seems to be a highly variable individual susceptibility as the syndrome develops in only a small proportion of those who are exposed and almost exclusively in small children [30]. There likely is a genetic component; two genetic polymorphisms associated with increased sensitivity to mercury have been identified [31].

The neuropathologic changes with elemental or inorganic mercury poisoning are different from the changes seen with organic mercury poisoning. Autopsy findings in patients who died after exposure to elemental mercury vapor reveal a well-preserved neuronal architecture, with the exception of decreased numbers of Purkinje and granular cells in the cerebellum [32] and prominent ischemic changes in the cerebellum in one patient and recent infarcts in the occipital lobe and the putamen in another [16].

Organic Mercury

The biochemistry of the methylmercury cation (CH_3Hg^+), the prototype of organic mercury poisoning, is similar to the inorganic cation. There also is a high affinity for sulfhydryl groups. Methylmercury does not induce metallothionein [2]. In high doses, methylmercury can cause severe damage to the adult brain and the developing brain. Methylmercury is toxic to the cerebral and cerebellar cortex, causing neuronal loss and reactive proliferation of the glial cells, microcavitation, vascular congestion, petechial hemorrhage, and edema [16]. The visual cortex (calcarine cortex), the auditory center in the temporal cortex, the cortical motor and sensory centers, and the cerebellar cortex are especially affected. In the fetal brain and developing brain, damage is diffuse because neuronal cell division and migration are

inhibited by blockage of the assembly process of microtubules in the neuronal cell [2]. As the experience in Minamata Bay dramatically illustrates, children can experience severe brain damage from prenatal exposure, even when the mother is much less affected [33].

Clinical Presentation

Elemental Mercury

After acute inhalation of vaporized elemental mercury, within hours of exposure, cough, chills, fever, headache, and shortness of breath can occur (mercury fume fever) [34, 35]. In addition, metallic taste; gastrointestinal complaints of nausea, vomiting, and diarrhea; salivation; excessive sweating; weakness; and visual disturbances can occur. Immune thrombocytopenia has been described in the acute phase [36]. At high concentrations, major pulmonary manifestations may develop, including necrotizing bronchitis, bronchiolitis, and pneumonitis, which can progress to pulmonary edema, respiratory failure, and death [37, 38]. Complications include multiple pneumothoraces, pneumomediastinum, and subcutaneous emphysema. Survivors of severe pulmonary manifestations may develop pulmonary fibrosis, granuloma formation, and residual restrictive pulmonary disease [39]. Children may be particularly susceptible to the pulmonary toxicity of mercury vapors [40].

The oxidation of elemental mercury to mercuric ions leads to features of inorganic mercury poisoning (described in the next section), characterized by renal toxicity, gingivostomatitis, and neurologic symptoms. Long-term, low-level exposure affects the neurologic system, with intention tremor and erethism (a condition characterized by increased irritability, excitability, anxiety, and shyness) as prominent features [41].

There are several case reports of other routes of exposure to elemental mercury. Aspiration of metallic mercury into the tracheobronchial tree has resulted in endobronchial hemorrhage and death [42]. Aspiration usually does not lead to acute or chronic mercury poisoning. Intravenous

injection of mercury can cause not only acute pulmonary embolus with respiratory failure but also pulmonary and systemic microembolisms. After oxidation to the mercuric cation, systemic inorganic mercury poisoning may occur. Subcutaneous injections or wounds contaminated with metallic mercury may cause local abscesses or granuloma formations. Systemic effects, including pulmonary embolization, have been reported but are unusual [43].

Inorganic Mercury Salts

After acute ingestion of mercury salts, the immediate features observed are related to the direct caustic effects of these salts, with mercuric ions being more toxic than mercurous ions [11]. After ingestion of mercuric chloride, effects can vary from severe irritation of the gastrointestinal tract to ulceration, necrosis, perforation, and acute hemorrhage, subsequently followed by hypovolemia, shock, electrolyte disturbances, and acute renal tubular necrosis with renal failure [8, 11, 44]. Immediately after ingestion, grayish discoloration of mucous membranes, metallic taste, nausea, vomiting, diarrhea, and severe abdominal pain occur. With the disruption of the gastrointestinal mucosa, mercury absorption can be extensive, and the direct toxicity of the mercuric cation on the proximal tubules further increases renal toxicity [8, 44]. Deterioration of renal function starts within hours after exposure.

If the patient survives these acute initial effects, systemic toxicity develops, as also is observed in subacute or chronic poisoning. Systemic toxicity includes renal dysfunction, gastrointestinal symptoms, neurologic toxicity, and cutaneous symptoms [26]. Chronic inorganic mercury poisoning also occurs after prolonged inhalation of elemental mercury vapor (owing to oxidation of elemental mercury) or after the *in vivo* dissociation of carbon–sulfur bonds of organic mercurial compounds, especially the aryl and long-chain alkyl mercurials [11]. The primary target organ is the kidney, with proximal tubular dysfunction. This dysfunction can range from asymptomatic, reversible proteinuria to tubular necrosis and

anuria [28, 29]. An immune glomerulonephritis may develop, which can lead to a full-blown nephrotic syndrome. Several cases of minimal change disease resulting in nephrotic syndrome have been published [45, 46]. Interstitial granulomatous nephritis has been described [29]. Oral symptoms of mercury intoxication include a metallic taste and burning sensation in the mouth, a blue lining of the gums, loose dentition, gingivitis, stomatitis, hypersalivation, and nausea [47]. Neurologic toxicity is expressed by tremor and syndromes such as neurasthenia and erethism, which include headache, irritability, excitability, delirium, anxiety, shyness, emotional lability, depression, loss of concentration and memory, fatigue, weakness, anorexia, and insomnia [41, 47]. Other neurologic manifestations include a mixed sensorimotor peripheral neuropathy, ataxia, constriction of visual fields, reduced color vision, and anosmia [41, 48].

As noted above, acrodynia (painful extremities) has been described primarily in children exposed to inorganic mercury. This is characterized by a pink maculopapular skin rash, particularly on the hands and feet, and hyperkeratotic induration also of the hands, feet, and face. In addition, excessive sweating, tachycardia, hypertension, photophobia, and neurologic symptoms, as mentioned previously, can occur [49]. Cutaneous manifestations of mercury toxicity may be a systemically induced allergic contact dermatitis, toxic contact dermatitis, or the formation of cutaneous granulomas, usually after injection of mercury [50].

Organic Mercury

Features of poisoning by long-chain alkyl and aryl organic compounds have some similarities to inorganic mercury toxicity but tend to be more subacute or chronic. Central nervous system toxicity is the hallmark of the short-chain alkyl compounds, particularly methylmercury. Clinical effects can be delayed for days to months after ingestion, depending on the amount ingested and the rate of enzymatic dysfunction. Neurologic effects start with paresthesias (facial and distal extremities) and headache and progress to ataxia,

dysarthria, visual field constriction, blindness, hearing disturbances, deafness, tremors, movement disorders, psychomotor retardation, and dementia. In severe cases, death ensues [1, 41]. Dimethylmercury poisoning has been reported in only a few cases of human poisoning, each proving fatal [51–53]. In a case of accidental dimethylmercury poisoning, a chemist spilled several drops onto a gloved hand. After cleaning up the spill, she removed her gloves. However, she developed delayed but ultimately fatal neurotoxic effects [53]. After ingestion of ethylmercury, gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and diarrhea can occur. High exposures to ethylmercury in the form of thimerosal have been reported to be associated with acrodynia, renal failure, and neuropathy, consistent with chronic inorganic mercury toxicity [41]. Thimerosal used as preservative in vaccines, with recent vaccines containing (if any) up to 0.01%, is safe. The only potential adverse effect documented in nearly 70 years of use in humans is a hypersensitivity reaction in a small number of cases [54]. A World Health Organization advisory committee concluded that it is safe to continue using thimerosal in vaccines [55]. Dermal exposure may cause dermatitis [50, 56].

Diagnosis

In measuring mercury concentrations in blood and urine, it is essential to use mercury-free collection materials; generally, it is best to obtain blood and urine containers from the performing laboratories. There is not a good correlation between blood and urinary mercury concentrations and clinical manifestations. There is considerable overlap in the concentrations of mercury found in the normal population, asymptomatic exposed individuals, and patients with clinical evidence of poisoning.

Urine Mercury Concentrations

Elemental and inorganic mercury exposure can be measured by determining urinary mercury

concentration, preferably using a 24-h urine collection rather than a spot urine level. If spot collection is used, adjustment for the creatinine concentration is essential. Provocative chelation should not be used as a diagnostic test [57, 58]. In chronic mercury exposure, the urinary excretion rate reflects the kidney content of mercury [2]. Urine mercury values have their greatest utility in confirming exposure and monitoring the efficacy of chelation therapy. Urine mercury concentrations less than 20–25 $\mu\text{g/L}$ (<100 – 125 nmol/L) are considered normal, although in occupationally unexposed persons, levels greater than 10 $\mu\text{g/L}$ (>50 nmol/L) (approximately 5-nmol/mmol creatinine) are seldom found [59]. Urine mercury concentrations greater than 100 $\mu\text{g/L}$ (>500 nmol/L) have been associated with minor neurologic signs [41], whereas levels greater than 300 $\mu\text{g/L}$ (>1500 nmol/L) usually are associated with overt clinical features of mercury toxicity [59].

Blood Mercury Concentrations

Soon after exposure to elemental and inorganic mercury, mercury concentrations in the blood may reflect mercury exposure accurately. As soon as redistribution takes place, these levels become less reliable in predicting toxicity. As a result of the relatively high concentration of methylmercury in red blood cells, whole-blood levels are more accurate in determining the acute/total body burden of methylmercury [60]. Whole-blood mercury concentrations are usually less than 10 $\mu\text{g/L}$ (<50 nmol/L), but levels less than 20 $\mu\text{g/L}$ (<100 nmol/L) still are considered to be in the normal range [41]. However, it is important to realize that (avid) seafood consumers may have higher total mercury blood and urine levels. In a study in adult seafood consumers in Long Island, NY, USA, blood Hg concentrations were positively associated with weekly tuna steak or sushi intake and monthly or weekly swordfish, shark, or marlin intake [61]. After long-term exposure to mercury vapor, whole-blood mercury concentrations of

above 35 $\mu\text{g/L}$ (175 nmol/L) may be associated with nonspecific symptoms [62].

Additional Laboratory Tests

Relevant laboratory tests, depending on the clinical scenario, may include arterial blood gas analysis, serum chemistry assessments including renal and liver functions, complete blood count, type and crossmatch of blood if exposed to caustic inorganic mercury, and screening for urinary markers of glomerular or proximal tubular damage (proteinuria, glucosuria, aminoaciduria, enzymes such as α -*N*-acetylglucosaminidase and β_2 -microglobulin) [63].

Radiographs and Other Diagnostic Procedures

With acute inhalation of elemental mercury vapor, chest radiographs initially may show interstitial or alveolar abnormalities (e.g., “bronchial thickening,” diffuse alveolar infiltrates, and edema) [64]. Thereafter, the radiologic features of the acute respiratory distress syndrome may be apparent, as may be signs of complications (e.g., pneumothorax, pneumomediastinum, and subcutaneous emphysema). Elemental mercury is radiopaque and can be seen on radiographs after ingestion, intravenous exposure, or subcutaneous exposure. Especially after subcutaneous or IV injection of elemental mercury (repeat), radiographs are useful in estimating the extent of mercury disposition and in guiding the removal of deposits. Reported pulmonary computed tomography findings in acute mercury vapor exposure are centrilobular nodules, ground-glass opacification, and alveolar consolidation, corresponding to acute interstitial pneumonitis [65]. Depending on the mercury compound involved, the circumstances of exposure, and the clinical features, other diagnostic procedures may be done, including endoscopic procedures, electrocardiogram, cardiovascular monitoring,

pulmonary function tests, electroneuro-myography, and neuropsychologic tests.

Treatment

Immediate Considerations

Assessment and management of the patient's respiratory function, circulation, and urinary output are primary. Acute inhalational exposure to elemental mercury vapor requires monitoring for respiratory failure. Supplemental oxygen or endotracheal intubation and mechanical ventilation may be necessary. There are no known aerosolized antidotes for acute inhalational exposures. Ingestion of corrosive inorganic mercury requires the establishment of rapid vascular access and treatment to prevent serious fluid losses and shock. Caustic injury to the oropharyngeal mucosa may cause severe local edema, and endotracheal intubation or tracheostomy may be required to overcome obstruction of the airway.

Indications for ICU Admission Mercury Poisoning

Pulmonary effects after inhalation of mercury vapor

Corrosive damage to the oropharyngeal and gastrointestinal mucosa with risk of airway obstruction and hypovolemic shock

Severe central nervous system effects

Decontamination

Initial decontamination measures after skin or eye exposure are removal of contaminated clothing and copious flushing of contaminated skin and eyes. After ingestion of corrosive inorganic mercury, as with any caustic ingestion, gastric lavage is contraindicated [66]. If perforation is suspected, direct endoscopic evaluation is indicated. Activated charcoal hardly binds metallic compounds

[67]. In the absence of caustic injury, whole-bowel irrigation with polyethylene glycol may be considered until the rectal effluent is clear and the radiopaque material is absent [68] (Grade III recommendation). With elemental mercury, whole-bowel irrigation mainly needs consideration in the rare case of massive ingestion or prolonged retention of elemental mercury (Grade III recommendation). After subcutaneous injection of elemental mercury, excision of mercury deposits in affected tissues is the most important treatment. Surgically, removal of mercury deposits is also indicated for intravenous mercury poisoning, provided the sites are accessible.

Role of Extracorporeal Removal Techniques

Extracorporeal removal techniques lack efficacy in removing mercury from the body. In a case of severe mercuric sulfate poisoning chelation treatment (DMPS) in combination with continuous veno-venous hemodiafiltration, 12.7% of the estimated ingested dose was recovered in the ultrafiltrate, mainly in the first 72 h [69]. Hemodialysis may be necessary if renal failure ensues. Although plasma exchange was reported to decrease plasma mercury in a 26-year-old woman with severe inorganic mercury poisoning [70], prompt institution of chelation therapy is preferable, and extracorporeal techniques should only be instituted if they are required for management of other secondary problems such as AKI.

Specific Treatment

Nonantidotal

Corticosteroids have been administered in the case of interstitial granulomatous nephritis due to mercury poisoning. Their efficacy has not been shown in a controlled trial, however. In mercury vapor poisonings, corticosteroids do not seem to have a clear effect on the eventual outcome [64].

Antidotal

Chelating agents effective in enhancing mercury excretion contain thiol groups, which are thought to compete with endogenous sulfhydryl groups for the binding of mercury. For years, elemental and inorganic mercury poisonings have been treated with dimercaprol and penicillamine. Dimercaprol was the primary chelating agent because it mobilizes mercury from the kidneys and protects against kidney damage (Grade II-3 evidence). Dimercaprol cannot be used for the treatment of alkyl organic mercury poisoning because it might worsen neurotoxicity after redistribution of mercury into the brain [14].

Today, 2,3-dimercapto-1-propanesulfonate (DMPS) and 2,3-dimercaptosuccinic acid (DMSA) have been shown to be effective agents in reducing the body burden of mercury and protecting against renal damage [71] (Grade II-3 evidence). These chelators are water-soluble analogues of dimercaprol and have the advantages that they can be administered intravenously and orally and they have better side effect profiles compared to dimercaprol. In animal studies comparing the various chelators, the highest efficacy for mobilizing mercury from exposed renal tissue was seen with DMPS [72]. In a patient treated with DMPS and hemodialysis because of anuric renal failure, after ingestion of mercuric chloride, mercury's half-life in the initial phase of elimination was estimated at 2.5 days. In the subsequent terminal phase, it was approximately 8.1 days. In this case, the nonrenal clearance of mercury through the biliary and gastrointestinal tract accounted for more than 80% of total elimination [73]. Chelation therapy with DMPS and DMSA in a patient with severe organic mercury poisoning resulted in complete recovery except for minor sensory deficits. Mercury elimination was biphasic, with blood mercury half-lives of 2.2 and 40.5 days [74]. Thiol resins taken orally are not absorbed from the gastrointestinal tract and may increase fecal excretion by binding to methylmercury that is in enterohepatic circulation, therefore decreasing its reabsorption. However promising, results originate mainly from animal models and need further evaluation in treatment of

people with high blood methylmercury levels [75]. Prompt institution of chelation therapy is believed to be important, however. Aggressive chelation therapy with DMSA was futile in a patient with rapid neurologic deterioration 3 months after exposure to dimethylmercury. From this case presentation, it was suggested that DMSA may have a limited capacity to distribute to and chelate organic mercury when this has been deposited in neuronal tissue or that DMSA cannot reverse tissue damage [53, 76].

Some studies have investigated a possible role for *N*-acetylcysteine in the management of methylmercury poisoning [41]. A striking increase in urinary excretion of methylmercury has been reported in animal studies. In mice that received *N*-acetylcysteine (10 mg/mL) in the drinking water starting at 48 h after methylmercury administration, the excretion of mercury in urine over the subsequent 48 h was 47–54% compared with 4–10% in control animals. In mice, *N*-acetylcysteine was able to mobilize methylmercury from tissues, including the brain. Clearance of inorganic mercury was not accelerated by *N*-acetylcysteine [77]. Most methylmercury poisonings have a chronic course, however, and the efficacy of *N*-acetylcysteine in these situations is not yet established.

DMPS. At present, the chelator of choice in elemental and inorganic mercury poisoning is DMPS (Grade II-3 recommendation). DMPS has a better side effect profile than dimercaprol and there are a large number of cases where it has been successfully used in the treatment of patients. However, timing is crucial and it is important to realize that metal mobilization does not always equal metal excretion. Our understanding of how certain chelating agents may contribute to the redistribution of specific metals within the human body is still incomplete [78]. In the case of organic mercury poisoning, there are conflicting results regarding the efficacy of DMPS and DMSA, possibly depending on the timing of chelation therapy. DMPS has been used safely for years in Europe. DMSA and dimercaprol are alternatives. Indications for chelation therapy after mercury intoxication are not

firmly established [4]. Chelation therapy should be started early after significant exposure in patients with features of severe poisoning and in patients with evidence of a large mercury burden shown by biologic monitoring [41, 78]. In this technical report on mercury in the environment, the American Academy of Pediatrics points out that although severe or symptomatic mercury poisoning can be treated by chelation therapy, it remains questionable whether (or to what extent) this chelation therapy decreases toxic effects or speeds recovery [78].

DMPS can be administered intravenously, dissolved in saline 0.9%, or orally. In a case of severe mercuric chloride poisoning in an adult, a dosage regimen was 250 mg intravenously every 4 h for the first 48 h and then 250 mg intravenously every 6 h for the second 48-h period, followed by 250 mg intravenously every 8 h afterward. The intravenous regimen was followed by oral treatment: 300 mg of DMPS three times a day for 7 weeks [73]. In a patient with minimal change nephrotic syndrome due to chronic occupational mercury vapor inhalation (blood mercury concentration before treatment 151.5 nmol/L (30 ug/L), 24-h urine mercury concentration of 1925.5 nmol/day, with a markedly elevated urine mercury/creatinine ratio of 127.5 nmol/mmol creatinine), the following DMPS schedule was used: 250-mg DMPS intravenously 4 times daily for 3 days, followed by 250-mg IV 3 times daily for 2 days, 200 mg orally twice daily for 3 days, and finally a maintenance dose of 200 mg PO daily for approximately 9 weeks. In addition, he was treated with prednisolone 60 mg daily. He made a full recovery with blood and urine mercury concentrations within the normal reference range [79]. Another treatment schedule consists of intermittent 5-day courses of high doses of oral DMPS (30 mg/kg/day) in three divided doses. Given the recommendation in this paper that intravenous DMPS should be given at least initially in a dose of 30 mg/kg/day, and taking into account the bioavailability of about 40% of oral DMSA, this oral dose is not excessive [80]. The duration of therapy depends not only on concentrations of mercury in blood and urine, but to a major extent on the

clinical condition of the patient and the extent of organ recovery during chelation therapy, for instance, in case of renal injury. There are no good data defining the optimal duration of chelation therapy, and clinical judgment is more important. Although not observed frequently, adverse reactions to DMPS include rash, nausea, and leukopenia. The clinical pharmacology of DMPS is discussed further in ► Chap. 168, “Unithiol.”

DMSA. DMSA can be administered intravenously, dissolved in saline 0.9%, or orally. In adults, the dosage, validated for use in enhancing lead excretion, is 10 mg/kg three times a day for the first 5 days, followed by 10 mg/kg twice a day for the next 14 days [81]. This same dosage schedule has been used in children, although a dosage based on body surface area may be a better choice because it prevents underdosing, especially in young children under the age of five. In children, DMSA is administered at a dose of 350 mg/m² three times a day for the first 5 days, followed by 350 mg/m² twice a day for the next 14 days. Repeated administration may be necessary, with a 2-week interval between treatments. Adverse effects usually are limited to a mild, transient elevation of hepatic transaminase levels and mild gastrointestinal discomfort. It is not necessary to discontinue DMSA therapy because of transaminase elevations. The clinical pharmacology of DMSA is discussed further in ► Chap. 165, “Succimer.”

Criteria for ICU Discharge in Mercury Poisoning

Patient does not require mechanical ventilation.
Patient is hemodynamically stable.

Dimercaprol. In case DMPS or DMSA are not available, then dimercaprol is the best alternative to use. Dimercaprol certainly has proven its efficacy [78], though DMPS and DMSA are the preferred chelators because of the ease of administration and a better adverse effect profile. Dimercaprol must be administered intramuscularly. It can be administered at a dose of 2.5–5 mg/kg every 4–12 h [59]. A decreasing dosing schedule for 10 days has been used,

starting with 5 mg/kg intramuscularly once, 2.5 mg/kg intramuscularly every 8–12 h for 1 day, and then 2.5 mg/kg intramuscularly every 12–24 h thereafter. The dimercaprol–mercury chelate is excreted into bile and urine. Common side effects of dimercaprol include hypertension, tachycardia, pain at the injection site, nausea, vomiting, headache, and diaphoresis. Convulsions have been reported. Hemolysis may be induced if the patient is glucose-6-phosphate dehydrogenase deficient [14].

Special Populations

Pregnant Patients

Methylmercury is of major concern in pregnant women because of its profound fetotoxicity. Maternal exposure can lead to spontaneous abortion or severe developmental delay, deformities, mental retardation, and the clinical features described earlier [33].

Key Points in Mercury Poisoning

1. Inhalation of high concentrations of mercury vapor rapidly produces pulmonary toxicity.
2. Ingestion of inorganic mercury may cause severe corrosive damage.
3. Be aware of nephrotoxicity.
4. Whole-blood mercury concentrations may be useful in confirming acute exposure to elemental and inorganic mercury.
5. In symptomatic patients, prompt institution of chelation therapy is important.
6. DMPS and DMSA are the preferred chelating agents.
7. The three major forms of mercury (elemental, inorganic, and organic) have specific toxicity profiles.
8. A single elevated mercury concentration in blood or urine does not prove toxicity in an asymptomatic patient.

DMPS, 2,3-dimercapto-1-propanesulfonate; DMSA, 2,3-dimercaptosuccinic acid.

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Elemental phosphorus has historical significance as a toxin that can cause impressive morbidity and mortality in patients with gastrointestinal (GI) or dermal exposures. Phosphorus is also recognized as an occupational toxin because of the epidemic of mandibular necrosis known as “phossy jaw” that occurred in the nineteenth century in the manufacturing of matches. Today, phosphorus exposures, either dermatological or via ingestion, are rare [1, 2]. In developing countries, however, reports of ingestion of phosphorus-containing firecrackers or pesticides, and of civilian phosphorus burns, continue to remind us of the severe toxicity of phosphorus [3, 4]. Nevertheless, it is important to recognize that elemental phosphorus can exist in different forms, with vastly different properties and toxicities. Moreover, chemically ambiguous or incorrect nomenclature can cause confusion and uncertainty when managing such exposures.

Chemistry

Phosphorus (atomic number 15) is an abundant element in living organisms, comprising about 1% of the body weight of an adult human, and plays a fundamental role in the biochemistry of life. Elemental phosphorus was the first element to be isolated since ancient times. Its discovery is credited to the alchemist Brand in 1669, who distilled urine in a quest for the mythical philosopher’s stone. It was named after the morning star (Greek *phos* + *phoros* or “light bearer”) because of its remarkable chemiluminescence. This faint green glow fascinated the alchemists and is now understood to be caused by its spontaneous oxidation when exposed to air. Indeed, it is far more reactive than nitrogen, which appears immediately above in the periodic table. Robert Boyle exploited this reactivity to ignite sulfur-tipped wood sticks, creating the first chemical matches in 1680. This ability to ignite and burn in the presence of oxygen in a controlled fashion ultimately allowed the full realization of Prometheus’ gift of fire on demand and justifies the name of “light bearer.”

The energy capture of molecular respiration in the phosphoanhydride links chaining together phosphate units into di- and triphosphates is essential to the energetics of living organisms. Phosphorus is also central to the regulation of many cellular processes and the framework of macromolecules. Together with nitrogen and potassium, it is one of the three “NPK” nutrient elements necessary and often limiting for plant growth, as denoted by the labeling convention of fertilizers (e.g., 10-20-10 representing the percentage by mass of each element) and by algal blooms in phosphate-rich runoffs. Phosphorus is thus essential to the fertilizer industry and global food production, constituting by far the major use of the element in modern times. In an irony of modern agriculture, phosphorus can also play a role in *reducing* unwanted insect growth via the organophosphorus pesticides. These compounds have special toxicological significance as potent inhibitors of acetylcholinesterase (see ► Chap. 92, “Organophosphate and Carbamate Insecticide”).

Nomenclature

Phosphorus (often misspelled *phosphorous*, which is an adjective for the element in a specific oxidation state, e.g., phosphorous acid = H_3PO_3 , which in turn is distinct from phosphoric acid, also called orthophosphoric acid = H_3PO_4) does not naturally exist in elemental form on the Earth, given its ready oxidation, nor is it available in the atmosphere. Instead, almost all phosphorus found on land exists as insoluble phosphate minerals in rock (e.g., the apatite group). Over geologic time, weathering allowed a small amount of phosphate to dissolve and become available for uptake by plants and microorganisms. Living organisms can only utilize soluble or the so-called inorganic phosphorus, which is better termed phosphate (or more precisely the orthophosphate ion, i.e., PO_4^{3-} , termed P_i for convenience), or the dimeric form pyrophosphate ($\text{P}_2\text{O}_7^{4-}$, denoted PP_i). Hospital laboratories often report a serum “phosphorus” (rather than phosphate) concentration,

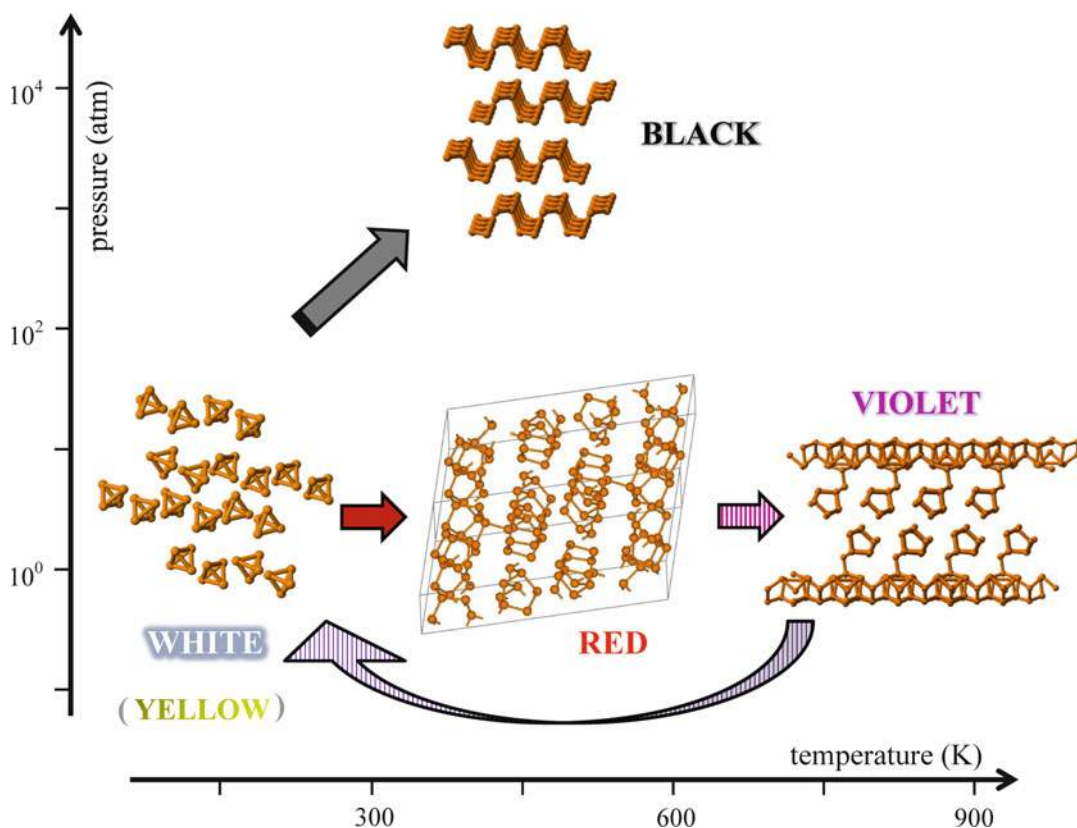


Fig. 1 Allotropes of elemental phosphorus. The molecular arrangement of phosphorus atoms in the four most common allotropic forms are shown. White phosphorus

(P_4 ; also called yellow phosphorus due to discoloration and impurities) is by far the most toxic form of elemental phosphorus

analogous to reporting a carbon rather than bicarbonate concentration.

These phosphate units are esterified (i.e., connected via P–O–links) to a variety of organic molecules, including phospholipids, nucleic acids, and proteins, or crystallize into a calcium salt called hydroxyapatite (also called hydroxylapatite, $Ca_{10}(PO_4)_6(OH)_2$) which makes up most of the mass of bone and teeth. Phosphoric acid (H_3PO_4) can release three protons into solution (pKa for each dissociation 2.1, 7.2, and 12), making the anion a useful buffer in the laboratory and the food industry and the second most important buffer in blood after carbonic acid (i.e., dissolved carbon dioxide, which has two pKa of 6.3 and 10 but circulates at a 20-fold higher concentration).

The elemental form of phosphorus can exist in different *allotropic* forms, just as pure carbon can appear as graphite or diamond. These different allotropes are denoted by their color, and the corresponding molecular arrangement of the phosphorus atoms is shown in Fig. 1. By far the most reactive and dangerous form is *white phosphorus*, also called tetraphosphorus (P_4), a waxy, translucent solid in which each of the four atoms are bonded to the others in a tetrahedron. The geometry of these bonds is highly strained, making this allotrope chemiluminescent in air, highly flammable and very toxic even to skin contact. This was the allotrope isolated by the alchemists, and almost all cases of acute toxicity involve this allotrope. It must be stored under water, in which it is poorly soluble, and will ignite spontaneously

at around 30 °C. White phosphorus was used in friction matches during the nineteenth century and is still used in fireworks and incendiary munitions. It burns with a characteristic garlic odor in oxygen to produce phosphorus pentoxide (P_4O_{10}), which itself is readily hydrated to phosphoric acid in a highly exothermic reaction. It is also called *yellow phosphorus* due to discoloration as the surface ages and the presence of impurities. Somewhat volatile, chronic exposure to vapors in match manufacturing led to the occupational disease termed “phossy jaw,” or osteonecrosis of the mandible, a condition now caused by therapeutic bisphosphonate use. The need to store in airtight matchboxes, the London matchgirls’ strike of 1888 and the acute toxicity when ingested for self-harm ultimately led to white phosphorus being replaced by phosphorus sesquisulfide (P_4S_3) in the heads of “strike anywhere” matches or by a more stable allotrope, red phosphorus, on the striking surface of “safety matches.”

Red phosphorus is an amorphous network of atoms which does not ignite below 240 °C unless it is powdered. It is harder and unaffected by exposure to the atmosphere. It is used in many pyrogenic applications such as highway flares. It is also used to reduce elemental iodine in the so-called “red, white, and blue” synthesis of methamphetamine from pseudoephedrine or ephedrine in clandestine laboratories. More recently, it has gained notoriety in the illicit manufacturing of desomorphine (“Krokodil”) from codeine. Red phosphorus (“red”) is mixed with iodine (“blue”) to form hydroiodic acid, which is the ultimate reducing agent in the formation of methamphetamine from ephedrine (“white”), and desomorphine from codeine. The heating of red phosphorus and iodine generates the extremely toxic phosphine gas (PH_3), a highly toxic fumigant and pesticide discussed in detail in ► Chap. 94, “Phosphate and Phosphine” [5, 6]. Deaths during the manufacturing of these drugs have been attributed to the inhalation of phosphine gas [5]. Another similar sounding toxic gas, phosgene (CCl_2O), is completely unrelated and contains no phosphorus.

The most stable allotrope is *black phosphorus*, a lattice of hexagonally linked phosphorus atoms

similar to the structure of graphite, in which each atom is linked to three noncoplanar neighbors. These wavy sheets have some metallic properties and are rather inert and essentially nontoxic. A far less common form is *violet phosphorus*, consisting of brilliant crystals which can sublime to white phosphorus.

Biochemistry

Phosphate units play a pivotal role in nearly all biochemical pathways that characterize life. Oxidative phosphorylation captures some (~ 7.3 kcal/mol) of the chemical energy released in respiration by attaching a third P_i to adenosine diphosphate (ADP) to form ATP, the energy currency of the cell. Plants capture the free energy of light to generate ATP. When two or more phosphate units are in close proximity, electrostatic repulsion between the negatively charged oxygen atoms and competition between adjacent phosphorus atoms for electron pairs on oxygen result in a high phosphate group transfer potential or willingness to release the terminal phosphoryl group to water. The release of this phosphate unit (i.e., hydrolysis of the phosphoanhydride link) drives the otherwise unfavorable reactions of macromolecule biosynthesis, active transport, signal amplification, and muscle contraction (Fig. 2). It is estimated that an adult can consume 1 kg of ATP every 100 s during exercise. At rest, each molecule of ATP is estimated to cycle to ADP every minute, on average. An inability to maintain a high ATP concentration characterizes irreversible death.

The release of pyrophosphate from the triphosphate tail on each of the four nucleotides allows their polymerization into RNA and DNA strands, and the stability of these repositories of genetic information is attributable to the ribose-phosphate backbone of the nucleic acids. Adding P_i to diglycerides creates the phospholipids that form the cell membrane and organelles. A rich variety of kinases phosphorylate proteins, lipids, nucleic acids, and other substrates, orchestrating the expression and regulation of the genome and proteome. Indeed, phosphorus the “light bearer” not

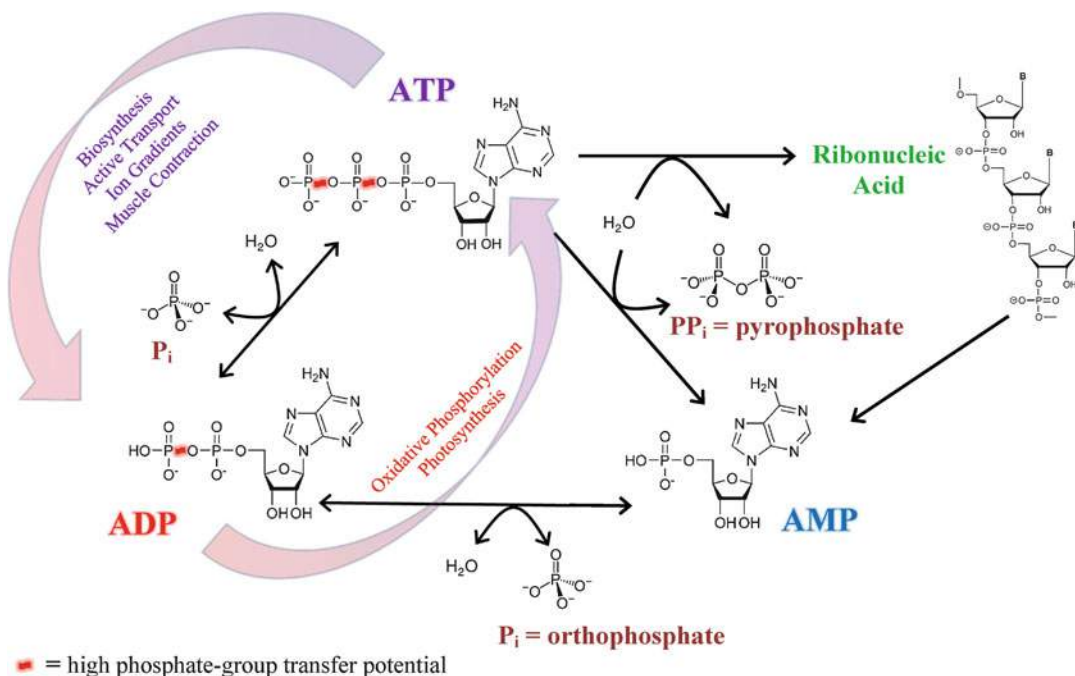


Fig. 2 Bioenergetics of living organisms. Adenosine with three phosphate groups (adenosine triphosphate; ATP) is the “energy currency” of the living cell. The ready hydrolysis of the phosphoanhydride links joining two or more phosphate groups (denoted by the *red squiggle*) provides the driving force for many processes essential to life, including synthesis of macromolecules, membrane pumps, and muscle contraction. It can also transfer a

phosphate group (P_i) to other molecules including nucleotides, proteins, lipids, and carbohydrates at key junctures of metabolism. The nucleotide triphosphates release pyrophosphate (PP_i) to be added to the growing nucleic acid strand. ATP is regenerated by proton gradients developed in mitochondria and chloroplasts during oxidative phosphorylation and photosynthesis, respectively

only carries the flame of life but also controls its energy flow in an intricately complex molecular symphony. Thus, the term “phosphorus” can refer to a highly toxic allotrope such as white phosphorus, or to an essential nutrient for life, depending on the context, spelling, and chemistry. From this vantage point, the toxicity of phosphorus can now be better examined.

Uses

Elemental phosphorus is used in the production of secondary compounds like phosphoric acid or phosphate, which are then used in fertilizers, foods, beverages, cleaners, and other commercial products [7]. White (also known as yellow) phosphorus has specific uses in military ammunition, incendiary devices, fireworks, and rodenticides

[7]. For example, white phosphorus is a component in round, penny-sized fireworks, known as *catapat* (Turkey) or *diablillos* (Ecuador). Often used by children, these fireworks are common causes of phosphorus exposures [3, 8]. A dilute paste of white phosphorus is still used as an insecticide or rodenticide in some countries but has been banned in many due to its severe toxicity. It should not be confused with zinc phosphide (Zn_3P_2), aluminum phosphide (AlP), or calcium phosphide (Ca_3P_2), not with highly toxic rodenticides and fumigants still widely used to generate phosphine gas (HP_3) in the presence of atmospheric moisture or in the stomach of vermin (see ► Chap. 94, “Phosphate and Phosphine”).

The clandestine synthesis of methamphetamine and desomorphine (“Krokodil”) involves the use of red phosphorus as a reagent [9]. For this reason, in 2001, the United States Drug

Enforcement Agency added red phosphorus, white phosphorus, and hypophosphorous acid (H_3PO_2) to List 1 chemicals, restricting the handling and selling of these chemicals [10].

Toxicokinetics

The toxicokinetics of elemental phosphorus are poorly understood [7]. White phosphorus is lipid soluble and absorbed well via most routes of exposure, though this has not been accurately quantified. Intestinal absorption may be enhanced in the presence of alcohol or lipids [11, 12]. Evidence of systemic toxicity after phosphorus burns from dermal exposures suggest systemic absorption of phosphorus through the dermis [13].

Elemental phosphorus appears to distribute widely after intestinal absorption. Phosphorus is initially concentrated in the liver and then later in the bone, kidneys, brain, and heart [7, 14]. Animal studies suggest that phosphorus excretion is primarily renal, with a minor component excreted in the feces [7, 15].

The severely toxic dose of white phosphorus is reportedly on the order of 1 mg/kg, though a 1930 textbook describes a child dying from the ingestion of only 3 mg [12, 16]. The historical reputation of white phosphorus matchsticks from the nineteenth century was that ingesting the contents of one matchbox was sufficient to kill an adult.

Pathophysiology

White phosphorus exposures, be they dermal, inhalational, or enteral, are associated with severe systemic toxicity. The exact mechanisms underlying the systemic toxic effects of phosphorus, however, are not entirely clear [17]. Phosphorus is often cited as being a “general protoplasmic poison.” Much of this reputation is based on electron microscopy observations in a 1969 study in which the earliest morphologic changes were noted in the rough endoplasmic reticulum, before any changes were observed in the nucleus or mitochondria [18].

Elemental phosphorus can alter ribosomal function and protein synthesis [19, 20], lipoperoxidation [14], and triglyceride secretion [21, 22]. On histology, one sees intracellular lipid accumulation in multiple organs, namely, the liver, heart, brain, and kidneys.

Dermal Effects

White phosphorus injury produces a combined thermal and chemical burn. When exposed to air, it spontaneously oxidizes to phosphorus pentoxide, which hydrolyzes to form phosphoric acid. Thermal burns result from these two exothermic reactions. Moreover, white phosphorus particles spontaneously ignite at temperatures above 30 °C [2, 23]. Any phosphorus particles embedded in a wound may continue to oxidize and lead to ongoing tissue injury even after the initial exposure has ended [24]. While some authorities suggest this component is negligible [23], phosphorus pentoxide is intensely hygroscopic, leading to rapid tissue dehydration. The result is a severe combination of chemical and thermal injury. Hospital stays are longer and wounds heal more slowly in patients with white phosphorus burns compared to patients with simple thermal burns [24, 25].

The systemic effects of white phosphorus burns include hypocalcemia and hyperphosphatemia, leading to ECG changes and bradydysrhythmias. Rarely, systemic toxicity may develop after dermal exposures to white phosphorus, including liver and renal damage, metabolic abnormalities, dysrhythmias, and sudden death [26, 27]. They have been well characterized in animals, but only a few human cases have been reported [13]. Whether these effects represent the sequelae of the burn or of systemically absorbed phosphorus is unclear.

Gastrointestinal Effects

Ingestion of white phosphorus generally causes significant gastrointestinal irritation as a result of its direct corrosive action on the local gastric

mucosa. Mechanisms similar to the dermal injury are likely involved. Within hours of ingestion, most patients develop nausea, vomiting, and abdominal pain or cramping [11, 12, 28, 29]. Gastrointestinal bleeding also has been reported [1, 11, 12]. Endoscopy findings include erythema, inflammation, erosions, and frank necrosis [12, 29, 30]. Occasionally, patients present without any significant gastrointestinal effects, so their absence does not rule out a significant ingestion [11, 29].

Inhalational Effects

As white phosphorus is known to rapidly oxidize in air, phosphorus smoke and the vapors in phosphorus factories likely contain a mixture of phosphorus oxides and unburned phosphorus particles [7]. Inhalation of these substances may cause irritation of the mucous membranes and respiratory tract, leading to cough, hoarseness, wheezing, and laryngeal edema or inflammation. The mechanism of injury is likely due to a combination of heat formation from the oxidation of phosphorus, and hygroscopic or caustic injury caused by the products of this reaction. Animals exposed to high concentrations of phosphorus smoke have developed severe respiratory tract lesions, and some have died [7]. Historically, chronic inhalational exposure to phosphorus fumes led to “phossy jaw” or mandibular osteonecrosis. Chronic inhalational exposures can also lead to anemia, leukopenia, and chronic cough [7].

Clinical Presentation

Classically, the clinical presentation of acute elemental phosphorus ingestion was described in a three-stage model [11, 12]. In the first stage, gastrointestinal symptoms predominate, likely a result of the direct corrosive injury of white phosphorus on the GI mucosa. Patients experience nausea, vomiting, abdominal pain, and diarrhea. There are many case reports of emesis and stools emitting a luminescent glow, or even smoke. Some authors have reported a garlic odor to the

emesis or stools. The first stage is believed to last approximately 24 h. During this time, a proportion of patients can have sudden cardiovascular collapse and succumb [11, 17]. Some authors have speculated that the sudden death occurs in patients who ingested larger amounts of phosphorus, and that the etiology is direct vascular toxicity. Next, from approximately days 1 through 4, a patient may enter a period of relatively quiescent symptoms. Stage 2 has reportedly lasted until 10 days [12]. Finally, the third stage presents, with multi-organ failure, most notably acute liver failure, acute renal failure, encephalopathy, coagulopathy, arrhythmias, and cardiogenic shock.

This three-stage model may likely be the exception rather than the rule. Authors have described many presentations where stages 1 or 2 are often difficult to recognize [11, 29]. The highest mortality is observed early, among patients who do not have time to develop jaundice or a clear-cut picture of hepatic damage [11].

Gastrointestinal Effects

Initial symptoms after white phosphorus ingestion include nausea, vomiting abdominal pain, and, less frequently, diarrhea. Patients can also present with hematemesis. In certain cases, hematemesis has been reported to occur later in the course of illness, on days 3 or 4, presumably because of abnormal coagulation [11]. The GI contents have been reported to luminesce (“phosphoresce”) or to “smoke,” likely due to the continued oxidation of phosphorus on re-exposure to air [28, 29].

Renal Effects

Patients with acute phosphorus poisoning develop renal toxicity within days of the exposure. Oliguria, hematuria, proteinuria, pyuria, and the presence of hyaline casts suggest a component of acute tubular necrosis which underlies the renal toxicity. In fact, animal studies/biopsies have shown tubular necrosis, cortical necrosis, and fatty infiltration [31]. In patients who survive, the acute renal failure often resolves within days.

Neurologic Effects

Altered mental status and coma are reported in association with phosphorus poisoning and can occur in the absence of any GI symptoms [11, 29]. Rarely, seizures and myoclonic twitching have been reported. Neurologic abnormalities are associated with worse prognosis. The etiology of neurologic dysfunction is likely at least in part due to other organ abnormalities, for example, hepatic encephalopathy secondary to the associated hepatic injury, as well as shock. However, accumulation of fat in the ganglion cells, glia and vessels of the brain, as well as pericellular coarse incrustations in the outer Golgi nets of the inferior olives suggests a direct toxic effect of phosphorus on the nervous system [32].

Cardiovascular Effects

White phosphorus poisoning can cause cardiovascular collapse within 24 h of ingestion, attributed to a direct toxic effect on the myocardium and on peripheral vessels worsened by intravascular volume depletion [20]. A case series of 55 patients with acute phosphorus toxicity reported electrocardiographic T wave inversion were most common and ventricular fibrillation within the first twenty-four hours in two cases with large ingestions [33]. Other transient ECG abnormalities due to electrolyte and renal abnormalities may also develop, including prolonged QT interval, bradycardia, and ST segment abnormalities [4, 34].

Hepatic Effects

Phosphorus is recognized as a potent hepatotoxin. Patients who survive the initial neurologic and cardiac stress of acute poisonings may manifest hepatotoxicity with hyperbilirubinemia, coagulopathies, hypoglycemia, and elevation in transaminases [1, 11, 29, 31, 36, 43]. These biochemical abnormalities usually worsen over several days, though there is evidence of liver abnormalities on histopathological studies early

on [12, 14, 43]. The acute hepatic injury will resolve over several weeks. Most survivors do not have permanent hepatic sequelae, although there are reports of residual cirrhosis, fibrosis, and scarring.

With ingestion of white phosphorus, the hepatic injury pattern is classically periportal [14, 31, 43]. Fatty infiltration has been noted within 6 h and cytoplasmic damage is reflected by the endoplasmic reticular changes noted above [18–20]. Other studies show extensive necrosis, ballooning degeneration, and steatosis [17].

There are also case reports of biochemical and clinical cholestasis developing after ingestion of phosphorus [35, 36].

Hematologic

In retrospective case series, patients with phosphorus exposures were reported to have leucopenia and leukocytosis [11]. Newer case reports describe patients with myelosuppression after ingesting phosphorus, including patients with considerable decreases in granulocyte counts that resolved spontaneously [37, 38]. The precise etiologies of myelosuppression associated with phosphorus exposures are unclear but may involve either direct bone-marrow suppression or immune-mediated destruction.

Dermatologic

When white phosphorus contacts exposed skin, necrotic and yellowish full-thickness burns can result due to both chemical and thermal injury [39, 40]. They have been reported to have a garlic odor [4]. Dermal exposures to phosphorus create complex injuries that are seen mainly in the military, yet have also been reported in civilians [4]. Phosphorus particles can embed themselves in a wound and combust, leading to smoke that is a strong irritant to mucosal surfaces [23].

Systemic toxicity may develop including hypocalcemia, hyperphosphatemia, dysrhythmias, [4, 13] and hepatic and renal dysfunction [2, 23, 26, 41].

Notably, there is significant mortality associated with dermal exposures. In rats, 12–15% surface area burns were associated with 50% mortality [41]. Similar reports of sudden death in humans with similar burn areas are reported [13].

Prognosis

It is generally well accepted that there is a dose–response to phosphorus toxicity and that patients with larger ingestions will have worse outcomes. Patients developing altered mental status within the first 24 h tend to do poorly. Survival for 3 days is a good prognostic sign, though late deaths from cardiac, hepatic, or renal failure can still occur [16, 33].

Diagnosis

There are no specific laboratory findings to establish a diagnosis of phosphorus poisoning. Serum elemental phosphorus levels are not clinically available. Serum phosphate (predominantly HPO_4^{2-} and H_2PO_4^- at physiologic pH) concentrations do not correspond to free phosphorus levels and cannot be used as a surrogate (see section “[Nomenclature](#)” above). Diagnosis is mainly done on history of exposure to a phosphorus-containing product [31]. A white phosphorus ingestion may be suggested by gastrointestinal outputs that smoke, luminesce, or have a garlic odor. White phosphorus burns are suggested by a military context involving munitions.

Treatment

There is no specific antidote for phosphorus poisoning. Treatment should be focused on decontamination, where appropriate, and supportive care. Close monitoring of patients is essential and includes cardiac and respiratory monitoring and frequent checking of potassium, calcium, and phosphate levels.

Protection of Health-Care Workers

Phosphorus in either liquid or solid form can harm health-care workers trying to decontaminate or treat a patient [39]. Caution should be exercised around all vomitus, diarrhea, and contaminated clothing for this reason. Clothing contaminated with white phosphorus should be placed under cold water to prevent combustion [16]. Smoke from oxidized phosphorus can be an irritant to the airway, GI, and conjunctival mucosa. Proper personal protective equipment must therefore include protection from such fumes and from direct skin contact when working with a patient who has potentially been exposed to white phosphorus.

GI Decontamination

There are no studies showing a benefit of GI decontamination. The literature includes reports of gastric lavage efforts performed as early as 15 min until several hours post-ingestion, often using irrigation fluids with their own potential for toxicity, including potassium permanganate and copper sulfate. There is no evidence to support the use of such fluids, and, in some cases, the associated harms are well established.

Despite the lack of rigorous evidence, we believe that the potential benefit of gastric lavage likely outweighs the risk when done shortly after a large ingestion of white phosphorus (Grade III recommendation). This recommendation applies only to the white phosphorus allotrope and only for ingestions on the order of 1 mg/kg, given the associated mortality despite supportive care [16, 42]. Minimizing the introduction of air and keeping the free end of the orogastric tube under water is prudent given the reactivity of white phosphorus with air, but this practice also establishes a siphon effect to help evacuate the stomach. We recommend lavaging with ordinary cold tap water, which serves as a heat sink given the highly exothermic oxidation of phosphorus. While the risk of esophageal erosion from mucosal burns is a prudent consideration, there are no reports of this complication developing shortly after

ingestion. Activated charcoal is unlikely to offer specific benefit.

Supportive Care

The mainstay of phosphorus poisoning is the provision of rigorous monitoring and aggressive supportive care. Monitoring and correction of vital signs, electrolytes, and renal and hepatic function is essential. Hepatotoxicity should be anticipated with all its complications, including encephalopathy, hypoglycemia and coagulopathy. These complications should be managed as they arise with conventional measures. Phosphorus poisoning may lead to renal failure, and standard indications can be used to guide renal replacement therapy. Corticosteroids have not been shown to have a benefit [43]. Acetylcysteine has been postulated to have a role in limiting oxidant injury, but a small case series was unable to demonstrate a survival benefit [36].

The only definitive treatment of fulminant liver failure from phosphorus poisoning is liver transplant. The outcomes have been poor in patients with encephalopathy prior to transplant, rendering the decision to transplant and its timing very difficult [17].

Dermal Exposures

Treatment of dermal phosphorus exposures involves rapid decontamination and supportive measures. First aid principles involve rapidly removing and storing contaminated clothing underwater. Wounds should be covered with saline-soaked gauze to reduce exposure to air. Continuous irrigation should be initiated with cold water (Grade III recommendation).

Decontamination is important because particles of white phosphorus that remain in contact with skin continue to oxidize in the presence of air, worsening tissue damage [2, 40]. Large particles should be removed with forceps and placed in water. Wounds should be thoroughly irrigated with tap water to clean the wound and to remove

any of the phosphoric acids produced by the oxidation of phosphorus [2, 44, 45].

In the past, recommendations included irrigating wounds with a solution of copper sulfate (CuSO_4) [7]. The rationale often provided was that copper (II) sulfate would combine with phosphorus to form a black inactive salt, copper (I) phosphide (Cu_3P). In theory, this reaction would minimize the ongoing oxidation of phosphorus while also improving the visualization of particles for removal. Copper sulfate however, can cause severe systemic toxicity when the copper ion is absorbed into the bloodstream. Patients have been observed to develop massive hemolysis and even death after irrigation of their phosphorus burns with copper sulfate [46, 47]. Moreover, the likely reaction product is a different complex, copper (II) phosphorus (Cu_3P_2), which is unstable and can decompose to release both copper and phosphorus ions, each with their own toxicities [47]. As a result, recommendations to use copper sulfate irrigation should be considered obsolete.

It is essential to remove all white phosphorus particles from the wound as early as possible. Because these waxy, yellow particles may be difficult to visualize, an ultraviolet light (i.e., Wood's lamp) fluoresces the phosphorus particles, allowing for easier identification [48]. While some authors suggest a role for a dilute copper sulfate solution (0.5–1%) for particle identification, followed promptly by irrigation with water, even this practice is no longer recommended [23, 24]. Dilute solutions of silver (I) nitrate (AgNO_3) could in theory also increase visualization of phosphorus particles in a wound by forming black silver phosphide (Ag_3P) and should not be associated with the systemic toxicity caused by the copper ion [47]. Silver phosphide is stable, insoluble, and presumed to be far less toxic than elemental phosphorus, and excess silver ions do not cause hemolysis [47]. There are minimal human data, however, to support this practice. Regardless, the wound should always be rinsed copiously and thoroughly with water to remove any residual elemental phosphorus [47]. If particles of phosphorus are embedded in tissue, or

remain despite efforts to remove them, surgical debridement is necessary [48, 49] (Grade III recommendation).

After decontamination and debridement of the wound, supportive care is similar to that recommended for other burn patients, including volume resuscitation, wound care, tetanus prophylaxis, and monitoring for signs of infections and other injuries. Given the risk of electrolyte abnormalities, dysrhythmias, and liver dysfunction from systemic absorption of phosphorus, we recommend that patients with white phosphorus burns be monitored for a minimum of 24–48 h.

Phosphorus burns are also associated with slower healing and higher morbidity than a comparable thermal burn [41]. For these reasons, consideration should be given to transferring all patients with white phosphorus burns to a regional burn center [49].

Special Populations

Pediatric Patients

In developing countries, children are at risk of exposure to elemental phosphorus because of its use in firecrackers and as a rodenticide. The practice of spreading yellow phosphorus paste onto food to entice pests is particularly dangerous for children. These rodenticides are no longer sold in most developed countries. The clinical course of phosphorus poisoning is no different than in adults, and treatment should be the same.

Pregnant Patients

Anecdotally, elemental phosphorus has been used as an abortifacient. It is known to cross the placenta, but no cases of fetotoxicity or teratogenicity have been reported. We recommend, therefore, that pregnant patients be managed similar to other patients, with aggressive decontamination and supportive care.

Military Personnel

Military personnel are at risk for white phosphorus burns and inhalational exposures given the widespread use of phosphorus compounds in obscurants, incendiary devices, and munitions.

Indications for ICU Admission

Significant exposure to “white” (also known as “yellow”) phosphorus

Large phosphorus burn (>10% body surface area)

Evidence of shock

Respiratory compromise

Mental status changes

Patients with nausea, vomiting, diarrhea, or gastrointestinal bleeding after ingestion, given risk of deterioration and delayed systemic toxicity

Criteria for ICU Discharge

For patients with minimal symptoms or whose initial symptoms were exclusively gastrointestinal, the absence of signs of systemic toxicity after an adequate observation period of 24–48 h

For patients who developed signs of systemic toxicity (i.e., altered mental status, hepatic function abnormalities, cardiac disturbances, renal injury, metabolic derangements), resolution of the mental status changes and cardiac disturbances, and improving hepatic, renal, and metabolic function

Common Errors

Mistaking elemental phosphorus for the chemically dissimilar phosphine, phosphide or phosgene

Failing to appreciate the difference in toxicity for the different allotropes of elemental phosphorus, with white (also known as yellow) being far more toxic than red phosphorus

(continued)

Using a serum “phosphorus” (i.e., phosphate) concentration to manage an elemental phosphorus exposure

Searching for outdated or harmful “antidotes” such as copper (II) sulfate or potassium permanganate solutions for wound irrigation, rather than proceeding with immediate cold water irrigation and removal of visible particles

Key Points

1. Ingestions of white (yellow) phosphorus can cause corrosive gastrointestinal injury followed hours to days later by systemic toxicity with multiple organ dysfunction, particularly hepatic damage.
2. Dermal contact with white phosphorus can cause severe burns and systemic toxicity.
3. Treatment is supportive; there are no specific antidotes for elemental phosphorus.
4. Early, aggressive decontamination may help prevent systemic toxicity.
5. Health-care providers and rescue personnel should avoid direct contact with white phosphorus, and contaminated clothing and body fluids should be placed immediately under cold water to reduce spontaneous oxidation.

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Thallium (Tl) was first discovered by Sir William Crooks in 1861, with its toxicity recognized shortly afterwards [1, 2]. The element is classified in group IIIA of the periodic table and forms both monovalent and trivalent compounds. Monovalent compounds such as thallium sulfate (Tl_2SO_4) and thallium acetate (CH_3COOTl) tend to be more toxic [2]. Thallium occurs naturally in various ores and is typically recovered from flue dust and residuals produced from the smelting of zinc, copper, and lead [3]. Thallium salts dissolve readily in water and are odorless and tasteless.

In the early twentieth century, thallium salts found use as both a rodenticide and medicinal agent. Therapeutic applications included the treatment of gout, syphilis, and tinea capitis [1]. Thallium was also utilized as a depilatory agent in consumer products. By the 1930s, cases of thallium poisoning were being attributed to depilatory products, pesticides, and contaminated foods [4–7]. Poisonings in the United States have dropped considerably since thallium was banned from use in rodenticides and pesticides in 1965. Similar patterns have been seen in other countries. Commercial uses are limited largely to semiconductor manufacturing, with other applications in the production of optical systems, thermometers, and photoelectric cells [3]. However, sporadic cases of malicious poisoning have been reported, along with ingestions of stored rodenticides pre-dating the 1965 ban [8, 9]. Despite a World Health Organization recommendation against the use of thallium in 1973, thallium compounds remain easily

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available internationally. As a result, poisonings from contaminated food and water still occur across the world in the twenty-first century [10, 11].

Clinical Pharmacology

Thallium is absorbed by the gastrointestinal tract after oral ingestion, by intact skin, and by the lungs after inhalation [3]. Oral bioavailability can exceed 90%. Following absorption, thallium demonstrates rapid intracellular redistribution with an estimated volume of distribution (V_d) ranging between 3 and 10 L/kg [12]. Thallium concentrates in tissue with higher perfusion, such as the kidneys, liver, intestines, and lungs [12, 13]. Signs of toxicity may occur with either acute or chronic exposure. The lethal dose in humans is estimated to be between 10 and 15 mg/kg, though fatalities have been reported with doses as low as 200 mg [2, 14]. In a proposed multi-compartment model, thallium is initially (within 4 h) distributed over a central or fast exchange compartment, consisting of well-perfused organs, such as the kidney, liver, and muscle. During a second phase (4–24 h), thallium is distributed to a slow exchange compartment which includes the brain, causing thallium's neurotoxicity [15]. This concept is supported by reports of rising thallium concentrations in the cerebrospinal fluid, despite falling serum level [16]. Due to extensive subsequent enterohepatic circulation, thallium's terminal half-life is prolonged with a calculated length of 2.2 days [17]. However, a wide range of half-life values has also been reported [12].

Pathophysiology

Multiple mechanisms have been proposed for thallium toxicity. Thallium ions are monovalent, similar in size to potassium ions (ionic radii 1.44 Å for thallium and 1.33 Å for potassium). As a result, thallium can substitute for potassium in many potassium-dependent processes, such as Na^+/K^+ ATPase [18, 19]. Thallium exhibits an estimated tenfold higher affinity for Na^+/K^+ ATPase than potassium [20]. This latter fact likely

explains thallium's concentration within the intracellular space. Many other important cellular functions require potassium binding for optimal functioning and can be inhibited by thallium binding, such as pyruvate kinase [21]. In addition, thallium binding disrupts potassium-dependent stabilization of ribosomes, thus impacting normal protein synthesis [21].

Similar to other metals, thallium also inhibits the function of sulfhydryl-containing enzymes [2, 18]. As in the case of potassium-dependent targets, some of the identified targets are critical in cellular metabolism. Important examples include lactate dehydrogenase and phosphoglycerate kinase [21]. Other effects on cellular function have been observed but do not appear to be mediated by sulfhydryl binding or substitution for potassium. Thallium has been shown to uncouple oxidative phosphorylation within mitochondria. The precise mechanism is unclear as thallium does not inhibit the enzymes of the electron transport chain nor act as an ionophore at the inner membrane [22]. Morphological studies have corroborated membrane disruption in mitochondria, as well as other subcellular organelles such as the endoplasmic reticulum [2].

Lastly, thallium forms an insoluble complex with riboflavin, a process once utilized to isolate riboflavin from milk [23]. It has been proposed that functional riboflavin deficiency may be responsible for some aspects of thallium toxicity (e.g., dermatitis, neuropathy, alopecia) [23, 24]. Animal studies, though, have shown that riboflavin supplementation does not prevent or ameliorate thallium toxicity [25]. There are no published reports of human thallium poisoning where simultaneous assessment of riboflavin deficiency was made.

Clinical Presentation

Thallium poisoning produces a wide array of clinical manifestations, likely due to its wide distribution. The classic triad of findings includes:

- Acute gastroenteritis
- Polyneuropathy
- Alopecia

Table 1 Time course of thallium toxicity

Early phase (within hours)	
Gastrointestinal	
Nausea	
Vomiting	
Abdominal pain	
Gastroenteritis	
Diarrhea	
Constipation	
Intermediate phase (hours to weeks)	
Cardiac	
Sinus tachycardia	
Hypertension	
Chest pain	
Neurologic	
Painful paresthesias	
Distal motor weakness	
Ptosis	
Ataxia	
Mental status changes	
Renal	
Reversible proteinuria	
Late phase (2–4 weeks)	
Dermatologic	
Alopecia	
Acne	
Mees' lines	
Chronic toxicity (>4 weeks)	
Neurologic	
Memory loss	
Dementia	
Muscle atrophy	
Ophthalmologic	
Ophthalmoplegia	
Optic neuropathy	

Table 1 describes the typical time course of findings, classified as early, intermediate, late, and chronic manifestations. It is important to note that the timing and order of signs or symptoms may vary depending on the severity and chronicity of thallium exposure. Patients have been known to present days to weeks later following ingestion [1, 5, 6, 11].

In the early phase (within hours), gastrointestinal disturbances, such as nausea, vomiting, abdominal pain, gastrointestinal bleeding, constipation, and diarrhea, predominate [1, 2, 14].

Autopsy findings in fatal cases have demonstrated gastric hemorrhage as well as diffuse necrotizing mucositis of the intestinal lining [14, 26]. The oral mucosa may also be affected following ingestion, manifesting with stomatitis and bluish discoloration of the gingiva [5, 27].

In the intermediate phase (hours to weeks), cardiac and neurologic manifestations become apparent. Cardiac signs, such as sinus tachycardia, hypertension, and chest pain, are the most common; bradycardia, ventricular arrhythmias, and atrial fibrillation, in the absence of structural heart disease, have also been described [1, 2, 28]. The cause of thallium's effects on the heart is probably multifactorial; some authors hypothesize a component of vagal nerve involvement [2].

Neurological signs are prominent in the intermediate phase. In some cases, these may be the first signs of poisoning, preceding any gastrointestinal symptoms [5, 10, 11]. In most cases, painful paresthesias affecting the distal extremities are the first manifestations of neurotoxicity. The lower extremities are affected before the upper extremities. Motor weakness may occur later, also localizing to the distal extremities [1–3]. Early in the course, reflexes are preserved, distinguishing thallium toxicity from Guillain-Barré syndrome, though the two can be confused if there is no known history of thallium exposure [11]. Muscle wasting may become apparent weeks after initial ingestion. Cranial nerve palsies have also been observed, with varied manifestations such as ptosis, dysarthria, dysphagia, weakened gag reflex, diplopia, and facial weakness [2, 10, 26, 29]. Cranial nerves I and VIII are not involved [26]. Additional findings include ataxia, tremor and myoclonus, blindness, and other visual disturbances [1, 2]. Neuropsychiatric symptoms resembling psychosis or delirium are also described in case reports and series [10, 27, 30]. The development of encephalopathy, coma, and seizures occurs late in severe poisoning, and generally carries a poor prognosis. Pathological examination of peripheral nerve fibers demonstrates axonal degeneration with variable damage to the myelin sheath. Nerve fibers within the spinal cord appear unaffected [26]. Nerve conduction velocity tests have shown that decreased velocities are limited to larger, fast-conducting fibers [31].

Compared to other heavy metals, thallium poisoning is associated with relatively milder renal effects. Proteinuria, as well as excretion of leukocytes and erythrocytes, may occur without an overall loss in renal function [2]. In experimental animal models, elevations of blood urea nitrogen (BUN) and loss of urine concentrating ability are detectable within 2 days of thallium exposure but normalize within 10 days. Cellular damage is localized to the thick ascending loop of Henle, with sparing of the glomeruli [20].

Dermatological changes typically occur during the late phase (2–4 weeks). Though thallium poisoning can cause a wide variety of skin changes, alopecia is the most characteristic feature [14]. Within a month of onset, alopecia may involve the entire scalp [1, 29]. Alopecia can also affect body hair areas such as the axillae, extremities, and pubis, though the medial eyebrows are spared [32, 33]. If the patient survives the acute poisoning episode, affected hair regrows over the next few months. Examination of shed hair roots may reveal a blackened appearance, though the lack of this finding should not preclude consideration of thallium exposure [8, 32]. Mees lines are another characteristic finding, due to disruption of nail formation [32, 33]. Other dermatological effects can include acne, glossitis, stomatitis, anhidrosis, palmar and plantar hyperkeratosis, and eczematous lesions [2, 14, 32, 33].

A number of persisting neuropsychiatric and ophthalmological findings have also been described in surviving patients, weeks to months following initial exposure. Memory deficits, depression, anxiety, and continued neuropathic symptoms have all been reported [11, 30]. Thallium can cause the formation of cataracts as well as retrobulbar neuritis. This latter condition may affect color vision and visual acuity, in addition to the formation of central scotoma [2].

Diagnosis

Thallium poisoning should be considered in any patient presenting with gastroenteritis, ascending polyneuropathy, and alopecia. However, as noted

earlier all of these findings may not be present simultaneously. Definitive diagnosis is made through the detection of elevated thallium concentrations in bodily fluids, typically a 24-h urine collection [18]. Reported urinary thallium levels in poisoning cases vary widely, ranging between 200 and 3000 µg/L in more recent case series [10, 11]. Normal urinary thallium levels are generally expected to be less than 1 µg/L. Regarding ancillary studies, nerve conduction studies may be helpful in confirming the presence of neuropathy. Overall, a high index of suspicion is required, as the differential diagnosis is broad and includes Guillain-Barré syndrome, systemic lupus erythematosus, botulism, poisoning by other heavy metals (arsenic, lead, selenium), other toxic exposures (chronic alcoholism, organophosphates), thiamine or riboflavin deficiency, and, rarely, porphyria.

Common Error in the Diagnosis of Thallium Poisoning

Not considering thallium poisoning in patients who present with gastrointestinal symptoms, peripheral neuropathy, and alopecia.

Treatment

Since there are no known therapies which directly antagonize the biological effects of thallium, treatment is focused on increasing elimination via urinary or fecal excretion. Due to the relative rarity of thallium poisoning, data from controlled trials is unavailable [34].

Fecal Elimination

The most widely recommended agent to enhance fecal excretion of thallium is ferricyanoferrate (II) or Prussian blue (PB). Prussian blue is not absorbed within the gastrointestinal tract and acts as an ion exchanger for univalent cations [18]. Prussian blue can bind thallium within the gastrointestinal lumen and thereby prevent enterohepatic circulation [34]. Early

studies in rats demonstrated substantial increase in fecal thallium elimination with corresponding decrease in tissue body burden and mortality following PB treatment [35]. These findings were corroborated in multiple other animal models [2, 18]. Though clinical trial data is lacking, a number of case reports and series have described the use of PB in human cases [10, 11, 30, 36, 37] (Grade III evidence). Mortality rates may still be high despite PB therapy, particularly if there are delays in instituting medical treatment [10]. Due to the potential morbidity and mortality and paucity of other treatment options, Prussian blue should be administered in all cases of known or suspected thallium poisoning (Grade III evidence). Prussian blue, under the trade name Radiogardase, has been approved for use by the US Food and Drug Administration for thallium and radioactive cesium poisoning. The manufacturer's recommended dose is 3 g orally, three times per day. 250 mg/kg twice per day is another alternate regimen [18]. Prussian blue appears to be well tolerated, with constipation reported as the primary adverse effect [38].

Activated charcoal has also been proposed as a treatment to disrupt enterohepatic circulation of thallium. Animal studies demonstrate increased fecal thallium elimination following charcoal therapy [39]. Thallium binding by activated charcoal has also been confirmed by in vitro experiments as well [40]. Multiple dose activated charcoal has been reported to be successful in cases where Prussian blue was not immediately available [8] (Grade III evidence). Finally, while sodium polystyrene sulfate also exhibits thallium binding, this effect is likely insignificant in vivo given that the high potassium concentration within the gastrointestinal lumen means potassium will likely be the dominant binding substrate [40].

Enhanced Elimination

Despite thallium's large volume of distribution, numerous reports have been published describing the use of hemoperfusion or hemodialysis in the

treatment of thallium poisoning. Individual case data demonstrates an approximate 50% decrease in blood thallium concentrations eight hours following a hemodialysis session [41]. Continuous veno-venous hemodialysis may produce greater relative decreases in blood thallium compared to intermittent hemodialysis [37]. However, the total amount of thallium removed via dialysis may be relatively modest; in one published case, 120 h of continuous dialysis was calculated to have removed a total of 143 mg of elemental thallium in a patient who ingested 2 g of thallium sulfate (1.6 g of elemental thallium) [42]. In regards to charcoal hemoperfusion, it may only be useful at relatively lower blood thallium concentrations due to saturation of the column [43]. The actual benefit of renal replacement therapies in thallium poisoning is difficult to gauge, as patients with good clinical outcomes typically receive other therapies such as PB [27]. Despite this limited data, an expert panel recently recommended that dialysis be used in cases of severe thallium poisoning, particularly when serum thallium concentration exceeds 1000 µg/L (Grade III recommendation). It was also recommended that dialysis treatment continue until serum concentrations fall below 100 µg/L [12] (Grade III recommendation).

Historically, forced diuresis has also been described as a method to increase urinary thallium excretion [42]. As with dialysis cases, patients treated with forced dialysis also received other forms of therapy, including PB. As such, forced diuresis is not recommended in cases of known or suspected thallium poisoning.

Indications for ICU Admission in Thallium Toxicity

Depressed neurological or respiratory status
Signs of cardiotoxicity

Other Therapies

Since the severity of thallium toxicity was recognized nearly a century ago, a large number of therapies have been proposed. Based on

thallium's interference with potassium-dependent processes, potassium supplementation was purported to be beneficial in treating thallium poisoning [44]. However, subsequent reports have raised concerns of worsening mental status with potassium treatment and it is no longer recommended [45]. Early animal studies found that dithizone (diphenylthiocarbazone) could increase both fecal and urinary thallium excretion, leading to its use in treating human poisoning cases [29, 39]. Use of dithizone has been abandoned, though, due to potential diabetogenic effects [29]. Dithiocarb (diethyldithiocarbamate) is another potential chelating agent that was discontinued for safety reasons; animal studies demonstrated increased thallium distribution to the brain following dithiocarb administration [46]. Dimercaprol (British anti-lewisite) has been shown to be ineffective in increasing thallium elimination [39]. In rat studies, treatment with other thiol-containing compounds (cysteine, methionine) has been associated with increased mortality compared to controls [47].

Special Populations

Pregnant Patients

Thallium readily crosses the placenta and is a potent teratogen in both chick and rat animal models. Observed malformations include reduced body weight, hydronephrosis, and impaired skeletal development [48, 49]. However, published reports of human prenatal thallium exposure are rare, with a literature review performed in 2000 finding only 18 reports containing adequate data [36]. The reported outcomes in the affected children ranged from no apparent abnormalities to severe effects (imperforate anus, cryptorchidism, long term psychomotor retardation) [36]. Prussian blue is currently listed as a pregnancy category C drug (evidence of teratogenicity in animals, but not in humans) by the US FDA and should be used in any pregnant patient with known or suspected thallium toxicity. Nursing is not recommended as thallium is known to transfer into breast milk.

Concluding Summary

The diagnosis of thallium poisoning is made on the basis of clinical findings and elevated thallium concentrations in body fluids, typically urine. In addition to supportive care, treatment with PB should be administered as soon as possible. The dosage regimen is 3 g, three times per day, or 250 mg/kg twice daily. Multiple dose activated charcoal is an acceptable alternative if PB is unavailable. Hemodialysis should also be utilized in any cases of severe thallium toxicity. Clinicians should have a low threshold for ICU admission as outcomes are difficult to predict and patients often decompensate suddenly many days after initial presentation.

Key Points in Thallium Toxicity

1. The diagnosis of thallium toxicity is made on clinical grounds and urine thallium determinations.
2. The three hallmarks of thallium poisoning are gastrointestinal symptoms, peripheral neuropathy, and alopecia.
3. Therapy consists of Prussian blue (or activated charcoal) and extracorporeal thallium removal.

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Part XV

Chemical Agents: Solvents, Glycols, and Alcohols

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Ethylene Glycol

Ethylene glycol is a colorless, almost nonvolatile liquid with an aromatic odor that is recognizable on the breath of some victims. It is used widely as antifreeze in internal combustion engines and as a solvent in various manufacturing processes.

There are many similarities between the pathophysiologies of ethylene glycol and methanol poisoning (see ► [Chap. 88, “Methanol and Formaldehyde”](#)). Although little comparable epidemiologic data exist, ethylene glycol poisoning seems to be more frequent than methanol intoxication in the developed world, whereas methanol poisonings are far more frequent in the developing world. Besides being the “poor man’s” substitute for ethanol, ethylene glycol has also been used as suicidal agent – sometimes in “copy-cat” epidemics among young people [1, 2].

Biochemistry and Clinical Pharmacology

Ethylene glycol is rapidly and completely absorbed after oral administration. The volume of distribution is approximately 0.7 L/kg based on studies in two male patients [3], although values of 0.54 L/kg [4] and 0.83 L/kg [5] also have been reported in men.

The elimination kinetic profile of ethylene glycol has not been completely clarified. There is evidence for a saturable elimination with linear (first-order) elimination for low-to-moderate plasma concentrations (<40 mmol/L [<250 mg/dL]) with a half-life of 6 h [4]. For higher plasma concentrations, the elimination seems to approach nonlinear (zero-order) kinetics.

In one male patient, the volume of distribution of glycolate, the major circulating ethylene glycol metabolite, was calculated to be 0.6 L/kg, with an estimated intrinsic half-life of 6 h over the concentration range studied [4]. When ethylene glycol metabolism was inhibited by fomepizole, the mean endogenous half-life of ethylene glycol was 10 h and the mean elimination rate was 1.1 mmol/L/h (6.8 mg/dL/h; $n = 4$) [6]. In one patient who

was admitted numerous times, a median ethylene glycol half-life of 12.9 h (range 10.0–17.3 h) was found during antidote treatment and normal renal function, indicating both glomerular filtration and tubular secretion of ethylene glycol in the kidneys [7]. The half-life of ethylene glycol during intermittent hemodialysis was 2.4 h, whereas the glycolate half-life in two admissions were calculated to 2.4 and 3.9 h, respectively. The latter were slightly shorter than elsewhere reported: 10.4 ± 7.9 h ($n = 4$) [6], 7 h ($n = 1$) [4], and 4.5 h ($n = 1$) [8].

Pharmacokinetics of Ethylene Glycol

Volume of distribution: 0.7 L/kg

Protein binding: none

Mechanisms of clearance: hepatic and renal

Active metabolites: glycolic acid and oxalic acid far more toxic than the parent compound

Methods to enhance clearance: hemodialysis

Pathophysiology of Toxic Effects

The potentially lethal dose of ethylene glycol in untreated patients is not well established, but 100 mL is the most frequently cited approximation. A value of 1–2 mL/kg seems reasonable [9].

The primary enzyme in ethylene glycol metabolism is alcohol dehydrogenase (ADH) (Fig. 1). Similar to methanol, the toxicity of ethylene glycol is mediated by its metabolites. In contrast to methanol, ethylene glycol causes central nervous system (CNS) depression and inebriation in a manner similar to ethanol.

The mechanisms for the toxicity of ethylene glycol are not completely resolved. The role of oxalate (see Fig. 1) was originally based on the visualization of oxalate-like crystals in the urine (see Fig. 2a, b) and the development of acute renal failure. Later, it was suggested that the aldehyde metabolites – mainly glycolaldehyde – were responsible for the toxic syndrome. It has been shown experimentally that these aldehydes were able to inhibit oxidative phosphorylation, glucose

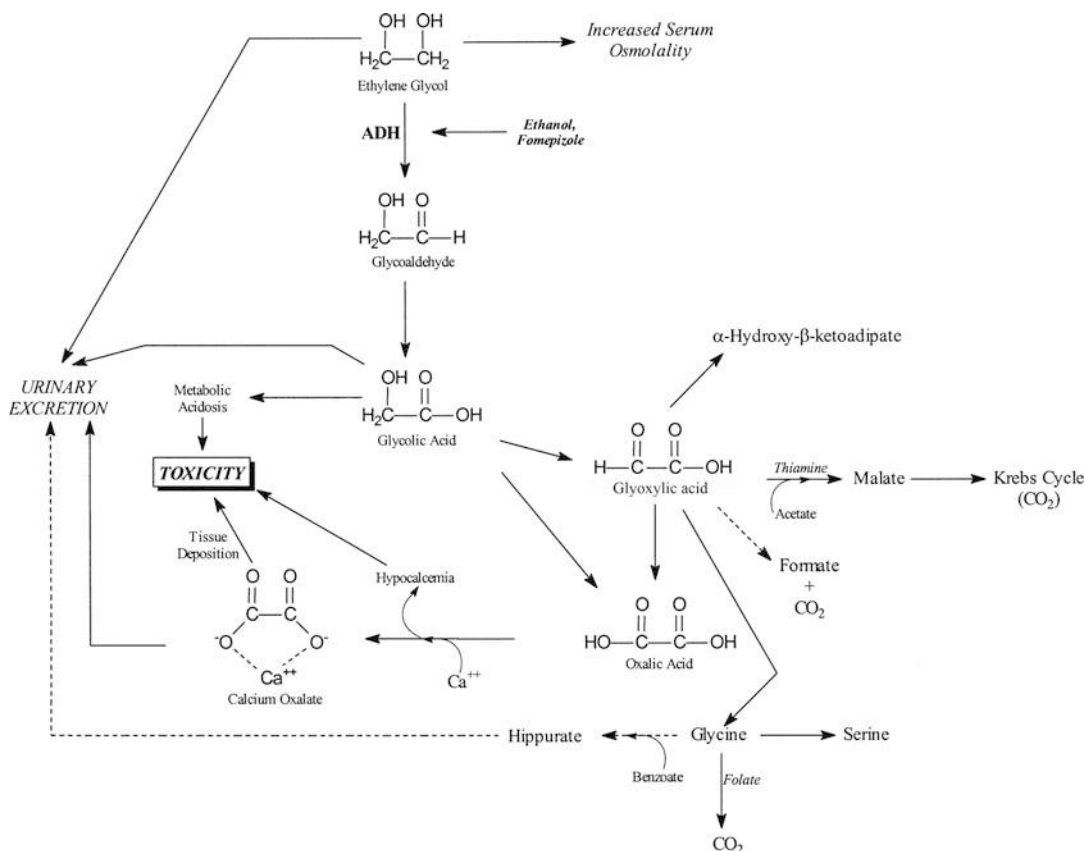


Fig. 1 The complex metabolism of ethylene glycol. *Solid arrows* represent major routes or pathways. *Dotted arrows* are theoretical or less important routes. Direct renal

excretion of ethylene glycol is a major pathway of elimination, provided that normal renal function is present. *ADH* alcohol dehydrogenase

metabolism, protein synthesis, DNA replication, and RNA synthesis; these aldehydes may also be able to oxidize intracellular sulfhydryl groups [10].

The mechanism for the renal toxicity of ethylene glycol is clearly associated with the accumulation of calcium oxalate monohydrate (COM) crystals in the kidney [11, 12]. Although older human case studies [13] and studies in animals [14] appeared to show tubular necrosis without the appearance of crystals, recent human [15] and animal studies [16] have confirmed that the insoluble COM is deposited in the renal tubules and causes the kidney damage with evidence of proximal tubular necrosis. Microscopically, necrotic damage is observed only in the presence of COM [15, 16], and metabolically, damage is

most severe in kidneys with the highest accumulation of COM [16]. In vitro studies of the toxicity of COM, glycolate, glycolaldehyde, and glyoxylate in normal human proximal tubule cells showed that only COM induced renal cell death at relevant concentrations [17], whereas none of the other metabolites including the oxalate ion had an effect on cellular viability.

As judged from experimental studies, there may be no major differences in the way rodents and humans handle ethylene glycol. This idea is based on the fact that both become acidotic and display kidney injury after exposure. As such, the measurement of the ethylene glycol metabolites in rodents may also have some validity in humans [18]. In experimental studies with ethylene glycol-intoxicated rats, dogs, and monkeys,

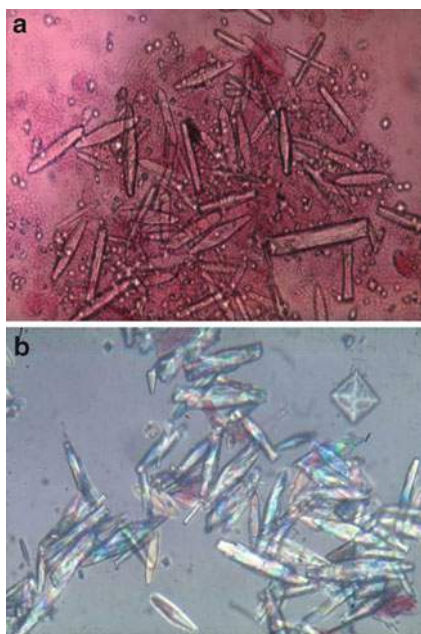


Fig. 2 Typical needle-shaped calcium oxalate monohydrate (COM) crystals in the urine during ethylene glycol poisoning (**a**) (Regular HE-staining). Envelope-shaped calcium oxalate dihydrate crystals (**b**) are less frequent but may occur in early stages of poisoning (Polarized light) [4]

neither circulating glycolaldehyde nor glyoxylate was detected using gas chromatography–mass spectrometry techniques [18–20]. In addition, in six patients poisoned with ethylene glycol, plasma glyoxylate levels were less than 1.2 mg/dL (<0.2 mmol/L), and the glycolate concentrations ranged from 100 to 175 mg/dL (17–29 mmol/L), demonstrating that of the relevant metabolites, only glycolic acid is present in the blood in amounts significant to produce the metabolic acidosis [21].

In summary, the toxicity of ethylene glycol is most probably due to a combination of the severe metabolic acidosis caused by glycolic acid and the precipitation of calcium oxalate crystals resulting in impaired organ function, especially in the kidneys (see Fig. 1). The toxicity of glycolate is probably less than that of formate, the major toxic metabolite in methanol poisoning [9, 22]. Hypocalcemia and the resulting tetany and

seizures are probably less important mechanisms of toxicity (see Fig. 1).

Clinical Presentation and Life-Threatening Complications

Many authors describe the clinical syndrome of ethylene glycol poisoning in three stages: (1) CNS depression, (2) cardiopulmonary complications, and (3) renal failure. Although there is some support for this classification, especially for the understanding of the pathophysiology, there is considerable clinical overlap between stages.

Ethylene glycol poisoning is characterized by an initial CNS depression phase associated with inebriation progressing to coma. After 4–12 h, signs and symptoms resulting from the metabolites appear if ethanol has not been coingested. The increasing accumulation of glycolic acid leads to metabolic acidosis, which may be severe, and to compensatory hyperventilation. In contrast to methanol poisoning, these patients are usually comatose when hyperventilation is pronounced, so there is most often no subjective feeling of dyspnea. Also, for unknown reasons, leucocytosis, elevated blood pressure, and tachycardia are usually prominent features.

For the first 12–18 h postingestion, urine output is generally still adequate, and if proper treatment is started at this stage, full recovery is usually seen, although the patient may have some degree of acute kidney injury (AKI) as evidenced by elevation of serum creatinine. However, in most cases, the AKI will have a good prognosis in the long run. Another complication of calcium oxalate precipitation, such as hypocalcemia-induced tetanic contractions, may occur. The prognosis of acute renal failure is good due to dialysis therapy, although the plasma creatinine may not return to normal for weeks to months [9, 23].

Without adequate treatment, seriously poisoned patients rapidly deteriorate. In addition to CNS depression possibly associated with the inebriating effects of ethylene glycol (similar to ethanol), cerebral edema, convulsions, oliguric

renal failure, and respiratory problems may develop. Pulmonary infiltrates may be observed radiologically, but these changes are thought to be noninfectious in origin. Calcium oxalate crystals have been observed in the lungs of patients who have died from ethylene glycol poisoning, as well as in brain tissue on autopsy. Given this observation, one could postulate that these changes may be an inflammatory reaction related to this precipitation. Although “cardiogenic pulmonary edema” is claimed to occur in ethylene glycol poisoning, this is not frequent. While the cardiac ejection fraction may be lowered (to about 40% in severely poisoned patients), this is not the major cause of the pulmonary infiltrates seen in these cases. The pulmonary capillary wedge pressure is often normal in this situation; as such, the diagnostic criteria for acute respiratory distress syndrome (ARDS) are fulfilled. The concomitant ingestion of ethanol may inhibit the metabolism of ethylene glycol to its toxic metabolites, thereby prolonging the initial CNS phase of inebriation and delaying the onset of the other clinical features of toxicity.

Patients admitted “in extremis” may survive with adequate treatment. These patients should undergo computed tomography or magnetic resonance imaging of the head to evaluate the degree of brain damage. Some of these patients develop (large) cerebral infarcts or cerebral edema resulting in brain death [3, 9], whereas patients without these findings may have excellent prognosis in spite of weeks in a coma. There are a few reports of ocular manifestations and methemoglobinemia associated with ethylene glycol poisoning [24, 25]. No analytic investigations were performed, however, to rule out methanol contamination of the liquid ingested. One ethylene glycol-intoxicated patient developed visual dyspraxia as a result of cerebral infarcts [3]. No objective ocular complications were observed.

Diagnosis

Ethylene glycol in biologic fluids can be determined easily by enzymatic methods [26], or by

gas chromatography [27]. Simultaneous determination of ethylene glycol and glycolate is also possible [28].

If specific analysis is not available, the use of the anion and osmolal gaps may suggest the diagnosis (see ► [Chaps. 88, “Methanol and Formaldehyde”](#) and ► [15, “Acid–Base Balance in the Poisoned Patient”](#)) [23, 29, 30]. An ethylene glycol concentration of 100 mg/dL (16 mmol/L) increases the osmolal gap by 16/0.93, or 17 mOsm/kg H₂O (see ► [Chap. 88, “Methanol and Formaldehyde,”](#) Table 1). Osmometry uses osmolality, which is expressed as milliosmoles per kilogram of water (mOsm/kg H₂O). Osmolarity is expressed as milliosmoles per liter (mOsm/L). Because serum consists of 93% water, one has to divide serum osmolality by 0.93 to compare these two parameters. Theoretically the sensitivity of the osmolal gap should be low at ethylene glycol concentrations less than 50 mg/dL (8 mmol/L). However, for unknown reasons, the osmolal gap tends to be higher than expected from the molar contribution of ethylene glycol at such low levels. A possible explanation for this could be that bicarbonate is replaced by glycolate in the “anion side” of the Gamble diagram, and this may increase the dissociation coefficient (1.86) used in the calculations of osmolality. At low ethylene glycol concentrations, the patients are usually most acidotic, and more bicarbonate is replaced by glycolate in the “anion side” (see ► [Chap. 88, “Methanol and Formaldehyde,”](#) Fig. 4).

Serum osmolality measurement must be performed by the freezing point depression method, not by the vapor pressure method. If ethanol is coingested, there may be no metabolic acidosis, or anion gap, before the ethanol is metabolized. The details of the calculation of the osmolal gap are given in ► [Chaps. 88, “Methanol and Formaldehyde”](#) and ► [15, “Acid–Base Balance in the Poisoned Patient”](#). If ethanol is present, calculation of the osmolal and anion gaps must be repeated periodically. In late stages of ethylene glycol poisoning, most of the parent compound is metabolized to glycolic acid. In this situation, the anion gap may be increased considerably, but the osmolal gap may be close to normal. As such,

a small or normal osmolal gap does not eliminate the possibility of toxic alcohol ingestion, especially in the presence of metabolic acidosis and significant anion gap [23] (see “► Chap. 88, “Methanol and Formaldehyde,” Fig. 4).

Many arterial blood gas analyzers use lactate oxidase for the enzymatic reaction, which can give a falsely elevated lactate concentration in the presence of glycolate. By subtracting the “real” level of lactate (as found by chromatography methods or by the use of lactate dehydrogenase), this “lactate gap” will indirectly indicate the presence of glycolate, hence ethylene glycol poisoning [31, 32].

Urine microscopy may reveal envelope-shaped calcium oxalate dihydrate crystals (typically in early stage) or needle-shaped calcium oxalate monohydrate crystals (typically in late stages) (Fig. 2a, b). These findings may be delayed, and a negative microscopy should be repeated if diagnosis is still unclear. About half of patients present with crystalluria on admission, and most, but not all, develop this sign later. The crystalluria may be massive and easy to detect, even by an inexperienced microscopist. In addition, there usually are erythrocytes, leukocytes, and different casts in the urine sediment [3, 33].

Treatment

Treatment of ethylene glycol poisoning should follow the well-established principles of supportive care. Activated charcoal is of no value in ethylene glycol poisoning.

Metabolic Acidosis

Although not studied in a formal clinical trial, it is generally accepted that the metabolic acidosis associated with ethylene glycol poisoning, particularly if severe, should be treated aggressively by infusion of sodium bicarbonate. In the first few hours, 600–800 mmol (milliequivalents) of bicarbonate may be needed, especially if antidotal therapy has not been initiated. Because ethylene glycol is metabolized faster than methanol, the

acidosis develops more rapidly if an ADH inhibitor (ethanol or fomepizole) is not given, in which case a so-called bicarbonate-resistant metabolic acidosis may develop. The rapid correction of acidosis in these patients may provoke tetanic signs, especially when hypocalcemia already is present.

Inhibition of Alcohol Dehydrogenase

For ethylene glycol-poisoned patients, it is critical that ethanol or fomepizole be given to inhibit the generation of toxic metabolites by ADH. (Grade II-1 recommendation) The major advantage of fomepizole compared with ethanol is its documented effectiveness, lack of CNS depression, ease of administration, and ability to reduce the need for hemodialysis [22, 34]. If fomepizole is given to a patient with ethylene glycol poisoning before renal failure develops, hemodialysis may not be necessary [34–36]. Fomepizole (molecular weight 82 g/mol) is removed by hemodialysis with a dialysance close to that of urea [37]. No drug concentration monitoring is necessary, however, during this procedure. There are only anecdotal reports defining the threshold for antidote use in ethylene glycol poisonings. However, a recent review suggests an ethylene glycol level of 10 mmol/L (62 mg/dL) as a reasonable cut-off value given no or only mild metabolic acidosis [22]. In conventional acidotic patients or patients with renal impairment, 20 mg/dL (3 mmol/L) seems appropriate, although this has not been validated. If no serum ethylene glycol concentration is available, the degree of metabolic acidosis should be considered. ADH inhibition should be undertaken if the base deficit is greater than 10 mmol/L or a progressive decrease in serum bicarbonate is seen in serial measurements. In borderline situations, one loading dose of ethanol (e.g., healthy adult with a serum ethylene glycol concentration <62 mg/dL (10 mmol/L) and base deficit <10 mmol/L) may be preferred over fomepizole, which is usually more expensive [22]. In serious ethylene glycol poisoning, however, fomepizole is the preferred antidote.

Indications for ICU Admission in Ethylene Glycol Poisoning

There should be a low threshold for patients with pronounced metabolic acidosis (>20 mmol/L base deficit). Patients may deteriorate rapidly, and early treatment with “many nurse hands” is *essential* for outcome. Treatment is complicated (bicarbonate, antidote, treatment of seizures); patients without “normal admission criteria” also should be considered for the intensive care unit in cases of significant poisoning, especially if ethanol is the antidote in use.

Dosing of Fomepizole

A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 h for four doses, then 15 mg/kg every 12 h thereafter until ethylene glycol levels have been reduced to <62 mg/dL (10 mmol/L). All doses should be given as a slow intravenous infusion over 30 min (dissolved in, e.g., 100 mL of isotonic saline or dextrose), or it can be given orally at the same doses. During hemodialysis, the frequency of dosing should be increased to every 4 h, whereas every 8 h is a likely sufficient dosing frequency during continuous dialysis modalities, continuous renal replacement therapy (CRRT)/continuous veno-venous hemodialysis (CVVHD)/continuous veno-venous hemodiafiltration (CVVHDF). (Grade III recommendation)

To reach a therapeutic blood ethanol level of 100 mg/dL (22 mmol/L) – see suggested dosing regimen in ► Chap. 88, “Methanol and Formaldehyde,” Table 3. The maintenance infusion should be increased or decreased according to measured blood ethanol concentrations.

If ethanol is used as an antidote, it should be given as in methanol poisoning (see ► Chap. 88, “Methanol and Formaldehyde”). The serum ethylene glycol concentration threshold for stopping

antidotal therapy has been set arbitrarily at less than 40 mg/dL (<6 mmol/L). If an ethylene glycol concentration is not readily available, an osmolal gap less than 10 mOsm/kg H_2O may be an indicative substitute value for stopping therapy, provided no metabolic acidosis or indication of renal dysfunction is present. Although the affinity of ADH for ethylene glycol is lower than that for methanol [38, 39], this makes little practical difference in therapeutic dosing.

Several studies have indicated that ethanol can significantly inhibit ethylene glycol elimination [4, 5, 8, 40]. Ethylene glycol is renally excreted. An apparent elimination half-life for ethylene glycol of 14–17 h during ethanol therapy has been shown in patients without renal failure [40], compared with an elimination half-life of 6 h without ethanol administration [4]. Similar half-lives were observed using fomepizole instead of ethanol in patients without kidney failure [7, 41]. The apparent half-life of ethylene glycol during antidotal therapy depends on urine output and the degree of renal impairment. Although fomepizole in many places has replaced ethanol as the antidote of choice in ethylene glycol poisoning [34, 35, 42], ethanol still may be used in some hospitals. Patients with CNS depression must be closely monitored if ethanol is given because this administration has been associated with respiratory arrest [40]. The American Academy of Clinical Toxicology published practice guidelines indicating that fomepizole should be the first-line ADH inhibitor in the treatment of serious ethylene glycol poisoning. Ethanol should be reserved for cases in which fomepizole is not available or the patient is allergic to fomepizole [43]. Note that celecoxib has a pyrazole structure as does fomepizole. It is unknown if there are cross reactions between the two in cases of allergic reaction to one or the other. In the case of patients who have had a significant reaction to celecoxib, fomepizole should, if needed, be administered with appropriate caution and preparation for a possible allergic reaction.

Hemodialysis

The dialysance of ethylene glycol is well documented [3, 5, 34]. As should be expected

from its higher molecular weight than that of methanol (62 d vs. 32 d), ethylene glycol is less dialyzable than the latter (130 mL/min vs. 160 mL/min, using a 1.6 m² dialyzer at blood flow of 200 mL/min) [3, 9]. The dialysance of the toxic metabolite glycolate has also been documented [6, 21]. Because ethylene glycol has no significant pulmonary elimination, hemodialysis becomes the major route of its elimination if renal failure is present and ADH metabolism is blocked. Hemodialysis offers the additional possibility of eliminating the toxic metabolites, particularly glycolate, and correcting the metabolic and electrolyte disturbances seen in these patients. There are no studies comparing the various dialysis modalities in ethylene glycol-poisoned patients, but intermittent hemodialysis is probably more effective than continuous renal replacement therapy (CRRT), as is seen in methanol poisoning [44]. In patients admitted late with established renal failure and low serum ethylene glycol levels or low osmolal gaps, CRRT may be considered especially if the patient is hemodynamically unstable.

If the patient is seen at an early stage (i.e., before severe metabolic acidosis and renal impairment have developed), hemodialysis may not be necessary, especially if fomepizole is the antidote used [7, 34, 36]. Under such circumstances, further metabolism of the glycol to its toxic metabolites is inhibited, and the glycol is excreted rapidly through the kidneys (half-life of 12–17 h). The onset of acute renal failure may require hemodialysis, CRRT, or peritoneal dialysis. The anion glycolate may have a moderate toxicity by itself, but it is a precursor for the nephrotoxic anion oxalate. As such, the degree of metabolic acidosis (reflecting glycolate levels) is an important indicator of the need for dialysis and glycolate removal [21].

As is evident from this discussion, it is not possible to establish strict indications for hemodialysis in ethylene glycol poisoning. This decision is difficult, and an experienced clinical toxicologist should be consulted. Hemodialysis may not be easily available in rural areas, and transport complications associated with critically ill patients must be taken into consideration,

especially if ethanol is the antidote given. The introduction of fomepizole also limits the need for hemodialysis. Because hemodialysis also removes glycolate, the degree of metabolic acidosis and the renal status of the patient are more important than the serum ethylene glycol concentration as such. Most patients with normal renal function and moderate metabolic acidosis (base deficit <20 mmol/L) are best treated with bicarbonate and fomepizole, even in patients with high serum ethylene glycol concentrations. The renal function of these patients must be monitored closely, however, because hemodialysis may be necessary later if oliguric or nonoliguric renal impairment develops. Patients with serum ethylene glycol levels of 558 mg/dL (90 mmol/L) and moderate metabolic acidosis [36] and in one case a patient with 700 mg/dL, a metabolic acidosis, and a high anion gap [45] have been treated with bicarbonate and fomepizole alone. Dialysis was, however, claimed to be necessary to avoid complications related to hyperosmolality in a case with serum ethylene glycol of >1000 mg/dL (161 mmol/L) [46].

When initiated, hemodialysis should be continued until the serum ethylene glycol concentration is less than 62 mg/dL (<10 mmol/L) and there are no acid–base disturbances. (Grade III recommendation). If blood ethylene glycol concentrations are not available, hemodialysis should be continued for at least 8 h, and longer if the acidosis is not corrected. If ethanol is used as an antidote, persisting acidosis indicates that too little ethanol is being given during hemodialysis. If hemodialysis is not available, peritoneal dialysis also removes ethylene glycol [47], although far less efficiently. Hemoperfusion has no role in the management of ethylene glycol poisoning.

Criteria for ICU Discharge in Ethylene Glycol Poisoning

Resolution of metabolic acidosis

Hemodynamic stability

If ethanol-treated, that treatment must be stopped, and the patient should be not inebriated

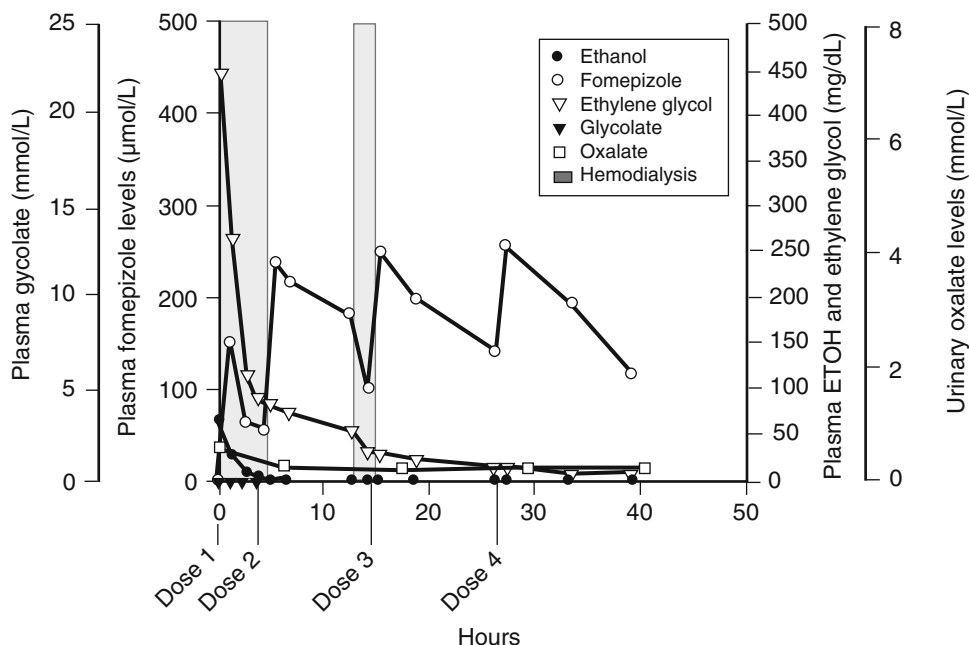


Fig. 3 Serial plasma glycolate, fomepizole, ethanol, and ethylene glycol concentrations and urinary oxalate excretion in a 35-year-old woman who presented 6 h after ingesting antifreeze in an attempt at suicide. Her initial arterial pH was 7.42. She was treated with fomepizole, underwent hemodialysis twice (initially for 4 h and subsequently for 2 h), and recovered uneventfully. To convert

the values for plasma ethylene glycol to millimoles per liter, multiply by 0.161. To convert the values for plasma glycolate to millimoles per liter, multiply by 0.132. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for plasma ethanol to millimoles per liter, multiply by 0.217 (From Brent et al. [34], 832–839)

The effectiveness of fomepizole and hemodialysis in an ethylene glycol poisoned patient is shown in Fig. 3. The possibility to treat an ethylene glycol-poisoned patient with normal renal function without hemodialysis during ongoing fomepizole treatment is shown in Fig. 4. The effectiveness of hemodialysis in a patient with acute renal injury and the difficulty of dosing ethanol is illustrated in Fig. 5.

Hypocalcemia and Seizures

The hypocalcemia associated with ethylene glycol poisoning may cause tetany and seizures, which should be treated with intravenous calcium gluconate (or chloride), usually 5 mmol IV each time. Calcium should not be given for hypocalcemia per se, however, because this may increase precipitation of calcium oxalate crystals in the tissues (see Fig. 1). If calcium therapy is not effective, convulsions can be treated

conventionally with benzodiazepines, or propofol/barbiturates in the most severe cases.

Pyridoxine and Thiamine

Pyridoxine and thiamine are thought to promote the alternative metabolism of glyoxylic acid to nontoxic metabolites (see Fig. 1). Data supporting this antidotal effect are sparse, however, and their use is not routinely recommended.

Prognosis

Outcomes are excellent for ethylene glycol-poisoned patients with early diagnosis and aggressive treatment. If acute oliguric or nonoliguric renal failure develops, the prognosis for the renal function is always good with normalization of serum creatinine within 2–3 weeks (rarely months). In severe cases, patients with late

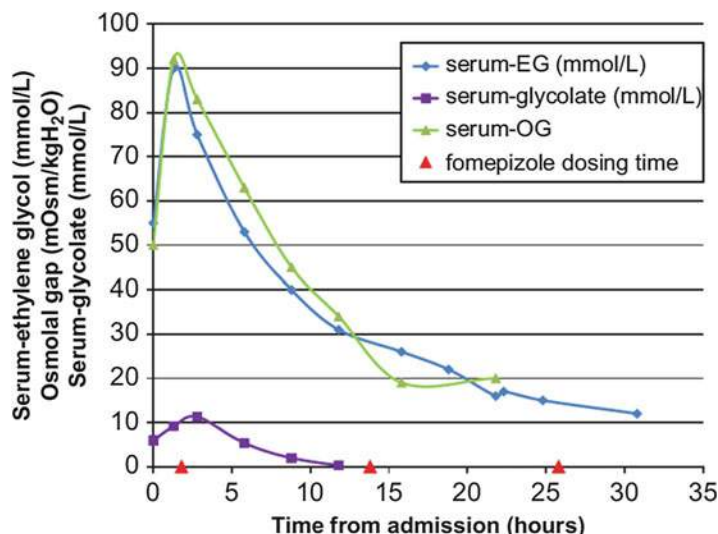


Fig. 4 S-ethylene glycol in healthy female treated with fomepizole and bicarbonate alone [7]. Note probable ongoing absorption due to early admission. Note also increasing S-glycolate before – and declining S-glycolate after – fomepizole administration. Half-lives of S-ethylene glycol

and S-glycolate during ADH inhibition were 10 and 2.4 h, respectively. The excellent correlation between S-ethylene glycol and osmolal gaps is also illustrated. Conversion factor mg/dL to mmol/L: EG: 0.016, glycolic acid: 0.013 (Reprinted with permission from Hovda et al. [7])

diagnosis and treatment may experience cerebral infarcts [9, 48].

It is important to note that in some severe cases, the prognosis may seem to be rather poor based on the overall clinical situation. If proper treatment is provided, especially dialysis in the acute stage with correction of acidosis (and removal of toxic metabolites), prognosis may be good even after weeks on mechanical ventilation and dialysis for acute renal failure. Treatment in the ICU must therefore not be discontinued early in these patients. A possible explanation for this could be that the extravascular precipitation of oxalate crystals causes a massive tissue edema (also in the brain) and that it takes time for this to resolve. Also, the crystals in the tissue and the cells may dissolve over time [49], which may partly explain the pathophysiology.

Special Populations

The toxicity of ethylene glycol in pediatric patients should generally be treated in a manner similar to that in adults. The experience with fomepizole in children is limited, but cases have been published, and ethanol [8] and fomepizole

both seem to be effective antidotes in children [47, 50, 51]. Use of new drugs such as fomepizole is generally discouraged in the first trimester of pregnancy, but in a study in pregnant rats [52], no adverse effects of fomepizole were reported. However, the alternative antidote ethanol has documented ability to cause fetal harm. In a pregnant woman with severe ethylene glycol poisoning, an antidote is obligatory, and either could be used – with a preference for fomepizole [22]. (Grade III recommendation)

Common Errors in Ethylene Glycol Poisoning

Delayed diagnosis because of failing to consider ethylene glycol poisoning in the differential diagnosis of high anion gap metabolic acidosis of unknown origin

Failure to appreciate that the absence of early clinical features and the presence of normal anion or osmolal gaps do not exclude a potentially toxic ethylene glycol ingestion

Failure to give enough ethanol, if this is the antidote chosen, especially during hemodialysis

Failure to closely monitor blood ethanol concentrations, if this antidote is used

(continued)

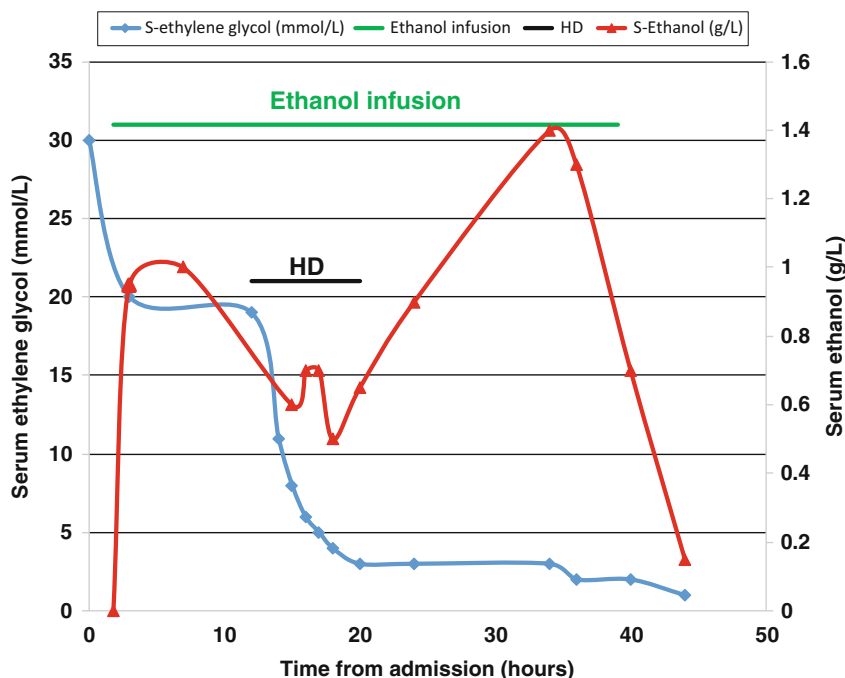


Fig. 5 Healthy adult male presenting with metabolic acidosis of unknown origin (gave no history). Elevated osmolar (30) and anion gaps (42; base deficit 21 mmol/L) and oxalate crystalluria indicated diagnosis (ethylene glycol measured later). He was treated with bicarbonate, ethanol and hemodialysis (HD) with uneventful recovery. Note dosing problems and variations in S-ethanol during

dialysis. Also note long half-life of S-ethylene glycol after terminated dialysis (ongoing ADH inhibition) because of transient acute kidney injury (AKI; no further dialysis necessary). As such, buffer and ADH inhibition would not have been sufficient treatment in this case with AKI. Conversion factor mg/dL to mmol/L: EG: 0.016

Failure to appreciate that prognosis may be good even in critically ill patients and over long periods if correct treatment is given

Failure to stay at the bedside until bicarbonate and antidotal therapy have been initiated because time is critical in severely poisoned patients

Key Points in Ethylene Glycol Poisoning

1. Ethylene glycol toxicity is caused by its metabolites.
2. The initial step in ethylene glycol metabolism is catalysis by alcohol dehydrogenase.
3. Treatment is based on inhibition of alcohol dehydrogenase, correction of metabolic acidosis, and removal of glycol and toxic metabolites by dialysis.

Diethylene Glycol

The clinical course and the pathologic features of poisoning with diethylene glycol (Fig. 6) have been described in some reports, among which “the 1937 sulfanilamide Massengill disaster” is probably the best known [53]. In that instance, diethylene glycol (73%) was used, because of a lack of knowledge of its toxicity, as the vehicle for preparing a liquid formulation of 10% sulfanilamide to treat infections. A total of 105 deaths due to renal failure were related to this sulfonamide formulation. No oxalate crystals were reported found in the kidneys or other organs of these victims, but the variety of the oxalate crystals (not only the envelope form) was probably not known for most clinicians before 1980

[33, 54]. Except for the lack of oxalate crystals, the pathologic findings in the various organs of these victims were similar to those found in ethylene glycol-poisoned victims.

In the 1995 Haitian episode, diethylene glycol-contaminated acetaminophen syrup caused renal failure in more than 100 children with a high mortality rate [55]. A similar episode also occurred in India [56] and in Panama in 2006 where an estimated minimum of 78 deaths were associated with consumption of a diethylene glycol-contaminated cough syrup [57]. The clinical features were renal failure, hepatitis, pancreatitis, bilateral peripheral neuropathy, and coma before death. Diethylene glycol is also found in brake fluids and other consumer products, such that sporadic ingestions also occur [58]. Because of the acute renal failure, it is difficult to relate the metabolic acidosis reported in some cases [59] to possible acidic metabolites of diethylene glycol metabolism by ADH. In one case report, there is an indication of a positive effect from hemodialysis for the removal of diethylene glycol [50]. In another case report, the use of fomepizole was associated with correction of the metabolic acidosis [60]. Topical application of silver sulfadiazine contaminated with diethylene glycol to patients with burns resulted in increased anion gap metabolic acidosis and acute renal failure. All five patients in this report died despite supportive treatment and bicarbonate replacement [61]. Autopsy was performed in one patient and no calcium oxalate crystals were observed.

Pathophysiology of Toxic Effects

Experimental studies in rats exposed to diethylene glycol showed similarities to ethylene glycol toxicity [62, 63]. The animals developed metabolic acidosis, as in ethylene glycol toxicity. Mortality was reduced if the animals were treated with bicarbonate, while administration of ethanol or fomepizole both prevented metabolic acidosis and reduced mortality to nil. Later studies in animals have demonstrated that diethylene glycol is metabolized to 2-hydroxyethoxyacetic acid, which is responsible for the metabolic acidosis

[62] and further to diglycolic acid (DGA), which accumulates markedly in the kidney and is the nephrotoxic metabolite [64]. No evidence that oxalate deposition actually occurs was noted, likely because the ether is generally resistant to metabolic degradation. During the Panama epidemic, urine and serum samples were collected as part of a case-control study such that the samples were collected late in the course (post case definition) [65]. These serum and urine samples were analyzed for concentrations of diethylene glycol and its metabolites – DGA was the only metabolite that was statistically related to case status. The serum and urine samples showed no evidence of conversion of diethylene glycol to ethylene glycol in humans. As such, DGA is of likely importance in human cases also.

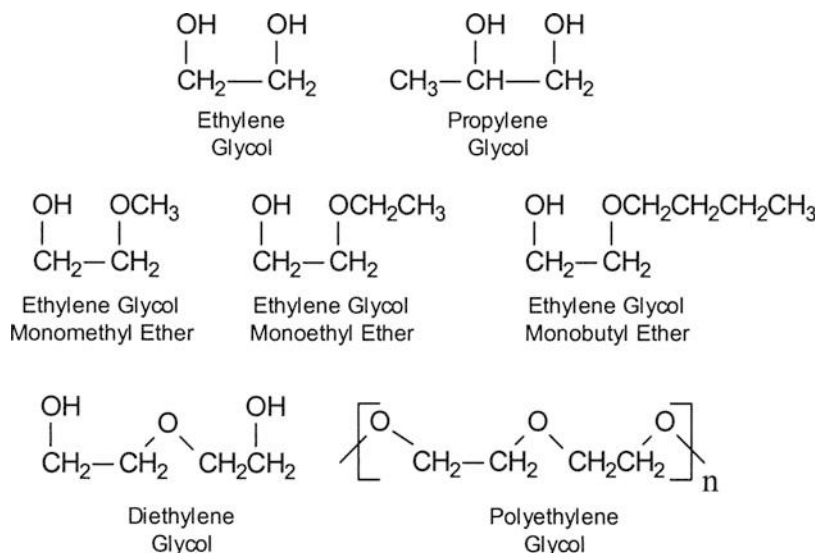
Clinical Presentation and Life-Threatening Complications

In humans exposed to diethylene glycol, the presence of acidosis was earlier questioned, but this may be due to the fact that these fatal cases were reported by pathologists with less emphasis on the clinical and metabolic features present prior to death [66]. Later studies have shown metabolic acidosis and gastrointestinal features followed by acute kidney injury after 1–3 days. In survivors, neurological features such as bilateral facial nerve palsy and peripheral neuropathy, coma, and death may develop after 5–7 days [67].

Diagnosis

If there is no history of ingestion of diethylene glycol, diagnosing this condition is difficult. There is no general laboratory analysis pointing to this diagnosis, except for specific analysis, which is rarely available in hospital laboratories. Clinical features that may suggest diethylene glycol would include acute kidney injury or bilateral facial nerve palsy or other neurological features. These patients should be observed for the development of metabolic acidosis (elevated anion gap), which should trigger treatment. Since the molecular weight is higher (106 g/mol, 1 g/L = 9 mmol/L which increases the osmolal gap with

Fig. 6 Chemical structures of common glycols and glycol ethers



only 10 mOsm/kg H₂O) than for the other alcohols that form toxic metabolites (methanol and ethylene glycol), calculation of the osmolal gap is likely less useful (see ► [Chap. 88, “Methanol and Formaldehyde,”](#) Table 1).

Treatment

The toxicities of ethylene glycol and diethylene glycol are similar in that the metabolic acidosis and kidney injury result from metabolism of the parent compound via ADH. At present, treatment of diethylene glycol poisoning should be as for ethylene glycol poisonings: bicarbonate and ADH inhibition should be given if metabolic acidosis is moderate or severe (base deficit > 10 mmol/L) (Grade III recommendation); hemodialysis should be performed in severely poisoned patients, especially if metabolic acidosis is pronounced (base deficit >15–20 mmol/L) or with evidence of renal injury. Assuming no protein binding of diethylene glycol and a volume of distribution close to 0.6 L/kg, this compound (MW 106 g/mol) should be removed by hemodialysis, which will correct acidosis and likely remove toxic metabolites. Because no strict treatment recommendations can be given, physicians dealing with these patients should consult a medical toxicologist or a poison center. Further

treatment is supportive. Although not documented, thiamine should be given to protect the patient from neurological complications – especially if ethanol abuse is present.

Polyethylene Glycol

The polyethylene glycols (see Fig. 6) (molecular weight approximately 400–4000 g/mol) can be liquids, but are solid when the molecular weight is greater than 1000 g/mol. The toxicity decreases with increasing molecular weight, probably as a result of poor absorption of the solid forms. In general, the toxicity is low but may be significant for the glycols with low-molecular weight. The polyethylene glycols are used as solvents or excipients for different purposes. They also are used, and well tolerated, in the electrolyte solution recommended for whole-bowel irrigation [68].

Little is known about the clinical features of polyethylene glycol poisonings, because few cases have been reported in peer-reviewed literature. The reported CNS depression, metabolic acidosis, and renal failure may point to some similarities with ethylene glycol poisoning [69].

Unexplained increased anion- and osmolal gaps were observed in three burn patients who died following a treatment with a polyethylene glycol-based burn cream. All three patients died

in acute renal failure. The concentrations of ethylene glycol found in the circulation of two patients (0.4–1.3 mmol/L) were unlikely to explain the osmolal or anion gaps; no oxalate crystals were reported in the kidney upon autopsy [70]. The authors attributed the toxicity to the effects of polyethylene glycols or their metabolites, not to ethylene glycol per se.

Treatment

The standard measures of gastric decontamination and supportive care are probably the mainstay of therapy in these rare poisonings if the patient is seen within 1 h. The efficacy of hemodialysis is hampered by the relatively high molecular weight of this group, but hemodialysis should be done if low-molecular-weight glycols are ingested (molecular weight <600 g/mol). If severe metabolic acidosis develops, fomepizole or ethanol treatment may be administered as in ethylene glycol poisoning, but the efficacy of this treatment has not been documented. Sodium bicarbonate should be given to correct severe metabolic acidosis.

Propylene Glycol

The use of propylene glycol (1,2-propanediol) (see Fig. 6) in various cosmetics has little toxicological significance. Its use as a solvent for intravenous drug formulations has shown that this compound is not completely inert from a toxicological point of view. Renal failure may result in retention of the glycol, causing CNS depression, as about 50% is excreted in unchanged form by the kidneys, whereas the rest is metabolized mainly to lactate, acetate, and pyruvate [71]. Metabolic acidosis may be pronounced because of its metabolism to lactate, and concentrations as high as 24 mmol/L (216 mg/dl) has been described when iv medications were given with propylene glycol as a vehicle [72]. One case also reports D-lactate levels up to 110 mmol/L from an overdose of propylene glycol [73]. The elimination half-life is about 19 h [74]. In two children, CNS

depression and seizures were observed after propylene glycol intoxication [75]. Propylene glycol is also found as a diluent in many drugs. One 50 year-old male with a iatrogenic overdose of lorazepam resulted in severe propylene glycol poisoning (peak level 659 mg/dL (87 mmol/L), pH 6.9, bicarbonate 5 mmol/L (5 mEq/L) and lactate 19 mmol/L). He was treated with fomepizole, continuous renal replacement therapy (CRRT) and CVVH. His metabolic acidosis resolved, but he died from anoxic brain injury [76].

Propylene glycol (molecular weight 76 g/mol) also may raise the osmolal gap (see ► Chap. 88, “Methanol and Formaldehyde,” Table 1). If lactic acidosis develops, this rare poisoning may raise the osmolal and the anion gaps. Propylene glycol concentrations of 760 mg/dL (100 mmol/L) did not cause CNS depression [77], whereas stupor and metabolic acidosis were present in a patient with serum propylene glycol concentrations of 70 mg/dL (9 mmol/L) [78]. In these two cases, the osmolal gap theoretically would be elevated by about 108 mOsm/kg H₂O (100/0.93) and 10 mOsm/kg H₂O (9/0.93). From these few cases, there does not seem to be any definite correlation between serum propylene glycol levels and toxicity.

Treatment

Treatment of propylene glycol poisoning is supportive. The effect of activated charcoal has not been documented. Hemodialysis will effectively remove propylene glycol in the rare cases where propylene glycol can cause severe poisonings [79].

Alkyl Ethers of Ethylene Glycol (Cellosolves)

The group of alkyl ethers of ethylene glycol consists of the mono alkyl ethers of ethylene glycol – ethylene glycol butyl ether (butyl glycol, Butyl Cellosolve), ethylene glycol monomethyl ether (methyl Cellosolve), and ethylene glycol

monoethyl ether (Cellosolve) (see Fig. 6). These compounds are used mainly as solvents in hydraulic fluids and in household cleaning products. Few cases of toxicity from these compounds have been published, and the mechanisms of toxicity are not completely understood. Coma, hypotension, and metabolic acidosis with hyperventilation are typical clinical signs of intoxication. The abnormal blood picture, including erythropenia, granulocytosis, hemolysis, and hemoglobinuria, seen in animals [80, 81] may also be seen in the clinical situation [82]. Until more data are available, supportive treatment is considered to be most important for this group of compounds.

Ethylene glycol butyl ether, also known as butyl glycol, poisoning has been reported after the suicidal ingestion of a window-cleaning agent containing butyl glycol and ethanol [82]. Coma and hypotension were present on admission with blood levels of ethylene glycol butyl ether and ethanol being 432 mg/L and 36 mg/L, respectively. Metabolic acidosis developed and was confirmed by the presence of the butyl glycol metabolite butoxyacetic acid and lactate. No increase in urine oxalate content was observed. The patient was treated with forced diuresis, bicarbonate, and hemodialysis. There was a suggestion of ethanol-induced inhibition of butyl glycol metabolism and a beneficial effect of hemodialysis in this patient.

In another case without concomitant ethanol ingestion, metabolic acidosis was accompanied by coma, hypokalemia, hemoglobinuria, oxaluria, and a transitory rise in the serum creatinine level in a patient who survived on supportive therapy alone [83]. The measured increased urinary excretion of oxalate and butoxyacetic acid in this case gives an indication of different metabolic pathways, one of which includes degradation of ethylene glycol butyl ether to ethylene glycol.

Two patients with methyl Cellosolve ingestion developed metabolic acidosis and coma [84]. The patient with the more severe metabolic acidosis developed slight acute renal failure, and urine oxalate crystals were observed. The other patient had no evidence of renal effect or oxalate crystals in the urine. Both patients had an uneventful recovery after treatment with bicarbonate and ethanol.

Treatment

Based on these case reports and overall theoretical considerations, it seems reasonable to treat these poisonings with supportive therapy, including possibly gastric decontamination if the patient is seen early (within 1 h), and bicarbonate to correct significant metabolic acidosis (base deficit > 10 mmol/L). Hemodialysis also seems justified if large doses are ingested and the patient is acidotic. The role of hemodialysis in these poisonings is theoretical and lacks empiric validation. The role of ADH inhibitors is controversial. Until more data are available, ADH inhibitors should be considered mostly in rare cases in which metabolic acidosis develops, to prevent an assumed formation of toxic metabolites by oxidation of the alcohol groups.

Because the role of ADH in the metabolism of these compounds is not clear, and because fomepizole is expensive in some countries, some clinicians may prefer to use ethanol. If ethanol is used, however, patients must be placed in an intensive care unit and monitored closely as described previously.

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Isopropyl alcohol (isopropanol, 2-propanol, propan-2-ol, IPA) is a clear, colorless, and volatile liquid that has a bitter taste and fruity odor similar to that of acetone [1–3]. Most commonly, isopropanol is found in rubbing alcohol as a 70% volume/volume solution in water. It is important to note that not all rubbing alcohol is made with IPA, as ethanol is also used. IPA also is found in solvents, inks, drug preparations, beauty products, de-icing agents, and hand sanitizers [4, 5]. Toxic effects of IPA are seen most commonly in alcoholics, who abuse it as a cheap, readily available substitute for ethanol [5–9]. However, most exposures occur in small children who develop toxicity through ingestion of IPA or who had long or repeated contact to IPA through dermal or inhalational exposure. Occupational exposure may occur by the dermal and inhalational routes [10–12]. The primary effects of IPA toxicity are central nervous system (CNS) depression, gastrointestinal irritation, and ketosis. Treatment is symptomatic and supportive.

Biochemistry and Pharmacokinetics

IPA is a volatile secondary alcohol. It has a volume of distribution of 0.45 to 0.7 L/kg [13–15] and is metabolized to acetone via hepatic alcohol dehydrogenase (ADH) (Fig. 1). In contrast to primary alcohols such as ethanol or methanol, the secondary alcohol, IPA, is metabolized to a

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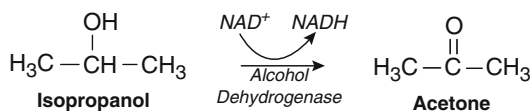


Fig. 1 Conversion of isopropanol to its primary metabolite acetone. Small amounts of isopropanol are excreted unchanged in the urine and expired air

ketone (acetone) but not to a carboxylic acid (see Fig. 1).

Pharmacokinetics of Isopropyl Alcohol

Volume of distribution: 0.45–0.7 L/kg

Protein binding: negligible

Mechanism of clearance: hepatic alcohol dehydrogenase metabolism, first-order kinetics

Half-life: isopropyl alcohol, 2–8 h; acetone, 7.7–27.7 h

Solubility: miscible in water

Vapor pressure: 33 mmHg

Data from references: [13, 14, 16, 17]

Pathophysiology

Central Nervous System Depression

Central nervous system depression may occur rapidly after ingestion of IPA [8, 13, 18–20]. Peak serum concentrations of IPA occur 30–60 min after ingestion due to its rapid absorption from the gastrointestinal tract [17, 21, 22]. In contrast to other toxic alcohols in which toxicity is largely dictated by metabolite production, IPA seems to be the primary chemical responsible for CNS depression because the onset of these manifestations clinically correlates with the time to peak serum IPA levels [5, 23, 24]. Patients also tend to clinically improve with declining serum IPA levels [8, 14, 20, 22, 23, 25]. However, they can also have prolonged CNS depression, despite declining serum IPA levels [7, 16]. Most of these cases show rising serum acetone levels, which has led to the theory that acetone may be responsible

for CNS depression. Acetone is known to cause CNS depression [26–30]. The literature also reports cases of patients with initial CNS depression whose mental status improved despite increasing acetone levels [8, 31]. Therefore it seems likely that both compounds are responsible for the CNS depression seen with IPA toxicity.

Based on animal studies, IPA is estimated to have twice the intoxicating effect of ethanol at similar serum concentrations [32]. This effect may be due to the higher molecular weight of IPA compared with ethanol [13] or perhaps the additive toxicodynamic effect of the acetone metabolite.

Respiratory depression and hypotension may accompany coma resulting from IPA intoxication [13, 17, 23–25, 33, 34]. These effects are most likely the result of peripheral vasodilation and depression of the brain stem [8, 13, 14, 17, 20, 23, 25, 35]. Tachycardia is common and may be a compensatory response to hypotension [36].

Common CNS effects of ethanol ingestion, such as ataxia, nystagmus, and dysarthria, occur but are not as common in IPA toxicity [36, 37]. Diminished reflexes are commonly seen in comatose patients with IPA toxicity [17, 31, 36]. Seizures are rare but have been reported in infants [35].

Gastrointestinal Effects

IPA may cause gastritis, mucosal irritation, and, in severe cases, hemorrhagic gastritis. Patients who ingested IPA may present with nausea, vomiting, and abdominal pain. It often is reported that hemorrhagic gastritis is caused by IPA [37, 38]. However, it is not clear that hemorrhagic gastritis is any more common than the upper gastrointestinal bleeding seen with ethanol abuse. Most abusers of IPA are alcoholics, and there is considerable overlap between these two groups. Systemic toxicity has been reported after rectal administration of IPA [39–41]. In these cases, serum IPA levels were comparable to serum levels attained after oral ingestion. Elevation of serum transaminases has been reported after IPA ingestion [42].

Metabolic Effects

Acetone is the major end product of IPA metabolism (see Fig. 1). Because no acidic product is generated, the metabolic acidosis associated with other toxic alcohols, like methanol or ethylene glycol, does not occur with IPA toxicity. Ketones or, more specifically, acetone can be measured in the serum and urine of patients with IPA toxicity. Acetone can be measured in the serum within 30–60 min of IPA ingestion but may not be measurable in the urine until 180 min after IPA ingestion [8, 21]. Patients poisoned with IPA often have a ketotic or sweet smell to their breath secondary to the presence of exhaled acetone [8, 20, 43, 44].

Other Manifestations

Hypothermia has been reported after IPA ingestion and is thought to be secondary to the CNS depression and peripheral vasodilation that can accompany IPA toxicity [14, 34, 45]. Hypothermia should be ruled out in all patients with decreased mental status, especially if they are found outdoors. Hypothermia may be secondary to the toxic effects of IPA, the environment itself, or a combination of the two.

Miosis and mydriasis have been reported in patients poisoned with IPA [13, 31, 34–36, 46]. Nystagmus has also been reported but is not a specific finding with IPA toxicity [31].

Mild hyperglycemia has occurred in patients who ingested IPA. Hypoglycemia should be suspected and ruled out in all patients with CNS depression.

Renal insufficiency and renal failure have occurred secondary to hypotension and rhabdomyolysis in IPA-toxic patients [34, 42, 47, 48]. Rhabdomyolysis should be ruled out in all patients who are found comatose, especially when the duration of the coma is unknown. Coingestants should be considered in all patients presenting with altered mental status.

Contact dermatitis, allergic dermatitis, and defatting dermatitis have all been reported in patients with prolonged contact to IPA

[49–51]. This may be more common in the occupational setting. Flushing and diaphoresis, though uncommon, have been reported after ingesting IPA [19, 34, 52, 53].

Clinical Presentation and Life-Threatening Complications

Patients most commonly develop CNS depression, ketosis, and a fruity breath odor but not metabolic acidosis [5, 7]. They also may present with abdominal pain, emesis, or gastritis. Patients with IPA toxicity should be monitored closely for rapid changes in their mental and cardiopulmonary status. Hypotension and respiratory failure have occurred after large ingestions of IPA [14, 17, 23, 34, 35, 45, 48]. If not monitored closely and treated, these conditions may lead to death.

IPA exposures occur primarily by ingestion; however, dermal, inhalational, and rectal exposures resulting in toxicity also have occurred [13, 18, 24, 33, 41, 45, 46, 54, 55]. A common exposure pathway in children is by bathing or sponge bathing with IPA to lower a fever [18, 31, 35, 38, 45, 46, 54, 55]. Dermal and inhalational exposures in adults may occur in the occupational setting.

Diagnosis

Isopropyl alcohol toxicity should be considered in the differential diagnosis of CNS depression. It also should be considered in an intoxicated patient who does not smell of ethanol, has a fruity breath smell, or has an unexplained ketosis. Non-acidotic ketosis should raise the possibility of IPA or acetone ingestion in the differential diagnosis. IPA also should be considered in patients with an unexplained osmolar gap.

Serum IPA concentrations may not be readily available in many hospitals [5]. If possible, however, they should be obtained in all patients who are suspected to have been exposed to IPA. Serum concentrations can be used to document IPA exposure. The patient's overall clinical condition,

not the IPA level, should be used to judge toxicity. Levels should be drawn at least 30–60 min after the exposure to identify peak IPA levels [5, 13, 17, 22]. The best method for measuring serum IPA levels is headspace gas chromatography with flame ionization or proton nuclear magnetic resonance imaging [5]. If IPA levels are determined by ADH-based enzymatic assays, the assay may interpret IPA as ethanol and give a falsely low IPA level [5, 44]. Although IPA may be detected with breathalyzers used to measure ethanol, these levels are unreliable [56]. A possible erroneous diagnosis of IPA poisoning may occur in patients with diabetic ketoacidosis. Cases of measurable IPA in these patients have been reported, although no exposure to IPA was known [57]. It has been theorized that the acetone produced with diabetic ketoacidosis might be reduced to IPA via ADH [5, 58]. It is also possible that in these cases, there was an unrecognized IPA exposure or that a laboratory error occurred.

Serum IPA levels greater than 120 mg/dL (20 mmol/L) have been associated with deep coma [14, 19, 48, 54]. An ingestion of 90 mL (3 oz) of 70% IPA can theoretically produce a serum IPA level of 100 mg/dL (16.7 mmol/L) in a 70-kg patient. As with ethanol, chronic alcoholics may tolerate higher IPA levels [7, 59].

Serum ketone or acetone concentrations may be helpful in the diagnosis of IPA toxicity. Acetone is not usually detected in the serum until 30–60 min post-ingestion [8, 13, 43]. Detection in the urine is usually delayed for at least 3 h post-ingestion [13]. An initial non-detectable urine acetone level should be repeated in patients if there is a high index of suspicion for IPA ingestion. Acetone levels increase as ADH metabolizes IPA. Acetone should be measurable even after IPA levels are undetectable.

Laboratory tests useful in the management of IPA-poisoned patients include serum electrolytes, creatinine, glucose, and creatine phosphokinase. If a significant metabolic acidosis is present, other causes must be considered (see ► Chap. 15, “Acid–Base Balance in the Poisoned Patient”). Acetone interferes with certain colorimetric assays used to determine serum creatinine levels; this has led to reports of falsely

elevated serum creatinine levels in patients with acetone in their serum [5, 31, 60–63]. Serum osmolality and an osmolar gap may be determined. Caution must be used, however, because not only are acetone and IPA osmotically active compounds, but other substances, such as methanol and ethylene glycol, are as well [64, 65]. The absence of an elevated osmolar gap does not rule out the presence of either compound and, in clinical practice, is not useful [66, 67].

Treatment

As with all toxic ingestions, treatment should focus on the overall clinical condition of the patient. The primary treatment centers on supportive care. Because IPA is a CNS depressant, the clinician must be vigilant with respect to the ability of a patient to maintain his/her airway. If the patient is unable to maintain a patent airway, endotracheal intubation should be performed and mechanical ventilation maintained. These patients warrant continuous cardiac monitoring and pulse oximetry. In patients who are initially able to maintain a patent airway, close monitoring for respiratory compromise is advised.

Any patient with altered mental status should have a rapid bedside assessment of the serum glucose to rule out hypoglycemia. Hypoglycemia can be treated with intravenous dextrose. Intravenous access allows for normal saline administration to maintain blood pressure and ensure adequate hydration and urine output. At least 100 mg of thiamine should be administered intravenously or intramuscularly to any patient in whom nutritional status is uncertain and who may be at risk for the development of Wernicke–Korsakoff syndrome (grade III recommendation).

Hypotension can be treated initially with intravenous fluids. In adults, normal saline can be bolused in doses of 250–500 mL each. When the total amount of intravenous fluids has reached approximately 2000 mL, one should be cautious not to fluid overload the patient. If the hypotension does not respond to intravenous normal saline, an intravenous pressor is the logical next step. Adequacy of cardiac pump function can be

ascertained by bedside echocardiography. No one pressor agent has been shown to be more efficacious than others in toxicant-induced hypotension. (See ► Chap. 14, “The Assessment and Management of Hypotension and Shock in the Poisoned Patient.”) Dopamine was traditionally the pressor of first choice because of its relative ease of use and its availability as a premixed intravenous preparation. However, in contemporary practice norepinephrine is often used. There have, however, been no comparative studies between pressors in cases of IPA toxicity. The dose administered should be based on clinical response. Hypotension that does not respond to the initial pressor of choice should be reassessed and may require higher doses or additional pressors [68].

Gastrointestinal decontamination is not likely to be of benefit in IPA ingestions because IPA is absorbed from the gastrointestinal tract within 30–60 min [24]. Gastric lavage is not likely to influence this absorption and should not be done. In a patient who presents within 30 min of a large IPA ingestion, nasogastric emptying with a standard nasogastric tube may decrease the total amount of IPA absorbed. Nasogastric emptying is theoretical and has not been tested [5, 69, 70]. However, if it is done, attention to protect the airway from aspiration is recommended [5]. Activated charcoal also is of questionable benefit, especially when used in the standard dose of 1 g/kg. An in vitro model showed that a 20:1 ratio of charcoal to IPA was needed to adsorb 87–92% of the IPA [71]. It would require a large amount of charcoal to adsorb even small amounts of IPA. Using such large amounts of charcoal becomes impractical for the treating physician and dangerous for the patient. It also is of questionable efficacy considering how rapidly IPA is absorbed from the gastrointestinal tract.

Indications for ICU Admission in Isopropyl Alcohol Poisoning

Coma

Hypotension

Respiratory failure

Patients needing hemodialysis

Criteria for ICU Discharge in Isopropyl Alcohol Poisoning

Mental status returned to baseline

Normotensive without pressors

Patient maintains own airway

Oxygenation maintained without supplemental oxygen

No further need for hemodialysis

Isopropyl alcohol can be absorbed through the skin with resulting toxicity [13, 18, 35, 46]. If dermal contact is suspected, washing the skin with a mild soap and water solution is appropriate for dermal decontamination.

Because of its small volume of distribution and negligible protein binding, IPA is easily dialyzable [13]. The clearance of IPA with hemodialysis has been reported as 137 mL/min [20, 23]. The acetone metabolite of IPA also is amenable to dialysis. Hemodialysis is rarely indicated in these patients, however. It has been suggested that patients who are hypotensive due to IPA toxicity may benefit from dialysis [72]. Another suggested indication for dialysis is for patients who have serum IPA concentrations greater than 400 mg/dL (66.6 mmol/L) [13, 72]. However, most patients do well with supportive care alone, even if the patient presents with hypotension or an initially high serum IPA concentration [5, 8, 19, 34]. There are risks associated with hemodialysis, and the overall clinical picture of the patient should be considered [73]. Peritoneal dialysis has been attempted in several reported cases, but the clearance of IPA with this method was only slightly better than the patients' endogenous clearance [74]. For patients who do not respond to aggressive supportive care or who are unstable due to high levels of IPA, hemodialysis should be considered in consultation with a medical toxicologist or poison control center.

There are no antidotes for IPA toxicity. Inhibiting ADH with ethanol or fomepizole would only prolong the time for the metabolism of IPA. Because acetone itself neither is life threatening nor causes significant end-organ damage, treatment with ADH inhibition is unnecessary [75, 76].

Special Populations

Pediatric Patients

Children may have a different susceptibility to dermal IPA absorption than adults owing to their larger body surface ratio and thin dermis. IPA has been applied dermally to reduce fever in children, with resultant significant toxicity [45, 46, 54, 55]. It is unclear if the toxicity is due solely to the dermal absorption or possibly to a combination of dermal and inhalational absorption. Infants have become toxic when IPA was applied chronically to the umbilicus for cleaning [35]. Coma, hypotension, and seizures all have been reported in children with IPA toxicity [33, 35]. Children also have been noted to experience dermal irritation and chemical burns when IPA was applied to the skin [77]. Unlike ethanol, hypoglycemia has not been reported to occur in children intoxicated with IPA [78–80]. A rare case of hemorrhagic gastritis has been reported in a pediatric patient with IPA toxicity [81].

Pregnant Patients

Based on the size of the molecule, its solubility, and its similarity to ethanol, IPA is expected to cross the placenta. Hypotension in the mother is a concern for the overall status of the fetus. Supportive care for the mother is paramount for protecting the fetus. IPA is not considered a human carcinogen, and its teratogenicity to humans is unknown [82].

Common Errors in Isopropyl Alcohol Poisoning

Not considering isopropyl alcohol as a potential cause in an intoxicated patient

Ruling out the diagnosis of isopropyl alcohol intoxication based on a normal osmolality and osmolar gap

Attributing an anion gap metabolic acidosis to isopropyl alcohol

Using hemodialysis instead of good supportive care as a cornerstone of treatment

Key Points in Isopropyl Alcohol Poisoning

1. Toxicity may occur after oral, inhalational, rectal, or dermal exposure.
2. Isopropyl alcohol can be a potent central nervous system depressant.
3. The hallmark of IPA toxicity is ketosis without metabolic acidosis.
4. Isopropyl alcohol toxicity may cause gastritis as with other alcohols.
5. Treatment should focus on supportive care.

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Knut Erik Hovda, Kenneth McMartin, and Dag Jacobsen

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Methanol

Methanol (methyl alcohol, “colonial spirit,” “wood alcohol,” “solvent alcohol”) is a highly toxic alcohol that is widely used industrially as a solvent and in the production of formaldehyde and methylated compounds. It is found in commercial products such as gasoline, antifreeze, gasohol, windshield washer fluid, copy machine fluid, canned heat (Sterno), paint, shellac, and solvents for removing wood finishes. There also is a continuous discussion on the possible use of methanol as an alternative energy source in combustion engines.

Most cases of methanol poisoning are isolated episodes caused by accidental or intentional ingestion. Epidemics of methanol poisoning may occur when it is mistakenly substituted for ethanol by alcoholics or when methanol contaminants are used to ferment (e.g., wine) or illicitly distill (e.g., moonshine whisky) alcoholic beverages. In such circumstances, hundreds of victims have been reported [1–3]. In recent years, both medical journals and the news media have identified methanol poisonings as a frequent problem in the developing world [4–9]. This has recently resulted in the involvement of a large NGO – Doctors Without Borders/Médecins Sans Frontières (MSF) – identifying this as a global problem [9].

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Biochemistry and Clinical Pharmacology

The chemical formula of methanol is CH_3OH . It is a colorless, volatile, highly flammable liquid with a density of 0.81 g/mL and a weak smell that resembles that of ethanol. Methanol is absorbed rapidly from the gut, skin, and lungs. It distributes in the total body water compartment of approximately 0.7 L/kg [10]. It is slowly metabolized first to formaldehyde and then to formic acid, which is responsible for the toxic effects in methanol intoxication (Fig. 1) [11]. The oxidation of formaldehyde occurs rapidly so that little formaldehyde accumulates in the serum. The metabolism of methanol by alcohol dehydrogenase, which accounts for about 90% of its elimination, is zero order, with a rate of 2.7 mmol/L/h (8.5 mg/dL/h) (half of that of ethanol) in one case [12]. Only small amounts are excreted in expired air and urine. The half-life of methanol is typically reported in the range of 45–80 h when metabolism is blocked by an antidote [10, 11, 13], 1.1–3.7 h during intermittent dialysis and antidote [14–17] and 8.1 h during continuous dialysis modalities and antidote [17].

The metabolism of formate depends on the folate pool [11]. Primates have a small folate

reserve and are the only animal order that accumulates formate and experiences methanol toxicity [18]. Formate can be reabsorbed in the proximal tubule cells by a H^+ /formate cotransport, as well as a nonionic diffusion of formate and indirect coupling of formate to Na^+/H^+ exchange [13, 19]. As such, the renal excretion of formate is pH dependent: The more acidotic the patient becomes, the less formate is excreted [13]: The half-life of formate is usually reported in the range of 2.5–5.0 h [13, 14, 20], but one extreme case of 77 h (2.9 h during dialysis) has been reported [21].

Toxicokinetics of Methanol

Volume of distribution: 0.7 L/kg

Protein binding: none

Mechanisms of clearance: hepatic, renal (minimal), pulmonary (minimal)

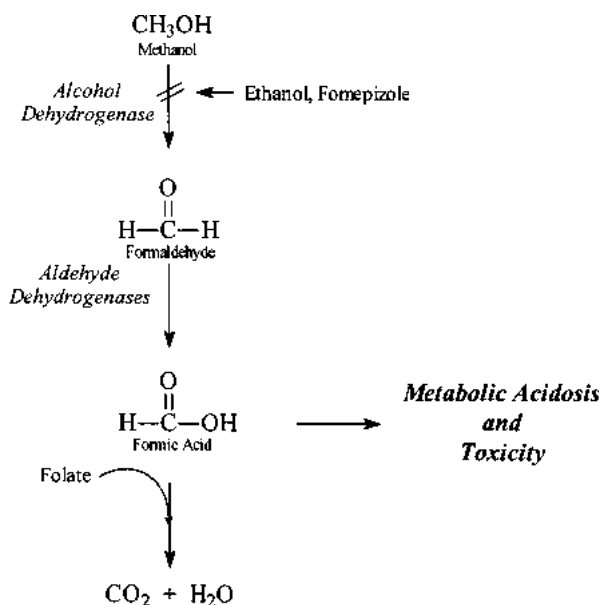
Active (toxic) metabolite: formic acid

Method to enhance clearance: hemodialysis

Pathophysiology of Toxic Effects

The lethal dose of methanol is variably given as 30–240 mL, with 1 g/kg (1.2 mL/kg) as the best

Fig. 1 Methanol metabolism. Ethanol and fomepizole inhibit metabolism by alcohol dehydrogenase. As a result of the small folate pool in primates, little formic acid is metabolized further, so it tends to accumulate in the body



estimate [11, 22]. The minimal dose that can cause permanent visual defects is unknown but most probably ingestion of more than 30 mL (adults) is necessary.

Similar to ethylene glycol, the toxicity of methanol is mediated through its metabolites. In contrast to ethylene glycol, however, methanol does not cause significant central nervous system (CNS) depression and ethanol-like inebriation. In the early stage of methanol poisoning, the toxic effects are due to the increasing metabolic acidosis caused by the accumulation of formic acid. Why the eye is the primary target organ for methanol's toxic effects is not fully understood [11, 23, 24]. Formate inhibits cytochrome oxidase, the final enzyme in the mitochondrial electron transport chain, by binding to the ferric iron in the heme moiety of that enzyme. This inhibition occurs in the 5–30 mmol/L range (16–96 mg/dL) [25], which is similar to the formate concentrations associated with retinal toxicity in humans [11] and other primates [26, 27]. Inhibition of mitochondrial energy metabolism markedly increases the production of reactive oxidative molecules and the likelihood of oxidative injury [28]. Formate also seems to increase retinal vulnerability to oxidative injury by causing a depletion of glutathione, which is the major endogenous molecule protecting against oxidative stress in the retina [29]. The retina is exposed to several sources of oxidative stress by virtue of its high intrinsic metabolic rate and its exposure to ambient radiation. Normally, retinal glutathione concentrations are relatively high compared with other organs [30]. Glutathione synthesis is highly dependent on mitochondrial respiration [31]. Studies using a folinic acid–dysfunctional rat model suggest that cones may be more sensitive than rods to long-term damage from methanol poisoning, possibly because of the greater number of mitochondria in cones than in rods [29].

In late stages, as formate accumulates, the toxicity is caused mainly by the histotoxic effects of formate, which inhibits mitochondrial respiration. The resulting lactate production increases the metabolic acidemia and toxicity of formate, as more formate is protonated and able to penetrate the blood–brain barrier [32]. A vicious hypoxic

cycle is initiated [33]. In the late stages, specific lesions of the lenticular nucleus (putamen and globus pallidus) may develop. It is not known why the lenticular nucleus is particularly vulnerable in late stages of methanol toxicity. Although the mechanism of these lesions is not known, it is reasonable to believe that the histotoxic effect of formate in late stages, causing a so-called *circulus hypoxicus*, is a contributing factor (Fig. 2). This increased lactic acidosis with increasing formate concentration was demonstrated in the recent Norwegian [34] and Czech outbreaks [3].

Clinical Presentation and Life-Threatening Complications

The classic pattern of methanol toxicity includes a latent period of approximately 12–24 h from the time of ingestion to the occurrence of signs and symptoms. This is the time it takes for sufficient amounts of formic acid to accumulate following methanol metabolism. This latent period may be longer if ethanol is coingested because the latter competitively inhibits methanol metabolism by alcohol dehydrogenase. A latent period of up to 90 h has been reported when ethanol is coingested [10]. Methanol itself has few direct effects. Mild CNS depression and ethanol-like intoxication have been reported [11] but may as well be due to the osmotic effect in the CNS. Methanol itself, however, is typically not considered to have any inebriating effects, and patients with high methanol concentrations (137 mmol/L [438 mg/dL]) also have been sober [10]. With ingestion of concentrated methanol, nausea, vomiting, and abdominal pain may develop shortly after ingestion. A few cases also may present as acute abdomen, probably because of pancreatitis [11, 12].

The first clinical features of systemic toxicity are usually a feeling of weakness, anorexia, headache, nausea, and vomiting, accompanied or followed by increasing hyperventilation as metabolic acidosis progresses [11, 22, 35, 36]. The first complaint may often be shortness of breath because of hyperventilation. Visual symptoms (blurred vision, decreased acuity, halo vision, tunnel vision, photophobia, and “snow fields”) may

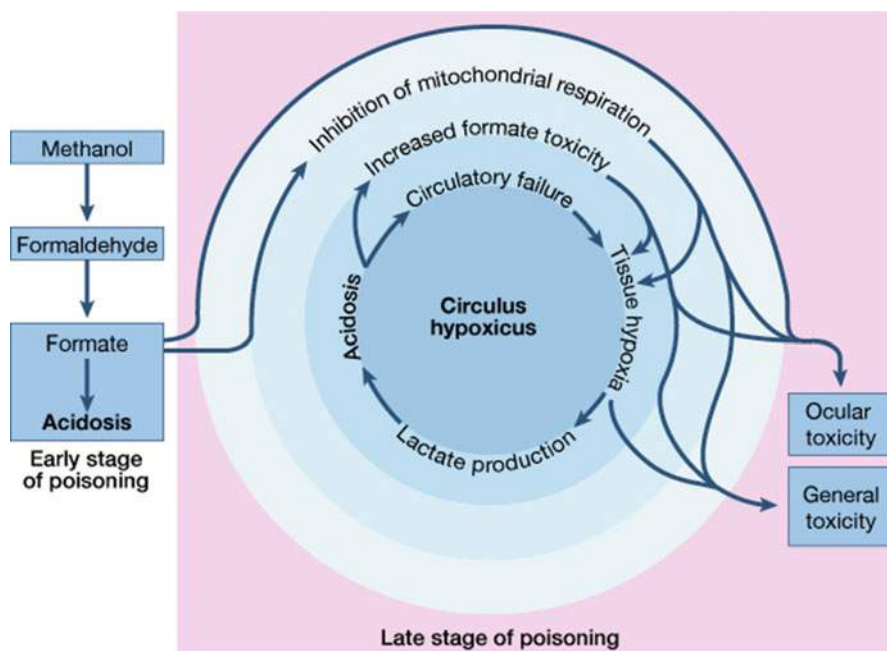


Fig. 2 The “circulus hypoxic” resulting from methanol ingestion (From Jacobsen [33])

appear first or with the abovementioned symptoms. Usually ocular symptoms precede objective signs, such as dilated pupils that are partially reactive or nonreactive to light and funduscopy showing optic disk hyperemia with blurring of the margins, so-called pseudopapillitis [11, 22, 36].

If treatment is not initiated at this early stage of poisoning, the patient may develop coma and respiratory and circulatory failure. A few patients also may develop methemoglobinemia with cyanosis, probably because of an interaction between formate and the ferric moiety of hemoglobin [11].

The toxic effect on the lenticular nucleus does not lead to detectable signs and symptoms in the acute stage because it is concealed by pronounced CNS depression. Survivors may manifest a Parkinson-like syndrome due to toxic effects on the globus pallidus when they recover from the acute condition, usually after several days to a week [37, 38].

Diagnosis

Methanol poisoning can be difficult to diagnose in the absence of a history, especially if ethanol is

coingested and the latency period is prolonged. The analytical alternatives at present are measuring methanol and formate and/or using the osmolal and anion gaps. Methanol is usually detected by gas chromatography or radioimmunoassay. Formate analyses using chromatographic or enzymatic methods [39, 40] are highly specific, but until now the availability has been limited. Therefore, a dry-chemistry, strip-based analysis for bedside measurement of formate is now under development [41]. Whether the laboratory or the bedside assay is used, a simple flow chart can easily guide the clinician on admission of the patient (Fig. 3). Laboratory evaluation of suspected methanol poisoning should also include arterial blood gas analysis; complete blood count; measurement of electrolytes, blood urea nitrogen, creatinine, glucose, osmolality, and amylase; as well as a urinalysis. The history should include the amount, concentration, and time of methanol ingestion, the nature and onset of symptoms, and whether ethanol was coingested. Patients also should be carefully questioned about the presence or absence of visual complaints, gastrointestinal symptoms, and feelings of intoxication.

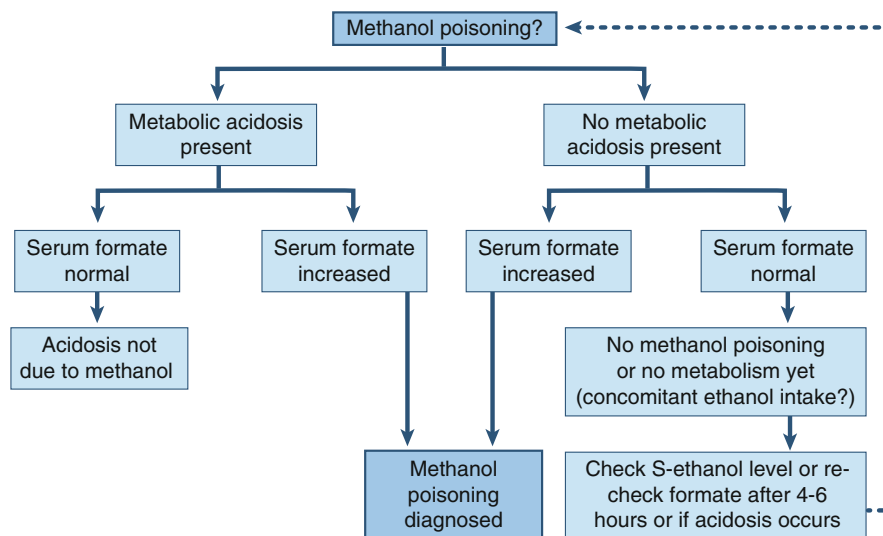


Fig. 3 A simple approach for clinical utility of the formate analysis in the diagnosis of methanol poisoning (Printed with permission from McMartin et al. [62])

The physical examination should focus on vital signs (especially respiratory rate) and the neurologic, visual, and cardiopulmonary status. Visual acuity and funduscopic examinations should be performed. The objective signs of ocular toxicity of methanol include dilated pupils, which are partially reactive or nonreactive to light, and optic disk hyperemia with blurring of the disk margins, and later pallor. This blurring of disk margin may look like papillary edema, but there is no diopter difference between the fundus and the disk (so-called pseudopapillitis).

Because the clinical diagnosis of methanol poisoning is difficult, methanol poisoning should be considered in every patient presenting with a metabolic acidosis of unknown origin. The general evaluation of a patient with a metabolic acidosis of unknown etiology is described in detail in ► Chaps. 2, “The Diagnostic Process in Medical Toxicology,” and ► 15, “Acid–Base Balance in the Poisoned Patient.”

The anion and osmolal gaps are indirect methods, but together they can give a clue to the diagnosis. The accumulation of formate causes a metabolic acidosis, generally with an increased anion gap [42]. Based on a study evaluating the

gaps in an unselected group of acutely hospitalized patients, the reference range of the AG ($[\text{Na} + \text{K}] - [\text{Cl} + \text{HCO}_3]$) was found to be 5–21 mmol/L [43]. Because of its low molecular weight (32 d) and the high concentrations associated with toxicity, methanol increases the serum osmolality, as do other alcohols. This effect can be detected by calculating the difference between the measured osmolality (O_m) and the calculated osmolality (O_c), $OG = O_m - O_c$:

$$O_c = [2 \times \text{sodium}] + [\text{blood urea nitrogen}/3] + [\text{glucose}/18]$$

$$O_c = (1.86 \times \text{Na} + \text{blood urea nitrogen} + \text{glucose}) / 0.93 (\text{SI units})$$

The “new” reference range for the osmolal gap in unselected patients is -9 – 19 mOsm/kg H_2O [43]. An osmolal gap greater than 19 (5 ± 2 SD) strongly indicates exogenous osmoles of some kind [1, 21]. A methanol concentration of 32 mmol/L (100 mg/dL) increases the osmolal gap by $32/0.93 = 34$ mOsm/kg H_2O . The denominator of 0.93 accounts for the serum being 93% water. The presence of ethanol influences the osmolal gap and must be subtracted. The osmolal

Table 1 Osmolal contribution from a S-concentration of 1 g/L (100 mg/dL) of relevant alcohols, glycols and acetone

	Molar mass (g/mol)	Osmolality per 100 mg/dL (mOsm/kgH ₂ O)
Methanol	32	34
Ethanol	46	24
Acetone	58	18
Isopropanol	60	17
Ethylene glycol	62	17
Propylene glycol	76	14
Diethylene glycol	106	10

contribution of various alcohols (plus acetone) is presented in Table 1.

Several conditions in medicine increase the anion gap or the osmolal gap, but except for methanol or ethylene glycol poisoning, few increase both at the same time. The exceptions include diabetic ketoacidosis (although this osmolal gap is typically reported to increase less than 14 mOsm/kg H₂O [44] and a high blood glucose can help point to the diagnosis), alcoholic ketoacidosis [45] (this acidosis will respond to intravenous fluids and thiamine), chronic renal failure [46] (the creatinine will give a diagnostic clue), or major trauma with circulatory shock [47]. By adding a “decision level” of 25 mOsm/kg H₂O for when to start antidote treatment without waiting for any further analyses, the diagnostic specificity increases further. Regarding the sensitivity, *no level of osmolal gap as a single test can exclude toxic alcohols as the cause* (Fig. 4) [34].

In late stages of methanol poisoning, most – sometimes all [3] – of the methanol already has been metabolized to formate [34]. At this stage, the anion gap is elevated, but the osmolal gap is normal; formate detection is the only way to confirm the diagnosis. In early stages, or if ethanol is coingested, only the osmolal gap is elevated because the metabolism of methanol to formate has not yet begun (Fig. 4) [34]. If the diagnosis is based on the osmolal and anion gaps, osmometry must be performed by the freezing point depression technique and not by the vapor pressure technique

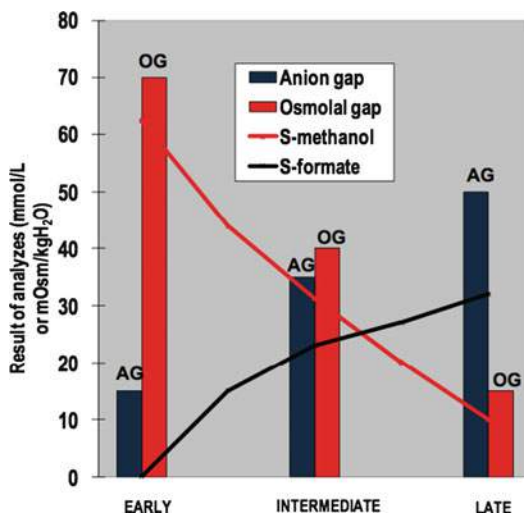


Fig. 4 The correlation between methanol and the osmolal gap and formate and the anion gap (Printed with permission from Hovda et al. [34])

because the latter does not detect the increased osmolality caused by volatile alcohols [36].

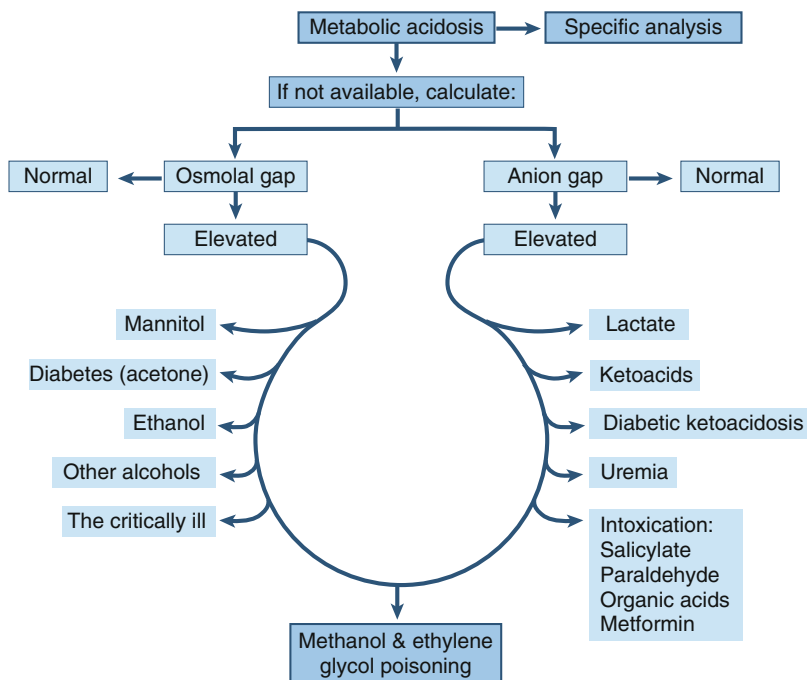
Increased anion and osmolal gaps also occur in ethylene glycol intoxication. Figure 5 enumerates various other causes of increased osmolar or anion gaps. Differentiating the two (methanol and ethylene glycol) may be difficult, but the treatments are essentially the same. Hypocalcemia, seizures, and urine oxalate crystals indicate ethylene glycol poisoning; optic disk hyperemia indicates methanol poisoning [1].

Computed tomography or magnetic resonance imaging of the brain may show necrosis of the putaminal areas, a finding seen late in the course of methanol poisoning [36–38, 48]. Diffusion-weighted MRI can provide a much earlier detection of cytotoxic edema in the same regions of the brain [49].

Treatment

Gastric decontamination is unlikely to be beneficial because methanol is rapidly and completely absorbed, and most patients do not present before onset of clinical features. Supportive treatment follows the established principles of intensive supportive care.

Fig. 5 Causes of an increased anion gap and osmolal gap. Elevations in both gaps strongly indicate methanol or ethylene glycol intoxication



The specific treatment of methanol poisoning includes bicarbonate to counteract the metabolic acidosis, ethanol or fomepizole to inhibit methanol metabolism to formate, and selective hemodialysis (intermittent high-flow (IHD) or continuous modalities (CRRT)) to remove methanol and formate. Folic acid or folinic acid (leucovorin) is of theoretical value in increasing the metabolism of formate (see Fig. 1), but the clinical utility of this effect has not yet been proven [15, 50]. The standard dose of folinic acid is 50 mg intravenously four times a day. See ► Chap. 149, “Folic and Folinic Acids” for information regarding the clinical pharmacology of these antidotes.

Correction of Metabolic Acidosis

Although not prospectively studied, most clinical toxicologists recommend that the metabolic acidosis be treated aggressively by infusing sodium bicarbonate; 500–800 mmol (mEq) or even more may be required during the first few hours. The goal should be full correction of the acidosis (Grade II-2 recommendation), which will require more bicarbonate the more acidotic the patients are, because of the need to buffer the proteins [51]. Bicarbonate treatment decreases the amount of non-dissociated

formic acid, resulting in less access of formate to the CNS [22, 32]. In contrast to other types of metabolic acidosis, metabolic acidosis resulting from methanol poisoning should therefore always be treated aggressively with bicarbonate. For acidotic methanol-poisoned patients, alkali treatment must be accompanied by ethanol or fomepizole; otherwise, the acidosis becomes bicarbonate resistant, as more formic acid is produced from the metabolism of methanol (see Fig. 2).

Indications for ICU Admission in Methanol Poisoning

Severe metabolic acidosis (manifested by a base deficit >20 mmol/L)

Need for hemodialysis

Significant clinical manifestations

If ethanol is used as an antidote (due to dosing and monitoring difficulties)

Inhibition of Formation of Toxic Metabolites

For antidotal treatment criteriae – see Table 2. Central to the treatment of methanol poisoning is

Table 2 Antidote treatment criteria^a (Adapted with permission from McMartin KE, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites [62])

	Recommended criteria
I	Serum methanol concentration ≥ 10 mmol/L (32 mg/dL) ^b
II	Documented/suspected recent history of ingestion with an osmolal gap ≥ 25 mOsm/kg H ₂ O ^c
III	Documented/suspected history of ingestion plus two or more of the following criteria
	A: Arterial pH < 7.3
	B: Serum bicarbonate < 14 mmol/L or base deficit (BD) > 10mmol/L
	C: Osmolal gap > 25 mOsm/kg H ₂ O ^c
	D: The presence of visual disturbances

^aAntidote should be given without delay, if toxic alcohol cannot be excluded as the cause. No osmolal gap will be able to exclude toxic alcohol as the cause

^bOnly if there is no significant metabolic acidosis (Base deficit < 10 mmol/L (10 mEq)) or no indications of organ toxicity

^cOG calculated after the ethanol contribution is subtracted

the inhibition of its metabolism to toxic metabolites (see Fig. 1). Guidelines suggest fomepizole being the antidote of choice, while ethanol can be used if fomepizole is unavailable; [52–55] however, no definite improved outcome with fomepizole has been documented yet [56, 57]. Clearly, the preference for fomepizole is mainly based on simplicity of use [58, 59], efficacy [53, 60], and lower degree of adverse events [61]. In some countries, for example, the USA, the acquisition costs of fomepizole and 100% ethanol are similar. In other countries, there is a higher acquisition cost of fomepizole which limits its use, especially in the developing world [62].

Regardless of the antidote used, early initiation of antidotal treatment is crucial. Zakharov et al. found a positive association between pre-hospital ethanol administration and improved clinical outcome during the methanol outbreak in the Czech Republic [63]. This is particularly important during mass outbreaks or with long transporting distances to hospital facilities with ICU and dialysis capacity.

Fomepizole. Fomepizole (chemically 4-methylpyrazole), the frequently used antidote

for the treatment of ethylene glycol poisoning [64, 65], is also documented for use in methanol poisoning [52, 66, 67]. As in ethylene glycol poisoning, the major advantage of fomepizole is its documented effectiveness, lack of CNS depression, ease of administration, few side effects, and ability to reduce the need for hemodialysis [62]. The lack of pancreatitis, a well-known side effect of ethanol, also makes fomepizole a more attractive antidote because pancreatitis is sometimes reported in methanol-poisoned patients [68]. Fomepizole can be administered intravenously or orally, although most, not all, pharmaceutical preparations are for intravenous administration [69]. If administered intravenously, fomepizole should be diluted in isotonic saline or dextrose and infused over 30 min. The initial loading dose should be 15 mg/kg, followed by 10 mg/kg every 12 h for four doses, then 15 mg/kg every 12 h, if necessary. During hemodialysis, the frequency of dosing should be increased to every 4 h, whereas every 8 h are likely sufficient during continuous dialysis modalities (CRRT) [62] (Grade III recommendation). Old guidelines have suggested treatment until the blood level of methanol is less than 6 mmol/L (20 mg/dL) and the patient is without symptoms, but increasing this to 10 mmol/L (32 mg/dL) seems reasonable, given no acidosis or end organ toxicity [62].

Ethanol. If ethanol is used to inhibit methanol metabolism, most authors recommend a therapeutic blood ethanol level of about 22 mmol/L (100 mg/dL). However, the amount of ethanol necessary to block methanol metabolism depends on the concomitant methanol level, because there is a dynamic competition for the enzyme alcohol dehydrogenase. If the blood methanol level is known, the molar ethanol concentration should be at least a quarter of the molar methanol concentration [11, 18, 62] (Grade II-2 recommendation).

A dosing suggestion to obtain a blood ethanol level of 22 mmol/L (100 mg/dL) is presented in Table 3 [62]. The maintenance infusion should be increased or decreased according to measured ethanol concentrations. Monitoring the blood ethanol concentration is important yet often not

Table 3 Simplified dosing suggestion for intravenous and oral ethanol treatment^a (Adapted with permission from McMartin KE, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites [62]).

Intravenous^b	IV 5% ethanol		IV 10% ethanol	
Loading dose	15 ml kg ⁻¹		7.5 ml kg ⁻¹	
Infusion rate (not regular drinker)	2–4 ml kg ⁻¹ h ⁻¹		1–2 ml kg ⁻¹ h ⁻¹	
Infusion rate (regular drinker)	4–8 ml kg ⁻¹ h ⁻¹		2–4 ml kg ⁻¹ h ⁻¹	
Infusion rate during HD^c (not regular drinker)	4–7 ml kg ⁻¹ h ⁻¹		2–3.5 ml kg ⁻¹ h ⁻¹	
Infusion rate during HD^c (regular drinker)	6–10 ml kg ⁻¹ h ⁻¹		3–5 ml kg ⁻¹ h ⁻¹	
Oral^b	5 % ethanol	10 % ethanol	20 % ethanol	40 % ethanol
Loading dose	15 ml kg ⁻¹	7.5 ml kg ⁻¹	4 ml kg ⁻¹	2 ml kg ⁻¹
Drinking dose/h (not regular drinker)	2 ml kg ⁻¹ h ⁻¹	1 ml kg ⁻¹ h ⁻¹	0.5 ml kg ⁻¹ h ⁻¹	0.25 ml kg ⁻¹ h ⁻¹
Drinking dose/h (regular drinker)	4 ml kg ⁻¹ h ⁻¹	2 ml kg ⁻¹ h ⁻¹	1 ml kg ⁻¹ h ⁻¹	0.5 ml kg ⁻¹ h ⁻¹
Drinking dose/h during HD^c (not regular drinker)	4 ml kg ⁻¹ h ⁻¹	2 ml kg ⁻¹ h ⁻¹	1 ml kg ⁻¹ h ⁻¹	0.5 ml kg ⁻¹ h ⁻¹
Drinking dose/h during HD^c (regular drinker)	8 ml kg ⁻¹ h ⁻¹	4 ml kg ⁻¹ h ⁻¹	2 ml kg ⁻¹ h ⁻¹	1 ml kg ⁻¹ h ⁻¹

^aThese suggestions is based on a paper by from [70] and are only suggestions for the initiation of ethanol treatment. Because of the large interindividual variability in ethanol metabolism, serum ethanol concentrations should be monitored every 1–2 if this is available. Effectiveness of blocking can be monitored by analysis of metabolite concentrations (ideally) or of arterial blood gases, if the metabolite and ethanol analyses are not available

^bEthanol can be very irritating, and IV formulations should be diluted with isotonic 5% glucose (dextrose) to a maximum of 10% ethanol by volume and administered through a central IV line. If ethanol is administered orally, a 20% or more diluted solution is usually better tolerated

^cDialysis (HD) refers to intermittent (high-flow) hemodialysis. During continuous renal replacement therapy (CRRT), the ethanol increase would be smaller than in table, about 20% above the non-dialysis dose is estimated [105]

available [9]. The blood ethanol concentration should be measured every 1–2 h if possible. Hemodialysis removes ethanol. As a rule of thumb, the maintenance dose of ethanol should at least be doubled during hemodialysis (see Table 3) [62].

If a blood methanol concentration cannot readily be obtained, fomepizole or ethanol therapy should be started in any suspected methanol-intoxicated patient with metabolic acidosis, clinical features (dyspnea, visual disturbances), or a history of a potentially toxic ingestion. By consensus, fomepizole or ethanol treatment should be discontinued when the methanol level decreases to less than 6 mmol/L (20 mg/dL). The use of this value has not been empirically validated, however. The lack of reported adverse effects associated with the practice of using the 6 mmol/L (20 mg/dL) value suggests that this practice is safe. It is likely, but unproven, that stopping therapy at higher blood methanol concentrations is

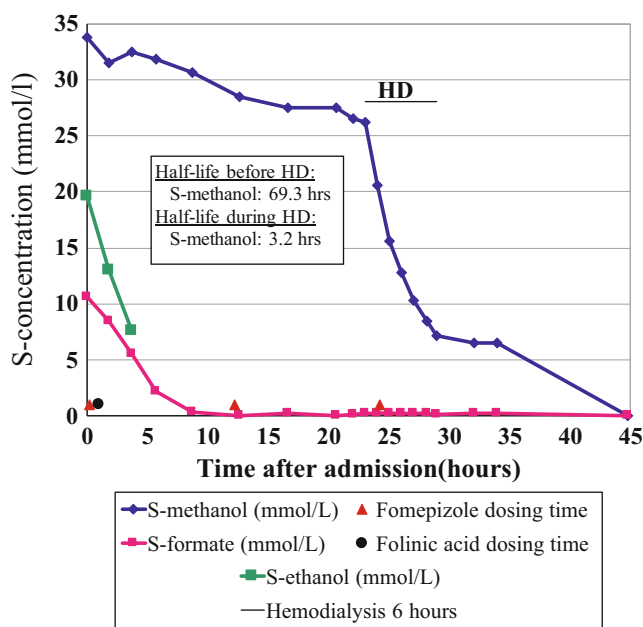
also safe, provided there is no metabolic acidosis. This is particularly true of patients treated with fomepizole, because the inhibition of alcohol dehydrogenase caused by this agent is likely to be effective for more than 12 h after the last dose.

Hemodialysis

Hemodialysis effectively removes methanol and formate and helps to correct the metabolic acidosis [11, 71]. Both intermittent and continuous modalities are frequently used in these patients, but intermittent dialysis is shown to be more effective [17]. Peritoneal dialysis may also remove methanol but not as effectively as hemodialysis [72]. Hemoperfusion is most probably ineffective.

It is difficult to establish strict indications for hemodialysis in methanol poisoning. The only generally accepted absolute indication for hemodialysis is a new visual impairment of any degree in a patient with metabolic acidosis or a detectable

Fig. 6 Healthy male patient admitted after drinking a methanol/ethanol mixture [16]. Note low S-formate and very high S-methanol that was very slowly eliminated during fomepizole treatment (half-life 77 h). Elective hemodialysis was therefore performed (during regular day time) to speed up methanol elimination (half-life during dialysis was 1.7 h). Further course was uneventful (Printed with permission from Hovda et al. [16])



methanol level. Relative indications include severe metabolic acidosis (particularly if unresponsive to bicarbonate and ethanol or fomepizole therapy), a blood methanol concentration greater than 16 mmol/L (50 mg/dL), and ingestion of more than 1 g/kg of methanol. The slow elimination of methanol during ethanol/fomepizole treatment (plasma half-life of 45–80 h) [10, 11, 13] must always be considered when the indication for hemodialysis is discussed. From a practical point of view (drunk patient for days in the intensive care unit), this means that ethanol therapy alone is not acceptable in patients with moderate methanol levels, even if they are admitted early or for some other reasons have little metabolic acidosis (concomitant ethanol ingestion). In some of these patients (e.g., blood methanol 32 mmol/L [100 mg/dL], no visual complaints, and almost normal acid–base status), where fomepizole is the antidote in use, hemodialysis can sometimes be obviated or postponed (Fig. 6) [16, 62, 73–75].

Provided there is no metabolic acidosis or visual disturbances, we recommend that hemodialysis is best continued until the blood methanol level is less than 10 mmol/L (32 mg/dL) and the acidosis is corrected [62] (Grade III evidence). If

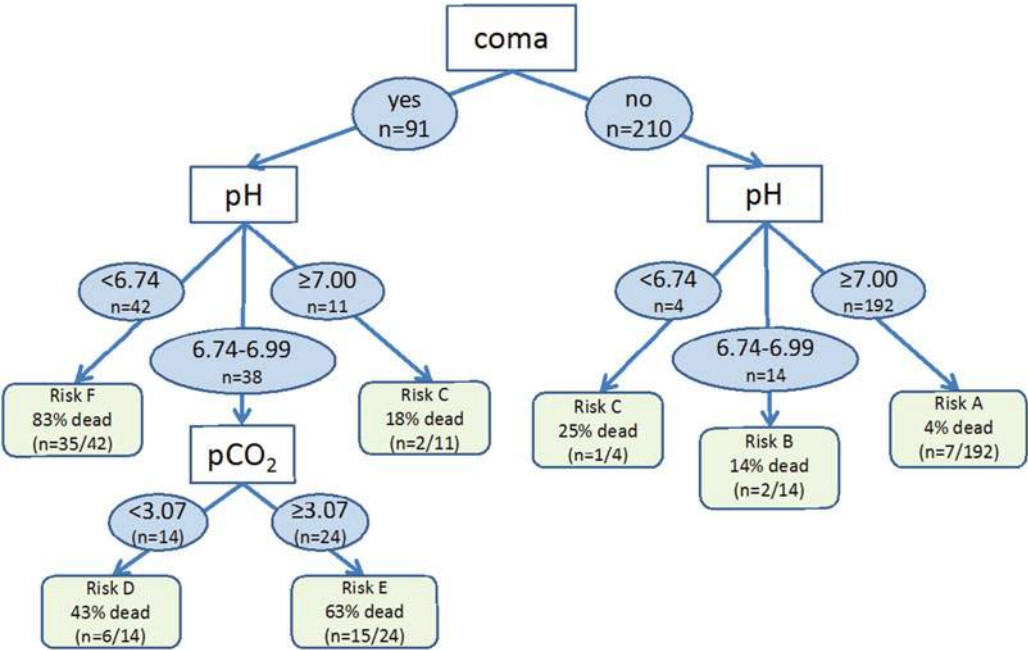
methanol analyses are unavailable, we recommend that hemodialysis should be continued for at least 8 h.

Folate/Folinic Acid

The use of folate/folinic acid in methanol poisonings is based on the theory that the endogenous metabolism of formate is folate dependent; thus, a saturation of the metabolizing enzymes occur. A positive effect of adding folate has been shown in animals [19, 76], but no clinical trials have been able to verify an improved outcome [50, 77], partly because of ethical problems designing such a study. However, the benefit of giving this B vitamin is likely to outweigh the risk (few side effects, relatively cheap treatment); hence, a dose of 50 mg four times a day (every 6 h) is recommended (Grade III recommendation).

Criteria for ICU Discharge in Methanol Poisoning

Metabolic acidosis corrected
 Hemodialysis terminated
 Serious acute clinical manifestation resolved



Risk group	Name on figure	Number in total	Dead in group	Total mortality risk	Odds ratio (95% CI) *
1	A and B	206/301	9/206	4%	1
2	C	15/301	3/15	20%	6 (1-23)
3	D	14/301	6/14	43%	16 (5-57)
4	E	24/301	15/24	63%	37 (13-106)
5	F	42/301	35/42	83%	109 (38-313)

*Odds ratio (OR) and 95% confidence intervals (CI) for death for all groups compared to risk

Fig. 7 Risk assessment chart for the evaluation of outcome based on simple admission parameters with a risk score based on the scheme above; pCO₂ values are given in

kPa. Conversion factor mmHg to kPa is 7.5:1. This chart is based on data merged from similar Figures [3, 56]

Prognosis

Unlike with ethylene glycol, a clue about the outcome in methanol poisonings may be found on admission to hospital. Clinical features such as the presence of coma on admission [1–3, 56, 78–80], the degree of metabolic acidosis [1–3,

56, 78–80], and the ability to hyperventilate if a severe metabolic acidosis is present (pCO₂ vs. pH) [1–3, 56] are all strong prognostic markers. Figure 7 illustrates how prognosis can be assessed on admission simply by evaluating the patient’s consciousness and blood gas. In addition, hyperglycemia has been suggested as a

prognostic marker on admission [3, 81], whereas methanol concentration itself has no prognostic value [1, 2, 56].

As for the long-term prognosis, visual disturbances and brain damage were found to persist or get worse 6 years after discharge in a follow-up study from Estonia [82]. Similarly, Zakharov et al. found the prevalence of long-term visual sequelae to be significantly higher than the visual sequelae on discharge (also in comparison to the literature), suggesting that the morbidity from these poisonings is an underreported feature: At least 22% of the patients without subjective complaints of visual disturbances that were discharged from hospital without detected visual damage had abnormal findings using advanced examination on follow-up [83].

Other

Consultation with a poison center or clinical toxicologist is strongly recommended if the treating physician is unfamiliar with the management of methanol poisoning. In addition, physicians who do not know how to obtain either methanol or formate blood levels may be able to obtain such information from these sources. When the diagnosis of methanol poisoning is made or suspected and hemodialysis is contemplated, a nephrologist should be consulted, especially when the patient is admitted in a late stage or after large ingestions.

All patients with suspected methanol poisoning for whom a serum methanol concentration is unavailable should be observed for continued clinical and laboratory evaluation: If an ethanol level is available, a patient suspected of drinking methanol recently should be monitored using blood gases for at least 6 h after the ethanol level is zero, based on the time needed for a detectable acidosis to develop after the antidote is eliminated. If formate analyses are available, they will be able to detect small levels of formate hours before the patient even have symptoms (see Fig. 3) [39]. Every patient with a definite diagnosis of methanol intoxication should be admitted and have an initial and follow-up examination by

an ophthalmologist as the incident may have legal and insurance implications [83].

If hemodialysis is unavailable, the patient who needs it, or will probably need it, should be transferred to a facility with this capability, and fomepizole or ethanol should be given immediately [63]. Alkali treatment should be provided if any indication of a metabolic acidosis is present. These treatments should be continued during transport. Because plasma ethanol concentrations should be monitored every 1–2 h due to the difficulty of keeping a constant ethanol level, fomepizole is the preferred agent for transfers that may last more than 1 h [62].

Special Populations

When treating a methanol-poisoned patient, it must always be borne in mind that other people may also have ingested the illicit spirit (containing methanol), believing it was ethanol. If so, these victims must be traced [7, 9] and evaluated in an emergency department.

Some patients presenting with coma (GCS 3) and extreme metabolic acidosis (e.g., pH 6.60, $p\text{CO}_2$ 1.4 kPa, BD 28 mmol/L, HCO_3^- 1 mmol/L) may not survive because of brain edema leading to “brain death.” It is, however, important to consider further optimal treatment and possible organ donation as the biochemical disturbances in other organs can often be reversed. In our experience such “hopeless cases” have been donor to up to six recipients – as also experienced by others [84–88].

Common Errors in Methanol Poisoning

Delayed diagnosis because of failure to consider methanol poisoning in the differential diagnosis of metabolic acidosis of unknown origin

Failure to consider that there may be multiple victims when the source of methanol is unknown or is known to be a contaminated ethanol beverage

(continued)

Failure to appreciate that the absence of early symptoms and the presence of normal anion or osmolal gaps do not exclude a potentially toxic methanol ingestion

Failure to observe all patients with known or suspected methanol ingestion until a methanol level can be obtained

Failure to give enough ethanol during hemodialysis because ethanol is removed as well

Failure to have visual function formally assessed by an ophthalmologist in patients with methanol poisoning

Formaldehyde

Formaldehyde, the one-carbon aldehyde (HCHO), exists in the gaseous state as a reactive chemical with a distinctive disagreeable odor. The odor is sufficient to provoke flight responses in that humans cannot remain in intolerable atmospheres [89]. The most common liquid form of formaldehyde is formalin, which usually contains 37% formaldehyde in water by weight, along with methanol in concentrations of 15% as a stabilizing agent (preventing polymerization). Cases of oral ingestion of formaldehyde (mostly formalin solutions) have been reported [90–95], albeit rarely because of the disagreeable nature of the solution.

Formalin is used as a disinfectant, tissue preservative, and embalming solution; occupational exposure generally involves inhalation or skin contact. Formaldehyde vapor is irritating to mucosal membranes and has caused problems in occupational settings where the concentrations reach levels of 1 ppm [96]. Formaldehyde is also present in resins, insulation, plywood, and textiles, such that it also has been found in the indoor air of residential and business areas, particularly where urea-formaldehyde resins are used in insulation or furnishings. Regarding such low level exposures, the US National Toxicology Program and the International Agency for Research on Cancer have classified formaldehyde as a human carcinogen [89, 97, 98].

Pathophysiology

Formaldehyde reacts readily and covalently with amine groups such as those found in proteins and nucleic acids. Animal studies have confirmed that formaldehyde produces protein–DNA cross-links [99]. Such covalent adducts or cross-links would produce a loss of protein or nucleic acid function, which is a potential mechanism by which toxicity could be produced.

Formaldehyde is highly irritating to mucosal tissues, such as the eyes, nose, and respiratory tract, either by direct caustic reaction or through covalent interactions. These reactions include tearing, coughing, sneezing, and sometimes bronchospasm. Formaldehyde also reduces mucociliary clearance activity [89] and may affect lower respiratory tissue if attached to particulates. Formaldehyde may provoke allergic responses, including contact dermatitis and asthmatic reactions [100].

Ingested formaldehyde is apparently absorbed rapidly into the bloodstream [90]. It is then rapidly degraded in the tissues by metabolism to formic acid, primarily through the enzyme formaldehyde dehydrogenase [101]. This enzyme catalyzes the reaction of glutathione, formaldehyde, and nicotinamide–adenine dinucleotide to yield S-formylglutathionine, which is hydrolyzed to formate and reduced glutathione by S-formylglutathionine hydrolase. These activities are widely expressed in all human tissues, although the highest activity is in the liver. Formaldehyde also can be oxidized to formate by a nonspecific aldehyde dehydrogenase and by the folate-dependent, one-carbon metabolic system [38].

Because of the widespread metabolism, formaldehyde is eliminated extremely rapidly from the blood, with a half-life of 1–2 min [102]. Several studies in animals and one case report have indicated that systemic formaldehyde is completely converted to formic acid within a relatively short time [90, 103, 104]. Formaldehyde is metabolized to carbon dioxide (via oxidation of formate), although a small amount is incorporated into macromolecules via folate-dependent pathways or direct interaction of formaldehyde

with amine groups. The systemic toxicity of formaldehyde primarily results from the accumulation of formic acid and the ensuing metabolic acidosis [90].

Clinical Presentation

Several case reports of formalin ingestion have provided a general clinical picture. Ingestion of 45 mL of the typical 37% solution [92] has produced gastrointestinal ulceration with little systemic toxicity, whereas massive systemic toxicity and lethality were observed after consumption of 120 mL [90]. Ingestion of formalin often produces immediate vomiting and severe abdominal pain. Ulceration of the oropharynx, esophagus, and stomach is widespread. The duodenum appears less affected and often normal. In one patient who survived, these lesions did regress over 4 weeks, although there was some residual scarring of the distal body and antrum [92].

Respiration becomes labored, with shortness of breath. Metabolic acidosis, with pH of 6.9, is reported [90, 94]. Chest radiographs show pleural effusions and infiltrates. Muscle spasm and the body may become stiff and rigid. There is laboratory evidence of rhabdomyolysis [94].

Formaldehyde causes weakness leading to stupor and coma. Hypotension and shock follow as the gastrointestinal damage and acidosis worsen. Ventricular tachycardia has been reported. Eventually anuria ensues, indicating development of renal failure. Death due to the failure of multiple organ systems can occur within 24 h [90].

Dialysis systems contaminated with formaldehyde have been associated with the occurrence of hemolysis [104] in patients. Chronic exposure to formaldehyde may therefore cause hemolytic anemia. Although significant formate accumulation seems to occur in patients with formaldehyde exposure, minimal ocular toxicity seems to be present. A patient with formaldehyde poisoning and metabolic acidosis should have vision checked, however, as noted earlier under methanol poisoning.

Diagnostic Considerations

A positive exposure history is the initial key to diagnosis. In a patient without confirmed ingestion, several features aid in the diagnosis. First, the odor of formaldehyde should be observed on the breath. On lavage in one patient, this odor was noted strongly in the gastric contents [90, 94]. Two indicators of potential formaldehyde exposure are the presence of severe lesions of the gastrointestinal tract, especially in the oropharynx, and a severe, systemic metabolic acidosis (a decreased arterial blood pH, an increased anion gap, or a decreased serum bicarbonate concentration). Because these indicators are not definitive, an accompanying increase in blood formate concentrations would suggest that there had been an ingestion of methanol, formic acid, or formaldehyde. Although the laboratory measurement of blood formate concentrations is rarely available, the treatment for either ingestion should be the same.

Treatment

Because of the potential for massive multiorgan damage, aggressive supportive care needs to be instituted rapidly [90, 94]. Rapid intubation and ventilatory support should be instituted for standard indications. Gastric lavage with saline or bicarbonate solutions, even if applied within 1–3 h of ingestion, is probably of little value because of the potential for further corrosive damage. If there is little corrosive damage to the esophagus, the benefit of decontamination must be weighed against the risk. The possibility of corrosive injury and the unlikely efficacy of the procedure suggest, however, that lavage should not be performed. Intravenous fluids help maintain cardiovascular and renal function. If necessary, vasopressors should be given to maintain blood pressure.

The mainstay of treatment beyond supportive care should be to aggressively counteract the systemic accumulation of formic acid. Initially, this counteraction should include intravenous administration of sodium bicarbonate to combat the acidosis [90, 94]. This may also increase the

renal elimination of formate (see above; Methanol Biochemistry and Clinical Pharmacology) [13]. Although never attempted in previous cases, administration of folate or folinic acid, as detailed earlier, should increase the metabolic elimination of formate. Hemodialysis should be initiated as soon as possible. Although not formally studied, it seems logical that the indications for hemodialysis are similar to those enumerated for methanol. In one patient who had consumed a lethal amount of formaldehyde and was nearly moribund, hemodialysis was started within 6 h of ingestion [94]. The patient improved rapidly, the acidosis was reversed by the end of dialysis, and the patient recovered completely.

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Part XVI

Chemical Agents: Pesticides

Sally M. Bradberry and J. Allister Vale

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Chlorophenoxy herbicides (phenoxy-carboxylic acid herbicides) are weed killers that act as synthetic auxins (plant “hormones”) and cause plant death by disrupting nutrient transport and growth. They are used widely for the control of broad-leaved weeds in pastures and cereal crops and along public rights of way. Chlorophenoxy herbicides are of limited persistence in the environment. They are occasionally coformulated with a hydroxybenzonitrile herbicide such as ioxynil or bromoxynil which is more toxic than a chlorophenoxy herbicide but are added to broaden the spectrum of herbicidal activity.

Chlorophenoxy herbicide poisoning is uncommon in developed countries but reported quite frequently in the developing world. For example, 181 patients presented with MCPA poisoning to just three hospitals in Sri Lanka between April 2002 and October 2003 [1]; eight patients in this series died.

Biochemistry and Clinical Pharmacology**Biochemistry**

Structurally, chlorophenoxy herbicides comprise an aliphatic carboxylic acid moiety attached to a chlorine-substituted or methyl-substituted aromatic ring. The most common herbicide of this class is 2,4-D [(2,4-dichlorophenoxy)acetic acid]; its structural formula and that of related

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compounds are shown in Fig. 1. Mecoprop-P is the stereoisomer of mecoprop (the racemate) and dichlorprop-P is the stereoisomer of dichlorprop. 2,4,5-Trichlorophenoxy acetic acid (2,4,5-T) has been largely withdrawn from use due to concerns that some formulations were contaminated with dioxin. Chlorophenoxy herbicides typically are formulated in commercial preparations as salts or esters, for example, the dimethylamine salt of 2,4-D.

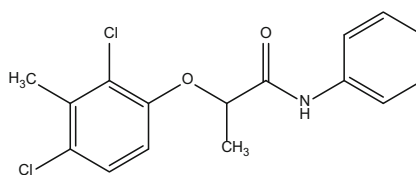
Toxicokinetics

Chlorophenoxy compounds are absorbed rapidly after oral administration in humans [2, 3], but dermal [3, 4] and inhalational [5] absorption is limited. When absorbed, the salts or esters of these herbicides dissociate or hydrolyze rapidly. The free acid binds to serum albumin; increased length of the acid chain, and increased substitution of the aromatic ring favor binding. Chlorophenoxy herbicides have relatively low volumes of distribution (approximately 0.1 L/kg for 2,4-D in humans) [6]. However, distribution is affected not only by the extent of protein binding, which is saturable, but also by the extent of herbicide ionization. Because chlorophenoxy herbicides are acids (the pK_a of 2,4-D is 2.73), at physiological pH only a small percentage is in the non-ionized form and available to penetrate lipid membranes.

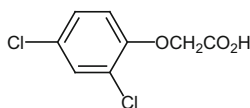
2,4-D undergoes little metabolic transformation in humans; the free acid is excreted predominantly unchanged in urine [2] with small amounts as a 2,4-D conjugate. Limited experimental data suggest a similar process for other chlorophenoxy herbicides [3]. Active renal tubular secretion has been shown as a primary mechanism of renal clearance in animals [3] though this is saturable at high doses. The elimination half-life of 2,4-D in humans is of the order of 20–30 h [2, 3].

Pathophysiology of Toxic Effects

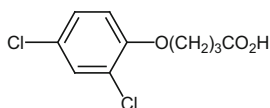
Chlorophenoxy-induced dose-dependent cell membrane damage [7] is likely to be important in the mediation of central nervous system



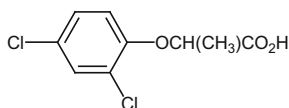
Clomeprop [(RS)-2-(2,4-dichloro-*m*-tolylxy)propionanilide]



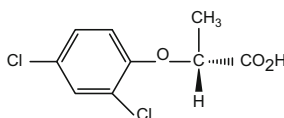
2,4-D [(2,4-dichlorophenoxy)acetic acid]



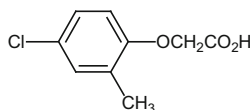
2,4-DB [4-(2,4-dichlorophenoxy)butyric acid]



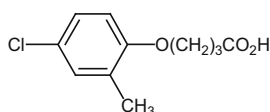
Dichlorprop [(RS)-2-(2,4-dichlorophenoxy)propionic acid]



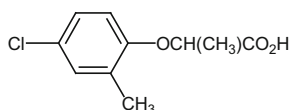
Dichlorprop-P [(2R)-2-(2,4-dichlorophenoxy)propionic acid]



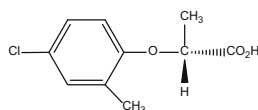
MCPA [4-chloro-*o*-tolylxyacetic acid]



MCPB [4-(4-chloro-*o*-tolylxy)butyric acid]



Mecoprop [(RS)-2-(4-chloro-*o*-tolylxy)propionic acid]



Mecoprop-P [(R)-2-(4-chloro-*o*-tolylxy)propionic acid]

Fig. 1 Chemical structures of the chlorophenoxy herbicides

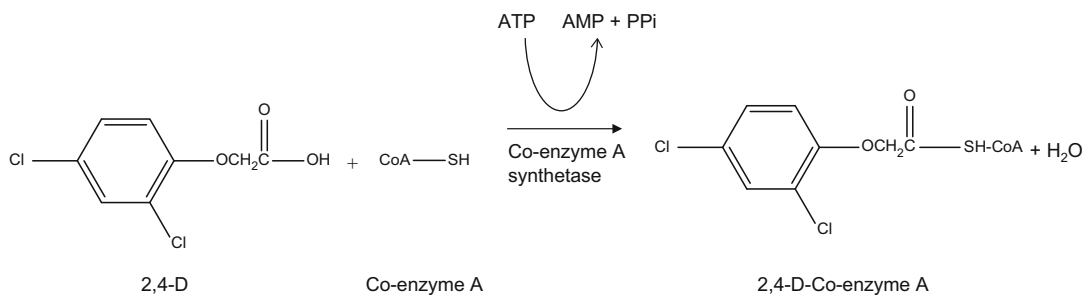


Fig. 2 Formation of 2,4-D-CoA. *ATP* adenosine 5'-triphosphate, *AMP* adenosine 5'-monophosphate, *PPi* inorganic pyrophosphate

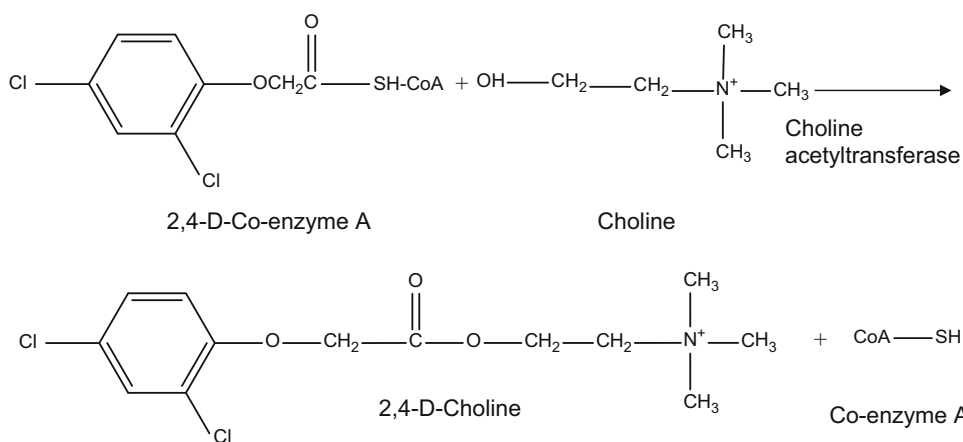


Fig. 3 Biosynthesis of 2,4-D-choline

toxicity both by damaging the blood–brain barrier [8] and by disrupting neuronal membrane transport mechanisms [9]. In addition, chlorophenoxy herbicides are related structurally to acetic acid and are able to form analogues of acetyl coenzyme A, such as 2,4-D-CoA [Fig. 2] which in turn can enter the acetylcholine synthetic pathway with the subsequent formation of choline esters such as 2,4-D-choline, which may act as false neurotransmitters at muscarinic and nicotinic synapses [10, 11] (Fig. 3).

Uncoupling of oxidative phosphorylation within mitochondria may result both from damage to intracellular membranes [12] and/or to impaired acetyl-coA metabolism. A variety of cellular activities may be compromised by subsequent adenosine triphosphate (ATP) depletion,

including ATP-dependent ion pumps, DNA and protein synthesis, and processes involved in the maintenance of cell shape.

Commercial preparations contain a variety of other ingredients including solvents, surfactants, sodium and potassium hydroxide, iron, cresols, and phenols that may contribute to the toxicity of the final product [13].

Clinical Presentation and Life-Threatening Complications

Most cases of serious poisoning involve deliberate ingestion of 2,4-D alone, in combination with other chlorophenoxy herbicides or in combination with ioxynil or bromoxynil. However, there were

eight fatalities (4.4%) in a series of 181 patients exposed to MCPA in Sri Lanka that could not be satisfactorily explained in terms of pathophysiological mechanism; the features in 154 of the 181 patients were minimal [1]. We have reviewed previously the toxicity of chlorophenoxy herbicides [14].

Ingestion

Vomiting is a prominent early feature of chlorophenoxy herbicide ingestion [1, 15–17] and may be accompanied by burning or ulceration in the mouth [15], abdominal pain, and diarrhea [1, 15]. Severe corrosive effects, including gastrointestinal hemorrhage, are rare and may be due to other ingredients in some formulations, such as sodium and potassium hydroxide, surfactants, iron, cresols, and phenols. Gastrointestinal fluid loss, vasodilation, and direct myocardial toxicity contribute to hypotension [1, 15, 17, 18], which may precipitate renal failure.

Rapid onset of coma is common in severe cases and may be preceded by a period of agitation and confusion. Coma is almost invariably in patients who die and often lasts several days in patients who survive [15, 17–20]. The incidence of other neurological features varies widely. Hypertonia, hyperreflexia, clonus, and occasionally extensor plantar responses suggest upper motor neuron involvement [21]. Miosis, nystagmus, ataxia, hallucinations, and convulsions also have been reported.

Coma is associated frequently with inadequate ventilation [1, 15, 17–20, 22]. Aspiration of gastric contents may contribute to pulmonary complications. Hemoptysis and pulmonary edema may occur. Hypoventilation secondary to central nervous system depression is the primary cause of hypoxia, although respiratory muscle weakness also may occur as part of a generalized myopathy. In such cases, there may be limb weakness or reduced or absent tendon reflexes and increased creatine kinase activity. Fasciculation and/or myotonia may also be present. Neuromuscular effects may persist for several weeks. A syndrome similar

to Guillan Barré has been described in a patient who survived severe poisoning with a mixture of MCPA, 2,4-D and MCPP [23]. Electromyography evidence of a peripheral neuropathy has been reported rarely [20, 24].

Metabolic complications include acidosis, hyperthermia in the absence of infection (possibly reflecting uncoupling of oxidative phosphorylation), and rhabdomyolysis. The latter may contribute to increased aspartate and alanine aminotransferase activities. Thrombocytopenia, hemolytic anemia, and hypocalcemia are recognized rarely.

The prognosis is poor in patients who rapidly become shocked and comatose but cases of delayed (>8 h post ingestion) sudden deterioration have also been reported. For example, respiratory distress, hyperthermia, hypotension, and metabolic acidosis escalated in one case between 8 and 20 h post ingestion, cumulating in a fatal cardiac arrest despite full ICU support including mechanical ventilation, vasopressors, and continuous veno-venous hemodialysis [25]. Conversely, full recovery can ensue over weeks to months despite initial severe toxicity.

Inhalational and Dermal Exposure

Because dermal and inhalational absorption of chlorophenoxy herbicides is poor, acute poisoning via these routes is uncommon. Local irritation to the skin and mucous membranes may occur, but there are very few reports of systemic toxicity after such exposures. Interpretation of cases in which systemic effects are described is complicated, and the etiologic role of chlorophenoxy herbicides in many has been challenged [26]. Reported features include mild-to-moderate gastrointestinal symptoms followed by variable manifestations of peripheral neuropathy or myopathy [27–33]. Despite widespread use, there have been no published reports of systemic chlorophenoxy herbicide poisoning after dermal or inhalational exposure since at least the 1980s and no reported fatalities from such exposures.

Diagnosis

There should be no diagnostic difficulty when a history of deliberate chlorophenoxy herbicide ingestion is forthcoming, but familiarity with the clinical presentation may hasten diagnosis when self-harm is suspected but no history is available. The presence of muscle fasciculation, weakness, and/or myotonia may result in misdiagnosis of organophosphorus insecticide poisoning. The toxicological differential diagnosis also includes poisoning by salicylates or psychotropic drugs. Measurement of plasma chlorophenoxy herbicide concentrations may be undertaken for diagnostic confirmation [34], although these assays are not widely available. There is no definite relationship between total plasma chlorophenoxy herbicide concentrations and severity of poisoning, although Flanagan and colleagues [15] suggested that a total plasma chlorophenoxy herbicide concentration greater than 500 mg/L is associated with severe toxicity.

Treatment

Initial assessment and treatment of patients exposed to chlorophenoxy herbicides should follow generally accepted guidelines of current practice for external and gastrointestinal decontamination and supportive care. In vitro studies showed that chlorophenoxy herbicides are adsorbed to activated charcoal [35]. The administration of oral activated charcoal, 50–100 g in an adult, may be considered reasonable in patients who have ingested a potentially toxic amount of a chlorophenoxy herbicide within 1 h. Activated charcoal therapy has not been shown, however, to affect the outcome of chlorophenoxy herbicide-poisoned patients. Although most patients can be managed with symptomatic and supportive care alone, controversy surrounds the use of urine alkalization, hemodialysis, and hemoperfusion in enhancing herbicide elimination in severely poisoned patients.

Urine Alkalinization

No controlled trials of urine alkalization have been carried out in chlorophenoxy herbicide poisoning. Despite several case reports claiming enhanced elimination with urine alkalization [15, 16], there are sufficient data to examine this claim only for one patient [20, 36]. The patient, a 39-year-old man, developed features of severe poisoning after the ingestion of a calculated 6.8 g of 2,4-D and 13.6 g of mecoprop. The admission urine pH was 6.4, and the plasma 2,4-D concentration was 400 mg/L. An “alkaline diuresis” comprising 14 L of fluid containing 69.3 g of sodium bicarbonate (825 mmol) over 48 h [20] was instituted approximately 42 h post ingestion, but a urine pH greater than 7.5 was not achieved until 70–75 h post ingestion.

The renal 2,4-D clearance corrected to a urine flow of 1 mL/min was related directly to urine pH ($r = 0.99$) and was estimated to increase almost fivefold for each unit increase in urine pH. The mean corrected 2,4-D renal clearance was 0.28 mL/min over the urine pH range 5.1–6.5 and 9.6 mL/min over the urine pH range 7.55–8.8 (Table 1) [36]. At pH 5.1 and 8.3, the *uncorrected* 2,4-D renal clearances were 0.14 mL/min and 63 mL/min. The plasma half-life of 2,4-D decreased from approximately 219 h before alkaline diuresis to 3.7 h at 96–112 h postingestion when the urine pH exceeded 8.0 [20], and the amount recovered in the urine was 6.66 g.

The renal mecoprop clearance corrected for a urine flow rate of 1 mL/min also was related directly to urine pH ($r = 0.94$). It approximately doubled with each unit increase in urine pH [20] from 0.38 mL/min over the urine pH range 5.1–6.5 to 2.08 mL/min over the urine pH range 7.55–8.8 (see Table 1). The plasma half-life of mecoprop was shortened from 39–14 h, and the amount recovered in the urine was 7.64 g [20]. Clinical improvement paralleled the decrease in 2,4-D and mecoprop concentrations, and consciousness was regained on the fourth day after ingestion, when the plasma 2,4-D and mecoprop concentrations were approximately 100 mg/L.

The uncorrected renal 2,4-D clearance (0.14 mL/min at urine pH 5.1) determined by

Table 1 Effect of urine alkalization on plasma half-life and mean corrected (to 1 mL/min urine flow) renal clearance of 2,4-D and mecoprop

Urine pH (range)	2,4-D		Mecoprop	
	Clearance (mL/min)	Half-life (hr)	Clearance (mL/min)	Half-life (hr)
5.10–6.5	0.28	219	0.38	39
6.55–7.5	1.14	42	0.65	22
7.55–8.8	9.60	4.7	2.08	14

Adapted from Park et al. [36]

Prescott and coworkers [20] was similar to that found previously (0.17–1.4 mL/min) [37]. A high 2,4-D renal clearance was achieved, however, only when the urine pH was greater than 7.5 and urine flow was greater than 200 mL/h. The maximum uncorrected 2,4-D renal clearance of 63 mL/min at pH 8.3 [20] would have required a urine flow rate of approximately 600 mL/h and compared favorably with that achieved with hemodialysis (56.3–72.9 mL/min) [19]. However, the *corrected* renal clearance data show that urine alkalization without high urine flow is markedly less efficient than hemodialysis as a means of removing 2,4-D.

The less beneficial effect of urine alkalization on mecoprop clearance compared with 2,4-D clearance may be explained by the much greater clearance of mecoprop by metabolism and the fact that mecoprop is a weaker organic acid (pK_a of 3.78 and 2.73). Renal mecoprop clearance would be less affected by changes in urine pH.

A Cochrane review of the role of urine alkalization for acute chlorophenoxy poisoning concluded in 2007 [38], “it is not unreasonable to attempt urinary alkalization. . . given that toxicity may be prolonged and result in death after 24 h, few significant adverse effects have been reported from urinary alkalization, and the potential for this treatment to provide some benefit.” The level of evidence for recommendation of urinary alkalization is thus Level III.

Hemoperfusion and Hemodialysis

Durakovic and associates [19] treated four patients with 2,4-D poisoning by hemodialysis,

though clearance data was only available in three cases and in two cases; resin hemoperfusion also was instituted. The dialysis clearance in one patient was 68.7 mL/min, and in the two patients receiving combined therapy, the clearances were 56.3 mL/min and 72.9 mL/min. Urine alkalization combined with a high urine flow (600 mL/h) produced similar clearance values [20, 36]. Several other authors [39, 40] have described a favorable outcome in patients with severe poisoning following ingestion of chlorophenoxy herbicide-containing formulations treated with hemodialysis, without giving clearance values, though apparent failures of extracorporeal elimination therapies have also been described [41].

The reported clearances of 2,4-D during hemodialysis alone or combined with hemoperfusion were relatively unimpressive and were similar to those reported with high-flow urine alkalization. Nonetheless, in cases of severe 2,4-D poisoning, hemodialysis should be considered, particularly if high-flow urine alkalization cannot be performed for clinical reasons. The level of evidence for this recommendation is Level III.

Indications for ICU Admission in Pesticide Poisoning

History of substantial ingestion in preceding 8 h, regardless of symptoms
Severe vomiting and/or diarrhea
Hypotension unresponsive to fluid resuscitation
Central neurological or neuromuscular symptoms or signs

Criteria for ICU Discharge

Resolution of severe vomiting and diarrhea without new features
 Resolution of hypotension, without new features
 Resolution of, or substantial improvement in, central neurological or neuromuscular symptoms or signs

Common Errors in Management

Failure to consider the potential contribution to the clinical picture of solvents and adjuvants in the formulation
 Presence of muscle twitching, fasciculation, and weakness leading to a misdiagnosis of organophosphorus insecticide poisoning
 Inadequate monitoring and clinical review in first few hours after a substantial ingestion
 Assumption that pyrexia must be due to infection when other metabolic explanations are possible

Key Points

1. Severe poisoning is likely only after ingestion.
2. The level of consciousness may deteriorate rapidly after substantial ingestion.
3. Neuromuscular effects may persist for several weeks.

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Fumigants are nonspecific pesticides that exist as gases or vapors or are capable of being changed to one of these states. They represent a diverse group of compounds (Table 1) that are dissimilar in their chemical structures, physical properties (Table 2), and mechanisms of injury. This broad category of substances includes liquids (ethylene dibromide, dibromochloropropane, formaldehyde) that can vaporize, solids that may release toxic gases when mixed with water (zinc phosphide, aluminum phosphide), cyanide salts (sodium or calcium cyanide) that liberate hydrogen cyanide gas when acidified, and gases (methyl bromide, hydrogen cyanide, ethylene oxide). Fumigants are used to control pests in confined, enclosed, or sealed environments. Examples of typical fumigant targets are rodents or insects in stored grain products, wood-destroying insects such as dry-wood termites or wood beetles, and nematodes and fungi in the soil that adversely affect crop production. Examples of specific confined areas are railroad hopper cars, silos, and storage areas. Cyanide is discussed in its own chapter and is not addressed here.

Fumigant gases or vapors are intended to dissipate after the enclosed space has been opened and ventilated. For organisms living within that enclosed space, the fumigants are indiscriminate poisons. They affect targeted pests and other organisms that may not be an intended target, including workers that may enter the treated area unknowingly. Therefore, treated areas should

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Table 1 Names and common uses of selected fumigants

Common name	Synonyms	Uses
Methyl bromide	Bromomethane, monobromomethane, embafume	Pesticide fumigant for soil, mills, warehouses, vaults, ships, freight cars, etc. Wool degreaser
Sulfuryl fluoride	Sulfur difluoride dioxide, vikane	Pesticidal fumigant, especially for structures with dry-wood termites or wood beetles
Chloropicrin	Trichloronitromethane, nitrochloroform, larvacide, picfume	Pesticidal fumigant for soil, cereals, and grains; chemical synthesis; military "tear gas"
Aluminum phosphide	Celphos, detia, phostoxin	Pesticidal fumigant, especially for animal feed, bulk grain, cottonseed, leaf tobacco, and flour mills; phosphine source, semiconductor industry
Zinc phosphide	ZP	Rodenticidal fumigant
Carbon disulfide	Serafume, vertifume	Pesticide, manufacturing
Chlorine dioxide	Alcide, doxide 50	Fumigant, algicide
Acrylonitrile	Acrylon, carbacryl, aculofume	Pesticides, semiconductor industry

Table 2 Properties of selected fumigants

Chemical	State	Color	Odor/irritation	Water Solubility (% g/dL)	Boiling Point (°F)	Vapor Pressure (mm Hg)	IDLH (ppm)
Methyl bromide	Gas	Colorless	Odorless	2%	38	1.9	250
Sulfuryl fluoride	Gas	Colorless	Odorless	0.2%	−68	15.8	200
Chlorine dioxide	Gas	Yellow	Acidic	3%	51.8	760	5
Carbon disulfide	Liquid	Colorless to yellow	Sweet aromatic	0.08%	114.8	359	500
Chloropicrin	Liquid	Colorless to yellow	Intensely irritating	0.2%	234	18	2
Aluminum phosphide	Solid	Dark gray or yellow	Fishy	NA	NR	NR	NR
Zinc phosphide	Solid	Dark gray	Phosphorus-like	NA	2012	NR	NR
Acrylonitrile	Liquid	Pale yellow	Slight peach	7.2%	171.1	100	85
Ethylene dibromide	Liquid	Colorless	Sweet chloroform	0.4%	267.8	11.25	100

NR not reported, NA not applicable, IDLH immediately dangerous to life and health

have warning signs (placarding) indicating the date and time of safe entry.

Methyl bromide and sulfuryl fluoride are prototypic fumigants. They are gases at room temperature and 1 atm pressure, are poorly water soluble, are odorless, and are not significantly

irritating to the mucous membranes. Because many fumigants have poor warning properties, chloropicrin (CCl_3NO_2) often is added as a warning agent. Chloropicrin is intensely irritating to all mucous membranes and has been used as an incapacitating lacrimator in military poison gases.

The specific mechanisms of action, including specific molecular targets, have not been elucidated in detail for many of the fumigants. The clinical signs and symptoms of poisoning by these compounds are well known, but for many their effects at the cellular and molecular levels still are being explored.

Phosphides

Aluminum phosphide (AlP) and zinc phosphide (Zn_2P_3) are solids and usually formulated as pellets or encased in packets. When either phosphide reacts with water or acid, phosphine gas (PH_3), the fumigant, is liberated. All typical routes of exposure may occur with fumigants, although inhalation is the most likely in the USA. In India, ingestion of fumigant pellets has become an important source of morbidity and mortality [1].

There is experimental evidence that phosphine noncompetitively inhibits mitochondrial cytochrome oxidase, interfering with cellular respiration and adenosine triphosphate formation [2]. Methemoglobinemia has also been described [3]. Myocardial cells are particularly sensitive to this noncompetitive inhibition of cytochrome oxidase [4]. Phosphine interferes with incorporation of amino acids into myocardial proteins, which can result in heart failure [4]. In the lung, phosphine directly damages the alveolar-capillary membrane, potentially resulting in the acute respiratory distress syndrome and hypoxemia. Phosphine is a small peripheral arteriole vasodilator that may cause decreased systemic vascular resistance, with possible hypotension, and distributive shock [5]. Spontaneous self-ignition due to phosphine has been described more than once [6, 7].

In a series of grain storage workers acute inhalational exposure to aluminum phosphide was reported to cause cough, dyspnea, chest tightness, headache, numbness, lethargy, and epigastric pain [8]. In a report of eight intentional aluminum phosphide ingestions, the same investigators described gastritis, altered sensorium, distributive shock, renal failure, and cardiac arrhythmias. Six patients died. Postmortem findings included pulmonary edema, intestinal edema, petechial

hemorrhages on the liver and brain, and desquamation of the epithelial lining of the bronchioles [9].

The diagnosis of phosphide poisonings is usually based on known exposure and the clinical presentation. While aluminum and zinc levels may be obtained, they are not required for either the diagnosis or prognosis. Phosphide in gastric contents can be confirmed via the silver nitrate test, whereby gastric aspirate is heated to 50 °C in a flask and the resulting vapor leads to blackening of silver nitrate impregnated filter paper [10].

Zinc is electron dense and presence of radio-opaque foreign bodies in a known exposure can suggest clinically significant exposure in initially asymptomatic patients [11]. Phosphide poisoning is discussed in greater detail in its own chapter.

Methyl Bromide

Methyl bromide (CH_3Br) is colorless, odorless, and three times as heavy as air. The latter attribute is important in that this gas, and others that are heavier than air, collect in low-lying places. This property is beneficial for fumigation but is potentially responsible for unintended exposures. By cooperative agreement, methyl bromide was phased out of use by 2005 in industrialized nations.

Methyl bromide typically is used as a soil fumigant. It also has been used to treat stored fruit in ship holds or in special fumigation chambers in aircraft. Nonfumigant uses of methyl bromide include use as a methylating agent, refrigerant, and fire retardant. The main routes of exposure to humans are inhalation and skin contact.

Methyl bromide is a potent alkylating agent with high affinity for sulfhydryl and amino groups. It binds to amine groups in amino acids, interfering with protein synthesis and function [12]. Sulfhydryl-containing amino acids and proteins can be damaged at their amino and sulfhydryl sites. Given that methyl bromide is an alkylating agent, it may methylate many other cellular components, including glutathione, proteins, DNA, and RNA [12].

Because of methyl bromide's lack of warning properties, the unwary worker may come into contact with dangerous concentrations of this gas unknowingly [13]. Symptoms may evolve over hours. Initially, mild symptoms, such as headache and eye, nose, and sinus irritation may be reported [14]. At higher concentrations, central nervous system (CNS) and respiratory complaints predominate [15, 16]. CNS complaints may include seizures, myoclonus, tremors, peripheral neuropathy, ataxia, vertigo, respiratory paralysis, coma, and cerebral edema [17, 18]. Respiratory tract irritation, burns, pulmonary edema, and ultimately ventilatory failure may occur [16, 19]. Skin irritation and burns may occur after large exposures [20]. The typical lesions are blisters with surrounding erythema [21]. Eye injuries may occur, with severe inflammation leading to temporary blindness [22]. Patients should have prompt skin and eye irrigation if indicated.

Methyl bromide exposure has been associated with increased incidence of stomach cancer in agricultural workers [23].

Sulfuryl Fluoride

Sulfuryl fluoride (SO_2F_2) is odorless and colorless. The exact mechanism of action of sulfuryl fluoride is unknown. Its vapor pressure is similar to water. The respiratory system, CNS, and cardiovascular system are the primary target organ systems [24]. Free fluoride anion is released soon after contact [24]. At autopsy, markedly elevated fluoride concentrations have been found in the heart blood of one of two sulfuryl fluoride poisoning victims. The blood fluoride concentration obtained 6 days after exposure was 0.5 mg/L [25]. When sulfuryl fluoride is combusted in the presence of water vapor, it may form acidic vapors, such as hydrofluoric acid. The latter is discussed in greater detail in its own chapter.

Fluoride combines with divalent cations, primarily calcium and magnesium, potentially resulting in hypocalcemia, hypomagnesemia, and hyperkalemia from cellular destruction [26]. This constellation of electrolyte abnormalities can manifest as CNS irritability with agitation, tetany, or seizures [26]. These electrolyte abnormalities

also may cause prolongation of the QT interval, torsades de pointes, bradydysrhythmias, wide QRS complexes, or asystole [27]. Acute bronchospasm has been reported after sulfuryl fluoride inhalation [28]. Limited exposures may cause nausea, vomiting, and diarrhea [28].

In one case report, a woman developed burning to her eyes, abdominal pain, hypotension, and convulsions, followed by torsade de pointes, ventricular fibrillation, and asystole despite aggressive treatment with endotracheal intubation, 7 gm of calcium salts, 6 gm of magnesium, 2 mg of epinephrine, 2 ampules of sodium bicarbonate, 1 mg of atropine, and fluids [29]. While supportive care with electrolyte monitoring and airway support are recommended, it is unclear whether such interventions have any effect on morbidity and mortality.

Chloropicrin

Chloropicrin is a lacrimator and a pulmonary irritant. It is a colorless-to-yellow liquid with a sweet, slightly aromatic odor. It is one of the more volatile fumigants. Chloropicrin is highly irritating to all mucous membranes and was used in World War I as a tear gas because of its strong lacrimating properties [28, 30]. Chloropicrin's mechanism of action has not been elucidated fully. It is slightly water soluble, intermediate between chlorine gas and phosgene gas, and its effects are similar to these gases [31]. Chloropicrin is corrosive with local toxic effects on exposed mucous membranes, the respiratory tract including the alveolar-capillary membrane, and the eyes [32]. Common clinical findings in patients after exposure to chloropicrin vapors include cough, erythema, tearing, rhinorrhea, headache, and irritation [14, 33]. After ingestion, irritation of the gastrointestinal tract would be expected due to the corrosive nature of this substance.

Ethylene Dibromide

Ethylene dibromide ($\text{CH}_2\text{BrCH}_2\text{Br}$) is a colorless substance, also referred to as 1,2-dibromoethane. Ethylene dibromide first found use in 1948; its biocidal properties led to its use as a soil sterilant.

In addition to its use as a fumigant, it was employed as an antiknocking agent in gasoline. In contrast to many other fumigants, ethylene dibromide is a dense liquid, and it has a sweet odor. The vapor pressure is approximately that of water, and poisoning typically occurs from direct contact. Of note, it is able to penetrate protective clothing, including neoprene and rubber [20].

Patients exposed to ethylene dibromide may have mucous membrane irritation, skin irritation and blistering, and respiratory distress [34–36]. Cardiac effects including bundle-branch blocks, supraventricular tachycardia, ventricular fibrillation, and asystole have been described [34–36]. In cases of severe intoxication, hypotension and shock may occur [35–37]. Hepatic failure and renal insufficiency have been reported after significant exposure to ethylene dibromide [38]. Pathology of ethylene dibromide-related liver injury is characterized as centrolobular necrosis [34]. Ethylene dibromide has weak anesthetic properties that may result in CNS depression and ultimately coma at high doses [34, 35, 39].

Ethylene dibromide is converted by hepatic microsomal cytochrome P-450 isozymes (CYP2E1, CYP2A6, CYP2B6) and cytosolic glutathione-S-transferase isozymes (A1-1, A2-2, M1a-1a, P1-1) in vitro to bromoacetaldehyde, bromoacetic acid, thiodiacetic acid, S-2-bromoethylglutathione, and S-(2-hydroxyethyl) mercapturic acid [40–44]. The principal mechanism associated with carcinogenicity and mutagenicity is conjugation of ethylene dibromide catalyzed by glutathione-S transferases [44, 45]. The conjugate rapidly rearranges to an episulfonium ion, which reacts with DNA [44, 46].

In a rat model, pretreatment with alcohol potentiated the hepatotoxicity of ethylene dibromide secondary to a reduction in ethylene dibromide conjugation, with a shift to the formation of reactive oxidative intermediates [47].

Ethylene Oxide

Ethylene oxide is one of the most common medical sterilants in use today. In addition to its use in the sterilization of medical devices, ethylene

oxide has found use as a fumigant, a fungicide, and an intermediate in the production of plastics. Although it often is discussed in terms of its mutagenic potential, it possesses the acute toxicologic properties of being a potent skin irritant and CNS depressant.

Ethylene oxide is a colorless gas at room temperature with an odor threshold of 250–690 ppm [48]. However, levels of 200 ppm may cause mucous membrane irritation. Direct skin contact with liquid ethylene oxide may cause significant cutaneous burns resembling toxic epidermal necrolysis [49]. Concentrations approaching 1000 ppm may cause chest pain, dyspnea, gastrointestinal disturbances, weakness, and ataxia [50]. Uncommon but life-threatening acute reactions include hemolysis and anaphylactoid reactions reported after exposure to ethylene oxide-treated cardiopulmonary bypass machines [51].

Acrylonitrile

Acrylonitrile (CH_2CHCN ; vinyl cyanide) is a colorless-to-pale yellow liquid with an unpleasant odor. It is highly flammable and when combusted or ingested may form cyanide gas. The vapor pressure of acrylonitrile is 100 mmHg (water is 25 mmHg), and its vapor density is 1.9 (air is 1). Acrylonitrile easily volatilizes but remains low to the ground unless disturbed by air currents. In addition to its use in the plastics industry, it may be used as a fumigant. Exposure to acrylonitrile may occur by the dermal, inhalational, or oral routes. In human volunteers inhaling 2.3 or 4.6 ppm of acrylonitrile, 52% of the administered dose was retained [52]. It is absorbed through the forearm skin at a rate of $0.6 \text{ mg/cm}^2/\text{h}$ [53].

Acrylonitrile is metabolized less efficiently in humans than in rodents, which may explain partially why the cyanide-like toxicity plays a lesser role in humans than in rodents [54]. Its proposed metabolic pathways are shown in Fig. 1. The typical half-life of acrylonitrile is approximately 3–6 h in rodents [55]. Four main metabolic products have been detected: glucuronides; glutathione adducts, which form cyanoethyl

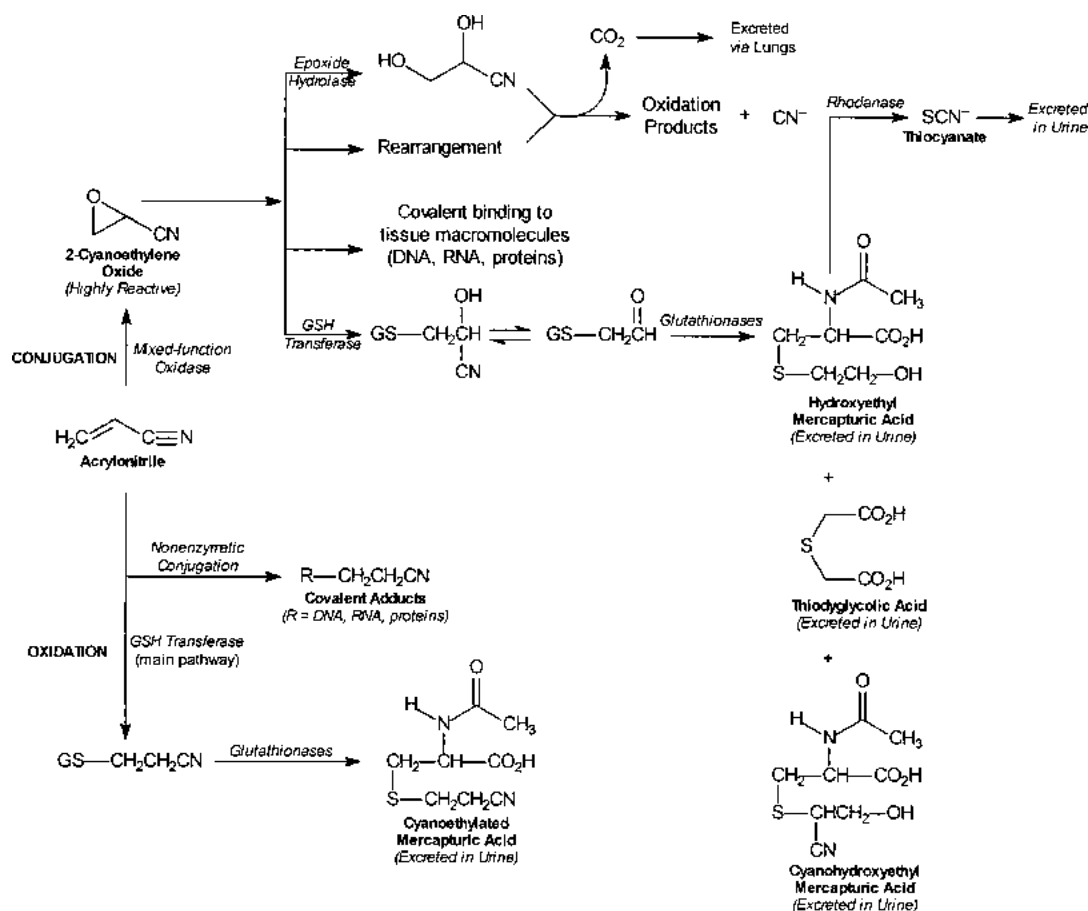


Fig. 1 Proposed metabolic pathways of acrylonitrile metabolism. Note specifically the glutathione and rhodanese pathways

mercapturic acid; protein thiol group adducts; and 2-cyanoethylene oxide, which is formed by epoxidation. The latter two pathways are considered to be responsible for acrylonitrile's toxicity [38]. The toxic mechanism of nitriles is via the liberation of cyanide in vivo and in vitro [56].

Acrylonitrile may cause mucous membrane irritation, chest discomfort, dyspnea, and nausea at low doses. More significant exposure may cause loss of consciousness, seizures, respiratory arrest, and cardiovascular collapse if the dose is sufficient [57]. The acute systemic toxicity resembles cyanide poisoning, with the formation of lactic acidosis and cyanide [58, 59]. Liver and kidney injury may follow large exposures

[60]. When acrylonitrile is ingested, the signs and symptoms may be slower in onset than after inhalation [61].

Carbon Disulfide

Carbon disulfide (CS₂) is a colorless but volatile liquid. With proper engineering controls in the workplace, exposures are rare. Its vapor pressure is approximately 300 mmHg (water is 25 mmHg). Carbon disulfide has been used principally in the manufacture of rayon, in the manufacture of cellophane, and in the semiconductor industry. It also found use as a fumigant when mixed with carbon

tetrachloride in a 20:80 ratio. Such a mixture has been used to fumigate boxcars of grain [62, 63]. The major target organs are the CNS, eyes, skin, cardiovascular system, liver, and reproductive organs.

Acute effects of carbon disulfide are rare and generally are due to inhalation or dermal contact. An early effect of sufficient concentrations is irritation of the mucous membranes. After major skin contact, full-thickness corrosive burns may occur with erythema and blistering. A wide variety of neurologic effects have been described including psychosis, hallucinations, suicidality, insomnia, labile mood, paranoia, excessive sexual behavior, ataxia, parkinsonism, delirium, blurred vision, seizures, and microangiopathy [64–66]. Ingestion of carbon disulfide has been rarely reported, albeit with catastrophic features, including muscle spasms, Cheyne-Stokes respirations, hypotension, coma, and death [67].

Chlorine Dioxide

Chlorine dioxide (ClO_2) is a fumigant that also has found use in the bleaching of cellulose, flour, leather, and textiles. It is a yellow-to-red gas at room temperature, with an acrid odor; it is heavier than air; and it has a high vapor pressure (760 mmHg). This compound typically is not used in routine fumigation processes. In 2001, anthrax spores were disseminated via the US Postal Service. One site where anthrax spores were found was the Hart Senate Office Building in Washington, D.C. In this case, chlorine dioxide was pumped into the sealed building to soften and kill the spores. Because of chlorine dioxide's strong oxidizing properties, it was thought that it would be the most effective fumigant based on the size of the job and risk to the building's inhabitants and adjacent urban population. After the fumigation process, the air was filtered through a scrubber containing the antioxidant ascorbic acid, which reacts with chlorine dioxide to inactivate the biocide.

Chlorine dioxide is an irritant gas that affects the mucous membranes and other moist tissue

owing to its relatively high water solubility [68]. Expected clinical features are irritation of the eyes, nose, and throat [69]. Larger exposures may affect the tracheobronchial tree with the possibility of pulmonary irritation from very large exposures. Ingestion of this oxidizing agent would be expected to cause a corrosive injury to the gastrointestinal tract if the dose is sufficient. Chlorine dioxide is absorbed rapidly after ingestion or inhalation, with peak concentration occurring within 1 h [70]. Acute renal failure with acute tubular necrosis has rarely been reported [71].

One novel source of exposure includes people who use the Miracle Mineral Supplement for medicinal purposes. The sodium chlorite solution, when mixed with citric acid, produces chlorine dioxide, which has led to nausea, vomiting, diarrhea, and severe dehydration and a warning from the US Food and Drug Administration [72].

Treatment

In all cases of fumigant exposure, it is important to remove the patient from further exposure. Rescuers must wear proper personal protective equipment. In many instances, removing the patient from the source is all that is necessary if these fumigants are in their gaseous states. For significant exposures with signs and symptoms that do not resolve, prompt evaluation at a medical facility is indicated.

During decontamination procedures, care should be taken to prevent secondary contamination of rescue workers; this is especially true for methyl bromide and sulfuryl fluoride in their liquid states. Secondary contamination may occur because a victim's skin temperature usually exceeds the boiling points of these substances, which may result in their volatilization.

Decontamination procedures should begin with the physical separation of the offending agent and the victim. If the product was in a liquid or solid state and skin contact has occurred, it is necessary to remove all clothing and personal items from the patient because these may contain residual fumigant. Current recommendations for

duration of decontamination range from 3 to 30 min and rely on expert opinion, limited retrospective case series, and radiotagged chemical simulations that may not reflect real life scenarios [73]. As longer decontamination has been shown to decrease residual contamination, and there appears to be little downside, the authors recommend that exposed individuals should be decontaminated with mild soap and water for at least 15 min (Level of Evidence [LoE] III) [74]. A mild liquid detergent is necessary because these substances have low water solubilities (Table 2) (LoE III). Attention to exposed skin in skinfolds, the axillae, the genital area, feet, and hair is important. It is not recommended to wash clothing because further exposure may occur during the intervals before washing the clothing.

Specific ocular decontamination may not be needed for patients exposed to these fumigants in their gaseous states; however, if there is irritation or if significant chloropicrin exposure has occurred, it can be presumed that eye decontamination by irrigation would be beneficial, large quantities of water or sterile saline solution are probably best. Use of irrigation lenses with ophthalmic local anesthetics, such as proparacaine, may make decontaminating the eyes more comfortable.

The fumigants discussed in this chapter all have poor water solubility that would diminish the efficacy of hemodialysis (see Table 2), with the possible exception of methyl bromide.

Criteria for Discharge

1. Asymptomatic patients with incidental exposure may be discharged after an observation period of 6–8 h.
2. Patients with ingestions, prolonged exposure in confined spaces, or significant symptoms should be monitored until asymptomatic with stable vital signs.

Indications for Admission

Patients with significant fumigant exposures should be placed on a cardiac monitor and

observed for dysrhythmias. If dysrhythmias occur, American Heart Association advanced cardiac life support guidelines generally are sufficient, with the exception of the use of calcium as a specific antidote in sulfuryl fluoride poisoning. Specific details of the treatment of fluoride poisoning may be found in ► Chap. 102, “Hydrofluoric Acid.”

The patient’s level of consciousness should be assessed continually. If seizures develop despite adequate supportive care and blood glucose, the patient should be treated with intravenous diazepam or lorazepam (LoE III). Status epilepticus can occur, necessitating high doses of intravenous diazepam or lorazepam and possibly the addition of a barbiturate. Further guidance can be found in ► Chap. 20, “Toxicant-Induced Seizures.” Tetany or seizures due to sulfuryl fluoride poisoning should be treated with intravenous calcium in addition to intravenous diazepam or lorazepam. Monitoring of liver and renal laboratory markers on a daily basis is indicated if there have been major exposures to these agents.

Phosphides

Lavage with activated charcoal and potassium permanganate (1:10,000) has been described. Potassium permanganate has been theorized to oxidize phosphine to nontoxic phosphate. However, there are no clinical data supporting this intervention, and there is doubt about this mechanism [75–77]. Additionally, there are no data demonstrating benefit of activated charcoal in phosphide poisoning [78]. Animal studies and case reports suggest that oral administration of sweet almond oil can improve survival (LoE II-3) [79, 80]. Oral bicarbonate is also commonly co-administered to reduce conversion of phosphide to phosgene (LoE III). Other small trials have described improved survival in animals and humans given N-acetylcysteine (LoE III) [81–83].

Shock, altered mental status, hyperglycemia, and electrocardiographic changes have been associated with poor outcomes [84, 85].

Further details regarding the treatment of phosphide poisoning can be found in ► Chap. 94, “Phosphate and Phosphine.”

Ethylene Dibromide

There are no specific antidotes for ethylene dibromide poisoning, and supportive care is the mainstay of treatment. As ethylene dibromide is highly protein bound, it is not readily removed by hemodialysis. In patients with significant exposure, early serial plasma exchange (less than 24 h post exposure) has been associated with improved survival in comparison to those who received plasma exchange later (greater than 24 h after exposure) (LoE III) [86]. As the study was retrospective and lacked controls, it is unclear if improved survival reflects the importance of early intensive supportive care or early serial plasma exchange. Tachycardia is considered a poor prognostic indicator [87].

Although not studied, *N*-acetylcysteine is a theoretically beneficial sulfhydryl donor in these patients. *N*-Acetylcysteine is discussed in detail in the chapter devoted to this topic.

Methyl Bromide

Hemodialysis and peritoneal dialysis have been shown to rapidly decrease serum bromide levels [88, 89]. However, clinical effects and prognosis do not correlate with serum bromide levels following methyl bromide exposure (not to be confused with bromine exposure) [90]. As such, hemodialysis is not routinely advised in the absence of other indications such as renal failure or refractory acidosis (LoE III).

Methyl bromide is known to form methylcysteine adducts in albumin and globulin [91]. Though some authors have postulated benefits from *N*-acetylcysteine, dimercaprol, or BAL there have been no convincing studies in human exposures to support their use (LeE III) [16, 92].

Acrylonitrile

Acrylonitrile is oxidized by the mixed-function oxidase pathway to an oxide (see Fig. 1). This oxide is metabolized further by epoxide hydrase, which releases cyanide. Most cases involve minor exposure, however, which resolve with supportive care. Human and animal data suggest that toxicity from acrylonitrile exposure may be mediated via the cyanide metabolite [93]. *N*-acetylcysteine may shift metabolism of acrylonitrile towards less toxic glutathione conjugation products and away from the oxidative pathway responsible for cyanide generation [60]. Given the safety profile of *N*-acetylcysteine and its history of use for acrylonitrile poisoning in Europe, patients with mild symptoms should receive *N*-acetylcysteine 150 mg/kg intravenously over 1 h (LoE III) [94]. Animal studies have supported use of sodium thiosulfate for treating severe acrylonitrile toxicity, similar to its use in cyanide exposure [95]. Another cyanide antidote, hydroxocobalamin, may also be beneficial in treating severe acrylonitrile toxicity. In patients exposed to acrylonitrile who are demonstrating signs of cyanide toxicity, altered mental status or lactate-associated metabolic acidosis, providers should administer hydroxocobalamin or sodium thiosulfate (LoE III). Animal models suggest the combination of cyanide antidote with sulfur-containing amino acids (similar to *N*-acetylcysteine) has a pronounced prophylactic effect when looking at mortality as an end point [95].

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Fungicides are a diverse group of structurally unrelated compounds that are widely used for agricultural, industrial, and domestic purposes. As a group, fungicides are responsible for a small proportion of human toxic exposures leading to acute morbidity and mortality. In 2013, regional poison control centers across the United States reported 1,054 cases of fungicide-related toxicities. Of these, only three cases reported life-threatening or disabling outcomes, and no deaths were reported [1]. Despite these findings, fungicides are important from a historical as well as an international health perspective. Some of the most serious poisoning epidemics of the twentieth century have been attributed to accidental fungicide exposures. Lessons learned from these disasters have led to severe restrictions or the discontinuation of several classes of fungicides, such as methylmercury and hexachlorobenzene (HCB). Unfortunately even with these restrictions, the acute and chronic effects of some exposures continue to pose diagnostic and therapeutic challenges.

This chapter is divided into six subsections based on chemical classifications of fungicides clinically relevant to the critical care physician (Table 1). Several of the modern organic fungicides (Table 2) are not discussed in detail. In general, many of the modern organic fungicides have irritant effects on the skin and mucous membranes, although systemic effects and acute poisonings have not been widely reported. When presented with a case of suspected fungicide poisoning, it is important for the clinician to recognize that other ingredients in the pesticide formulation, including solvents or adjuvants, may be important contributors to overall toxicity. When the other ingredients of the pesticide formulation are uncertain, the manufacturer may be able to provide additional specific information useful in identifying additional hazards.

The manufacturer of benomyl (Benlate) voluntarily canceled sales and production of this widely used fungicide, citing difficulties encountered in defending the product from claims of adverse human health effects and environmental impact. Although benomyl has been suggested to be a weak dermal sensitizer [2], reports of reproductive

Table 1 Major classifications of clinically relevant fungicides

Organomercury compounds (methylmercury, phenylmercuric acetate)
Chlorinated phenols (pentachlorophenol)
Substituted benzenes (hexachlorobenzene)
Dithiocarbamates (metam sodium, thiram, ethylene bisdithiocarbamate compounds)
Copper compounds (copper sulfate)
Organotin compounds (triphenyltin, tributyltin oxide)

Table 2 Miscellaneous organic fungicides (trade names)

Benomyl (Benex, Benlate, Tersan 1991)
Captan (Orthocide, Captan, Merpan)
Chlorothalonil (Bravo Ultrex, Chloronil, Daconil)
Dodine (Carpene, Curitan, Melprex, Venturol)
Etridiazole (Aaterra, Ethazol, Koban, Pansoil, Terrazole, Truban)
Iprodione (Glycophene, Rovral)
Metalaxyl (Ridomil, Subdue)
Strobilurin (Abound, Bas, Cabrio, Headline, Honor)
Thiabendazole (Apl-Luster, Arbotect, Meretect, Tecto, Thibendazole)
Triadimefon (Amiral, Bayleton)
Triforine (Denarin, Funginex, SaproI)

toxicity (anophthalmia and microphthalmia) do not seem to be supported by the weight of the scientific evidence [3, 4].

Organomercury Compounds

Organomercury compounds are a class of fungicides formulated as dusts and aqueous solutions that are used primarily as seed protectants. Although their use has been banned or greatly restricted in many countries, they are of historical importance because of their severe toxicity in humans. In 1971, a poisoning epidemic in rural Iraq was the result of the people ingesting bread prepared from wheat treated with methylmercury – acting as a fungicide. This outbreak resulted in 50,000 exposures and at least 439 deaths [5]. The scientific study of this tragedy has provided further insight into the toxic effects of methylmercury on the central nervous system (CNS).

Biochemistry and Pharmacokinetics

Organomercury fungicides (Fig. 1) can be divided into short-chain alkyl (e.g., methylmercury) and aryl (e.g., phenylmercuric acetate) compounds. Their absorption, distribution, and metabolic fate are dependent upon their chemical structure [6]. Ingestion is the predominant route of human exposure to methylmercury, since absorption is nearly complete across the gastrointestinal tract. Methylmercury has a high volume of distribution and is readily transferred across the blood–brain and placental barriers. When absorbed, more than 90% of methylmercury detected in blood is bound to hemoglobin. About 10% of the body burden of methylmercury is found in the brain, where it undergoes a slow metabolic transformation into inorganic mercury, becoming relatively fixed in neural tissue [6]. CNS injury is likely due to neuronal apoptosis at low concentrations and necrosis at higher concentrations [7]. It is unclear whether the CNS injury is likely due to methylmercury, inorganic mercury, or the biotransformation process between the two forms. Human's major route of excretion is biliary and fecal elimination, with a whole-body half-life of approximately 70–80 days [6]. Approximately 10% of a given dose of methylmercury is excreted in urine [6].

Pharmacokinetics of Methylmercury

Volume of distribution: >1 L/kg

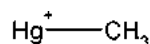
Protein binding: >90%

Mechanisms of clearance: 90% biliary, 10% renal

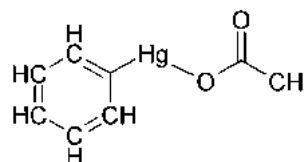
Active metabolite: inorganic mercury

Methods to enhance clearance: DMPS (?), DMSA (?)

In contrast to short-chain alkyl compounds, phenylmercuric acetate is not well absorbed through the gastrointestinal tract and undergoes more rapid transformation into inorganic mercury [6]. Dermal absorption and inhalation may be important routes of exposure to phenylmercuric acetate. A case of acrodynia was reported in a child whose house was painted with latex paint



Methylmercury



Phenylmercuric acetate

Fig. 1 Chemical structures of organomercurials.

containing phenylmercuric acetate [8]. In a follow-up epidemiologic study, higher levels of mercury were found in the urine of individuals whose houses had been recently painted with products containing phenylmercuric acetate as a preservative [8].

Pathophysiology

The pathophysiology of inorganic mercury toxicity is believed to relate to its ability to form covalent bonds with protein's sulfhydryl groups, resulting in enzyme dysfunction and cellular toxicity [9]. The biochemical mechanism of toxicity from methylmercury exposure is complex and not well understood [10]. It has been theorized that the damage may be due to dysregulated release of neurotransmitters at the presynaptic terminals mediated by changes in intracellular calcium concentrations. Chronic exposures lead to mitochondrial structural changes with accumulation of methylmercury within the mitochondria, where it may lead to inhibition of mitochondrial enzymes causing inhibited protein synthesis, induction of lipid peroxidation, mitochondrial changes, and microtubule dysfunction [11]. However, no single mechanistic pathway has yet been identified.

Clinical Presentation

The clinical course of methylmercury poisoning is most remarkable for its effects on the CNS

[12]. The cardiovascular, renal, and gastrointestinal systems are not usually significantly affected [13]. A latent period of 2–8 weeks between the time of exposure and the onset of symptoms has been described. Initial signs and symptoms include peripheral and perioral paresthesias, followed by prominent cerebellar findings, including incoordination, ataxic gait, and dysarthria [13]. Visual disturbances are frequently present, consisting of constriction of the visual field, reduced acuity, abnormal funduscopic examination, and blindness [12]. Audiologic impairment and dysequilibrium are also frequently reported [12]. Emotional lability, confusion, and delirium develop in severe cases. Most fatalities are attributed to respiratory failure [13].

Diagnosis

Mercury can be measured in whole blood and urine using atomic absorption spectroscopy. Blood is generally considered the most appropriate biomarker of acute methylmercury exposure [14]. There are conflicting data on the correlation between blood mercury levels and clinical findings after methylmercury poisoning, an observation that might be attributed to differences in the timing of clinical presentation and specimen collection [12, 15]. If blood mercury measurements are obtained after distribution to the CNS and other tissues is complete, the blood level may underestimate the total-body mercury burden. Although methylmercury distributes and accumulates in the kidneys, a relatively small proportion of methylmercury undergoes renal excretion (10%), as such urine mercury concentrations are less useful than concentrations in blood in the diagnosis of methylmercury poisoning [6]. Urine mercury concentrations are useful, however, in monitoring response to chelation therapy. Compared with whole-blood mercury measurements, urine mercury concentrations are a more valid biomarker of exposure to phenylmercuric acetate, which is rapidly converted to inorganic mercury after absorption [8].

Methylmercury incorporated into hair is stable, and hair analysis using various analytical techniques has been used to document the timing of

exposure in epidemiologic studies [16, 17]. Hair analysis may be useful in the diagnosis of methylmercury exposure occurring in the weeks or months before presentation. An important source of error in hair analysis for mercury is the presence of inorganic mercury from environmental contamination, an error that may be reduced by washing the sample before analysis [18]. When considering sending mercury levels, careful history should be obtained since cosmetic applications of mercury-containing products may result in elevated levels. All of the methods used to measure mercury in biologic specimens are subject to considerable variation as a result of contamination during preparation and analysis. Only an experienced laboratory should perform the collection and analysis of specimens.

Treatment

The clinical management of organomercury intoxication begins with the identification and removal of the source of exposure. For the majority of methylmercury ingestion cases, the development of symptoms occurs after a considerable latent period, which limits the potential benefit, if any, of gastrointestinal decontamination [12, 13]. Owing to the extensive enterohepatic recirculation of methylmercury [6], orally administered thiolated resin has been investigated as a means to enhance elimination. In one study [15], thiolated resin was found to significantly decrease the blood half-life of methylmercury-exposed adults and children, although there was no observed improvement in clinical signs and symptoms. In one of the cases treated with thiolated resin, an individual with an initial blood mercury concentration of 3,622 ppb and mild neurologic signs at presentation had no further deterioration in neurologic status on longitudinal follow-up. In the same study, other treatment groups received sodium 2,3-dimercaptopropane-1-sulfonate (DMPS), penicillamine, and *N*-acetyl-D,L-penicillamine (an experimental analogue of penicillamine). Treatment with each of these agents resulted in a significant decrease in the blood half-life compared with untreated controls. DMPS was reported to have the best efficacy

(Grade II-3 evidence). Although no adverse effects were noted, none of these therapies resulted in observable clinical improvement. This finding is consistent with more recent reports of poisoning with organomercury compounds, in which the therapeutic benefit of chelating agents has been questionable [19].

Indications for ICU Admission in Methylmercury Poisoning

Cerebellar signs
Visual impairment
Delirium

Although dimercaprol (British anti-Lewisite; BAL) is considered the chelator of choice in the treatment of acute inorganic mercury poisoning. Based on experimental animal data suggesting that organomercurials may be redistributed to the brain after the administration of dimercaprol [20], it is not recommended as a therapeutic option in the treatment of methylmercury or phenylmercury toxicity. The role of dimercaptosuccinic acid (DMSA) has not been defined in methylmercury toxicity. In a case report of dimethylmercury poisoning, DMSA has been used effectively to enhance the urinary elimination of mercury; however, no clinical improvement was observed [19]. A larger trial involving workers after an industrial exposure to elemental mercury found that when some of the exposed workers were given DMSA, they had a fivefold rate of urinary mercury excretion [21]. The limited available human data suggest that the initiation of chelation therapy after serious neurotoxicity has developed provides little to no clinical benefit [16]. In the absence of data supporting the safety and clinical efficacy of chelating agents, a grade III recommendation against the routine use in methylmercury poisoning is made. The large volume of distribution and extensive protein binding of methylmercury predicts that extracorporeal removal techniques would not be successful in enhancing the elimination of the compound, thus it is not recommended as a removal technique. This recommendation is based on expert opinion and receives a grade III recommendation.

Criterion for ICU Discharge in Methylmercury Poisoning

Resolution of neurologic symptoms

Special Populations

Studies of intrauterine exposure to methylmercury have identified gross impairment of motor and mental development among infants whose mothers were exposed to high levels of methylmercury during pregnancy [22, 23]. A follow-up of methylmercury-exposed Iraqi infants over 2 years found that most children showed considerable neurologic improvement; an exception to this, however, was infants that were most severely affected at birth [24].

Common Misconceptions About Methylmercury Poisoning

1. Chelation may improve clinical outcomes.
2. Toxicokinetics is similar to that with inorganic mercury.

Key Points in Methylmercury Poisoning

1. Predominant effects are neurologic (central nervous system).
2. Symptoms may develop after considerable latency.
3. No specific antidote is available.

Pentachlorophenol

Due to its broad antimicrobial properties, pentachlorophenol (PCP) (Fig. 2) and its sodium salt have been used extensively as a biocide and wood preservative in industry for many years. Although its availability to the general public has been restricted in the United States and other countries, PCP continues to have wide industrial application as a fungicide and wood preservative. There have been several historical accounts of acute poisoning caused by PCP exposures. In 1967, a cluster of cases of critical illness in a newborn nursery occurred as a result of the misuse of sodium

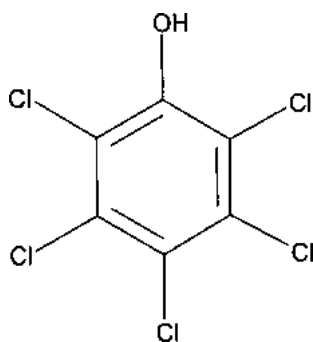


Fig. 2 Chemical structure of pentachlorophenol

pentachlorophenate as an anti-mildew agent in the hospital laundry; nine poisoning cases and two fatalities were reported [25]. This and other accounts of accidental occupational exposures provide ample toxicologic evidence of the risks from acute exposure to PCP [26, 27].

Biochemistry and Pharmacokinetics

PCP exists as colorless crystals that produce a sharp, phenolic odor when heated. While PCP is largely insoluble in water (14 mg/L), the sodium salt of PCP can be dissolved in water (330,000 mg/L). PCP has considerable environmental persistence, with a reported half-life of 5 years in soil [27]. The industrial production of PCP can yield unwanted contaminants, including dioxins. Although the detection of dioxins may be of concern for the development of chloracne, its presence as a contaminant in commercially available solutions of PCP is debated, and suppliers in some countries, including the United States and Canada, are now required to limit the content of certain dioxins (Hexachlorodibenzo-para-dioxin and 2,3,7,8-tetrachlorodibenzo-para-dioxin) in their products [28].

Pharmacokinetics of Pentachlorophenol

Volume of distribution: >1 L/kg

Protein binding: >90%

Mechanism of clearance: renal

Active metabolites: none

Methods to enhance clearance: exchange transfusion in neonates (?)

Human exposure to PCP can occur through dermal absorption, ingestion, or inhalation of vapors. Percutaneous absorption is an important route of exposure in neonates and adults. Accidental poisoning has been described in the occupational setting after dipping wood in liquid PCP formulations, immersing unprotected hands in solution, and applying PCP to wood products [27]. The epidemic of critical illness described among newborns suggests that even dermal contact with articles inappropriately treated with PCP (diapers, linens, blankets) may result in significant toxicity.

Pathophysiology

The pathophysiology observed in PCP toxicity develops as a result of the uncoupling of oxidative phosphorylation [29]. As a lipophilic weak acid, PCP can migrate across the inner mitochondrial membrane, bypassing the normal flow of protons of the electron transport chain that lead to the production of adenosine triphosphate (ATP). In this way, the normal process of capturing energy in the formation of ATP is altered. Since the energy generated cannot be stored as ATP, it is instead released as heat. This effect is most pronounced in organ systems dependent on high-perfusion and oxygen delivery, including the kidneys, heart, and CNS. On pathologic evaluation vacuolization of hepatocytes, proximal tubular cells, and myocardial tissue, as well as signs of mitochondrial injury have been shown in fatal cases involving neonates and adults [26, 30]. Pentachlorophenol is also an inducer of cytochrome CYP3A [31], which could influence the metabolism of other drugs used in the critical care management of poisoned patients (e.g., diazepam, alprazolam, and midazolam).

Clinical Presentation

The clinical features attributed to PCP toxicity are best explained by the uncoupling of oxidative phosphorylation. Fever, tachypnea, tachycardia, and marked diaphoresis, all signs of a hypermetabolic state, are the most consistent

findings [25–27]. Additional physical examination findings include hepatosplenomegaly in affected neonates [25]. Early in the clinical course, mental status is usually normal, despite the presence of moderate fever, although progression to confusion, delirium, and coma occurs rapidly [25–27]. In one adult case of occupational exposure to PCP, the patient developed a core temperature of 105 °F, and death occurred within 1 h of presentation, despite aggressive cooling measures [26].

Diagnosis

Laboratory findings in PCP poisoning reflect the uncoupling of oxidative phosphorylation. A high anion gap metabolic acidosis is commonly observed, particularly in neonates [25]. Ketonemia and ketonuria are also common findings [30]. In severe cases, rhabdomyolysis has been reported, with resultant elevation in serum creatine phosphokinase and myoglobinuria [27]. Less specific laboratory findings include elevation in the blood leukocyte count and proteinuria [27]. A consistent finding at autopsy is the almost instantaneous onset of extreme rigor mortis. This has been described as a hallmark of PCP poisoning [26, 27, 32]. PCP can be detected in serum, urine, and other body fluids by gas chromatography, although measurements obtained from cases of intentional or accidental poisoning can be comparable to levels found in unexposed controls, limiting their prognostic value [26].

Treatment

The clinical management of PCP toxicity requires the identification of, and removal from, the source of exposure. The skin can be decontaminated thoroughly with soap and water if dermal exposure is suspected. Based on its physical properties, the adsorption of PCP to activated charcoal is predicted to be poor, thus limiting its therapeutic benefit in single or repeated doses, leading to a grade III recommendation against its empiric administration.

Successful management of PCP toxicity relies on the early recognition and aggressive

management of hyperthermia and its complications. Continuous monitoring of core body temperature is necessary to monitor the response to therapy. Passive cooling techniques (administration of intravenous fluids, cooling blankets, ice bath immersion) should be instituted immediately and are given as grade III recommendation. Consideration of iced gastric lavage may be of therapeutic benefit in the setting of hyperthermia and may also lead to decontamination. Given the pathophysiology of PCP toxicity, antipyretics would not be expected to be of any therapeutic benefit. Salicylates are theoretically contraindicated due to the potential to worsen the hyperthermia through further uncoupling of oxidative phosphorylation.

No effective antidote for PCP poisoning has been identified. The mainstay of therapy is aggressive supportive management in a critical care unit. Invasive hemodynamic monitoring may be used for standard indications. Exchange transfusion has been used successfully in the management of neonates with PCP toxicity [30]. In all patients treated with exchange transfusion, dramatic clinical improvement was described immediately after the procedure. One of the patients with less severe clinical signs did not undergo exchange transfusion and recovered uneventfully. In this case series, it is unclear whether the successful outcomes could be attributed to exchange transfusion or earlier recognition of the diagnosis. A grade II-3 recommendation is made for the use of exchange transfusions as a therapy in infants to enhance the elimination of PCP.

PCP is a highly lipophilic compound. Lipid emulsion has been used in the management of toxicity due to lipophilic compounds such as local anesthetics. No data is available on the use of lipid emulsion in PCP; however, it has an octanol coefficient of 3.3 at a pH of 7.25 (measure of lipophilicity) similar to that of amitriptyline (octanol coefficient of 3.0 at pH of 7.4) for which there have been limited reports of success in overdoses after intervention with lipid emulsion. Thus, in a severe toxicity scenario, use of lipid emulsion may be worth pursuing and is given a grade III recommendation [33, 34]. There are no data indicating that this treatment changes the outcome in PCP poisoned patients.

**Indications for ICU Admission
in Pentachlorophenol Poisoning**

Fever
Tachycardia
Metabolic acidosis

**Criteria for ICU Discharge in Pentachlorophenol
Poisoning**

Hemodynamic stability
Absence of hyperthermia

Although some authors have recommended forced diuresis as a means to enhance PCP elimination [35], the data supporting this approach are based on computer-simulated pharmacokinetic models, whereas the toxicokinetics of PCP remains poorly understood. There is no controlled evidence that forced diuresis improves clinical outcomes, and for this reason the emphasis on fluid management in PCP toxicity should focus on restoring and maintaining normal hemodynamic function.

**Common Misconception About
Pentachlorophenol Poisoning**

Forced diuresis improves outcomes in pentachlorophenol toxicity.

Key Points in Pentachlorophenol Poisoning

1. Hyperthermia and diaphoresis are common clinical findings.
2. Severe toxicity may develop following exposure.

Hexachlorobenzene

Of the substituted benzene fungicides, hexachlorobenzene (HCB) (Fig. 3) is the best studied. Although the acute toxicity from ingestion or inhalation exposure is low with HCB, the systemic effects from chronic exposure are well documented. Between 1955 and 1959, an epidemic of 5000 cases of porphyria cutanea tarda (PCT) was described in

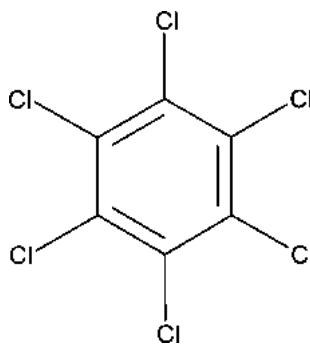


Fig. 3 Chemical structure of hexachlorobenzene

Turkey [36]. The cause was traced to the consumption of wheat treated with a seed protectant containing 10% HCB. HCB has been detected frequently as a contaminant in the industrial production of many chlorinated solvents, which may be important in the context of occupational and environmental exposures. Although single case reports have reported PCT in association with occupational exposure to HCB, larger-scale epidemiologic studies have not confirmed this relationship [37]. The differences in clinical manifestations between occupational exposure to HCB and the outbreak in Turkey may be related to the dose, duration, and route of exposure. Other substituted benzene formulations continue to be used as fungicides in the United States, although systemic poisonings and PCT have not been widely reported with these compounds.

Biochemistry and Pharmacokinetics

HCB (see Fig. 3) is a chlorinated aromatic hydrocarbon that is highly lipid soluble and well absorbed from the gastrointestinal tract [38].

Pharmacokinetics of Hexachlorobenzene

Volume of distribution: >1 L/kg

Protein binding: 45%

Mechanism of clearance: >90% fecal

Active metabolite: pentachlorophenol (clinically insignificant)

Methods to enhance elimination: none

Pathophysiology

Animal studies have shown that when absorbed, HCB has a large volume of distribution and bioaccumulates in adipose tissue [38]. Altered heme synthesis is induced by HCB through the inhibition of uroporphyrinogen decarboxylase activity, leading to the accumulation of uroporphyrin and the induction of aminolevulinic acid synthetase. Consistent with other organochlorine compounds, HCB is capable of inducing several families of the cytochrome P-450 system. Toxicokinetic data in humans are not readily available, but an investigation of a population with a high level of HCB due to high airborne exposures associated with a chlorinated solvent factory suggested that excretion occurs predominantly through the feces [39]. A small proportion appears in the urine as chlorinated phenols, including PCP, although signs of toxicity relating to this metabolite have not been reported in individuals with high body burdens of HCB.

Clinical Presentation

The latency between exposure and the development of signs and symptoms of PCT varies depending on dose, but epidemiologic studies suggest a delay of several months after repeated ingestion [40]. In mild cases, early skin lesions consist of bullae containing clear fluid, occurring in sun-exposed areas (particularly the face and hands). The skin is unusually sensitive, and the epidermis easily rubs off from slight mechanical trauma (Nikolski’s sign) [40]. The bullous lesions may subsequently burst and become infected, forming pigmented scars and contractures. In addition, there is marked hypertrichosis throughout the body. Weight loss and hepatomegaly are frequently present, usually without abdominal pain or neurologic symptoms [41]. These clinical findings distinguish PCT from acute intermittent porphyria, another disease associated with abnormal heme biosynthesis in which abdominal pain and neuropsychiatric symptoms are frequently prominent.

Table 3 Laboratory diagnostic patterns of porphyria cutanea tarda

Urine concentration
Porphobilinogen and aminolevulinic acid are not increased
Uroporphyrinogen is increased greater than heptacarboxylate
Fecal porphyrins
Isocoproporphyrinogen, heptacarboxylate present
Erythrocyte porphyrins
Not increased

Diagnosis

In addition to the prominent dermatologic signs of toxicity, the diagnosis of PCT can be supported on the basis of urinary findings. A dark red urine, which under Wood’s light exhibits intense red fluorescence, has been described [41]. In contrast to other types of porphyria, urine concentrations of porphobilinogen and aminolevulinic acid are not increased, although elevated levels of uroporphyrinogen may be detected [42]. Table 3 summarizes urinary, fecal, and erythrocyte porphyrin findings suggesting PCT. Evidence of mild iron overload (elevated ferritin) frequently is present [42]. HCB may be measured in blood using gas chromatography, although a reference range is not established, and a threshold dose that corresponds with the development of PCT is not known [37, 39].

Treatment

No specific antidote for HCB-induced PCT has been identified, and no specific methods of gastric or skin decontamination have been reported. A case series has described the use of oral and intravenously administered ethylenediaminetetraacetic acid (EDTA) in the clinical management of PCT associated with HCB ingestion [43]. The administration of EDTA was reported to transiently increase the excretion of porphyrin, which was associated with improvement in skin lesions and weight gain. Given the single nature of this study, a grade III recommendation is

given. Studies in rats have shown that HCB is eliminated fecally via nonbiliary transfer within the large intestine. In these experiments, oral treatment with mineral or hexadecane resulted in enhancement of elimination. Current grade III therapeutic recommendations for PCT include avoidance of sunlight exposure and supportive management, with special attention to skin care [42]. Phlebotomy may be effective therapy in PCT to deplete excess iron stores, and the avoidance of alcohol and exogenous estrogens has been recommended and is given a grade III recommendation [42]. Low-dose hydroxychloroquine (Plaquenil) has been investigated as a therapeutic agent for PCT in controlled studies and has been reported to be safe and effective at normalizing urinary porphyrin excretion and improving skin lesions. Thus, it is given a grade II-1 recommendation [44].

Indications for ICU Admission in Hexachlorobenzene Poisoning

Extensive skin involvement (>10% body surface area)

Superinfection of skin lesions

Criterion for ICU Discharge in Hexachlorobenzene Poisoning

Resolution of skin lesions and infection

Special Populations

In the epidemic of PCT in Turkey, a second disorder called *pembe yara*, or *pink sore*, was described in breast-fed infants of mothers who had PCT or had ingested HCB-contaminated bread [42]. Symptoms and signs included pink cutaneous lesions, fever, diarrhea, vomiting, weakness, hepatomegaly, and convulsions. The skin lesions characteristic of PCT were not observed in these infants, and the mortality rate was high (95%). No porphyrinuria was observed in these infants.

Common Misconceptions About Hexachlorobenzene Poisoning

1. Chelation is effective therapy.
2. Porphyrin cutanea tarda and acute intermittent porphyria are the same disease.
3. Infants exposed via breastmilk will experience similar symptoms to adults.

Key Points in Hexachlorobenzene Poisoning

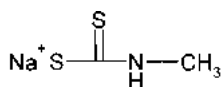
1. Skin manifestations include bullous lesions and generalized hypertrichosis.
2. Breakdown of bullous lesions can lead to scarring and contractions.
3. Urinary findings may provide important diagnostic clues.

Dithiocarbamates

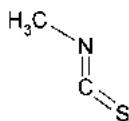
As a class of general- and restricted-use fungicides, the dithiocarbamates are available in a variety of formulations, including water suspensions, wettable powders, and dusts. They have many agricultural applications, including the protection of seedlings, turf, vegetables, fruits, and ornamentals from fungal growth. Compared with the known toxicity of several of the classes of fungicides described above, the dithiocarbamates have considerably lower acute toxicity due to their rapid metabolism and lack of persistence in mammalian systems. In contrast to the *N*-methyl carbamates, dithiocarbamates have poor efficacy as insecticides because they do not have significant effects on cholinesterase activity [45]. Certain dithiocarbamates warrant further discussion, due to their potential for causing acute illness through several different mechanisms.

Biochemistry and Pharmacokinetics

The chemical structure and environmental fate of the dithiocarbamates are predictive of their spectrum of toxicity (Fig. 4). Metam sodium is an aqueous solution used as a soil biocide and



Metam-sodium (dithiocarbamate)



Methyl isothiocyanate

Fig. 4 Chemical structure of dithiocarbamate and its decomposition product, methyl isothiocyanate

fumigant. Although it is nonvolatile, it quickly degrades on soil or water contact to produce methyl isothiocyanate, leading to its fungicidal activity. Thiram is another important dithiocarbamate due to being a known skin sensitizer and a common component of natural rubber latex. Other subclasses of the dithiocarbamate family, the metallobisdithiocarbamates and ethylene bisdithiocarbamates, are named for the metallic component in their formulation (zinc, manganese, iron). These subclasses do not interact with acetaldehyde dehydrogenase.

Pharmacokinetics of Dithiocarbamate

Active metabolites: carbon disulfide (all dithiocarbamates); methyl isothiocyanate (metam sodium)

Methods to enhance elimination: none

Pathophysiology

Metam sodium and thiram are thiurams, in the same chemical class as disulfiram (Antabuse), and theoretically could induce a disulfiram-like reaction in a susceptible individual through inhibition of acetaldehyde dehydrogenase. Methyl isothiocyanate is a potent mucosal irritant, and its effects have been observed well below the threshold for odor detection [46]. The toxicokinetic profiles of dithiocarbamates have not been studied in humans.

Clinical Presentation

Contact dermatitis and upper airway irritation are the most common clinical presentations following dithiocarbamate exposure. Workers involved in the cleanup of an accidental metam sodium spill into the Sacramento River developed erythema, rash, itching, and scaling of the lower extremities (the areas that had come into contact with contaminated water) [47, 48]. The same chemical spill resulted in the emergency triage of 360 individuals, most of whom had mild irritant upper airway symptoms that did not require hospitalization [49]. A follow-up study of adults living within 0.5 mile of the site of the accident identified 20 cases of persistent irritant-induced asthma and 10 cases of persistent asthma exacerbations [46]. Although effects consistent with aldehyde dehydrogenase inhibition were not reported in this cohort, a few case reports have described signs and symptoms consistent with a disulfiram-like reaction after individuals consumed ethanol following the use of topical products containing thiram [50]. A retrospective study of all calls received between 1992 and 2009 to the Poisons and Toxicovigilance Centre of Angers University Hospital serving the western region of France revealed 102 true exposures. The authors of this study revealed rapid recovery among 101 of those exposed and 1 death that was likely complicated by asphyxia. A review of symptoms included: eye irritant (76), nose and throat irritant [65], skin erythema [1], vomiting [3], nausea [7], cough [3], mild dyspnea [1], nausea [4], headaches [6], asthenia [3], dizziness [1], malaise [1], and paraesthesias [2]. In this case series no disulfiram reactions were observed despite two patients having consumed alcohol after exposure. However, these were the same individuals who reported a strange taste in their mouths.

Other systemic effects purportedly related to dithiocarbamate exposure have been described, although the results of these studies are not conclusive. A case report of severe CNS depression and hypothermia in a 7-year-old child has been reported in association with maneb. In this case, there was no clear history of exposure to the

fungicide, except for a laboratory detected level of maneb in a blood sample [51]. A single case of Henoch-Schönlein purpura was reported, and it was temporally associated with thiram exposure in a tree planter [52]. The exposure history consisted of falling down a hillside while carrying a bag of seedlings treated with a solution of 42% thiram. There have been no similar cases of acute renal failure or Henoch-Schönlein purpura reported in association with dithiocarbamate exposure. Signs and symptoms consistent with manganese toxicity, including muscle rigidity with cogwheeling, nervousness, and, memory problems, have been associated with chronic occupational exposure to maneb in a case-control study [53], although no significant difference in blood manganese concentration was noted between cases and controls.

Diagnosis

Dithiocarbamates undergo metabolism in mammals into ethyleneurea. Gas chromatography-mass spectrometry has been used to identify and quantify exposures in Italian vineyard workers for the presence of ethyleneurea while being monitored via urinary spot samples. Unfortunately, this testing does not occur quickly and requires specialized laboratory resources. As such, diagnosis depends on a careful exposure history and physical examination.

Treatment

When dermal exposure is suspected, decontamination with soap and water is indicated. When inhalational exposure to metam sodium or its breakdown product, methyl isothiocyanate, is suspected, respiratory distress or signs of obstruction can be treated with supplemental oxygen, inhaled bronchodilators, and continuous pulse oximetry monitoring in an intensive care unit. The treatment of isocyanate exposure is described further in the chapter on isocyanates. If a disulfiram-like reaction is apparent, standard supportive symptomatic management is indicated.

Indications for ICU Admission in Dithiocarbamate Poisoning

Respiratory distress

Severe disulfiram (Antabuse) reaction (tachycardia, hypotension, refractory vomiting)

Criteria for ICU Discharge in Dithiocarbamate Poisoning

Resolution of signs of respiratory distress

Hemodynamically stable

Common Misconception About Dithiocarbamate Poisoning

Dithiocarbamates affect cholinesterase activity.

Key Points in Dithiocarbamate Poisoning

1. Primary clinical effects are dermatologic (irritation, sensitization).
2. Decomposition product of metam sodium is a potent mucosal irritant.
3. Disulfiram (Antabuse) reaction is possible with certain dithiocarbamates.

Copper Compounds

Several copper compounds are available as fungicides for commercial use. Intentional and accidental ingestion of copper compounds has historically been a common cause of morbidity and mortality outside the United States, an observation that may be related to their widespread international availability and use [54].

Biochemistry and Pharmacokinetics

The soluble copper salts (e.g., copper sulfate) are not well absorbed across the skin or gastrointestinal tract. The organic copper compounds (copper

naphthenate, copper quinolinolate) have a higher bioavailability [55].

Pharmacokinetics of Copper Compounds

Volume of distribution: >1 L/kg

Protein binding: >90%

Mechanism of clearance: >90% biliary

Active metabolites: none

Methods to enhance clearance: dimercaprol (?), calcium ethylenediaminetetraacetic acid (?)

Pathophysiology

The predominant mechanism of toxicity of copper compounds is through mucous membrane irritation and corrosive effects on the gastrointestinal tract. Corrosive injury is discussed in detail in ► Chap. 101, “Caustics.”

Clinical Presentation

With massive ingestions, greenish blue emesis, hematemesis, and melena may develop [56]. Acute effects on the liver include jaundice and pathologic findings of centrilobular necrosis [57]. Intravascular hemolysis, Heinz body formation (precipitation of oxidatively denatured hemoglobin), and methemoglobinemia (► Chap. 30, “Toxicant-Induced Hematologic Syndromes”) have also been described [58].

Diagnosis

Copper concentrations may be measured in serum, whole blood, and urine using atomic absorption spectroscopy and inductively coupled plasma-atomic emission spectroscopy. There are also sensitive colorimetric assays for copper. In one case series, whole-blood copper concentrations greater than 2.87 mg/L (45.9 $\mu\text{mol/L}$) correlated with gastrointestinal symptoms, and levels greater than 7.98 mg/L (127.7 $\mu\text{mol/L}$) correlated with hepatorenal

dysfunction or shock [59]. In this case series, whole-blood copper levels correlated better than serum copper concentrations with the severity of clinical illness. Urine levels have been investigated in the diagnosis of diseases associated with copper excess (Wilson’s disease), although their diagnostic and prognostic value in copper fungicide exposures has not been evaluated.

Treatment

The role of gastrointestinal decontamination after accidental or intentional ingestion is simplified because spontaneous emesis is expected after significant ingestion of copper compounds. No data supports the efficacy of activated charcoal to decrease absorption of copper compounds after accidental or intentional ingestions.

Because of the corrosive gastrointestinal injury associated with acute copper exposure, parenteral chelators, such as dimercaprol and calcium disodium edetate, theoretically would be considered the therapy of choice after significant exposures. There are few pharmacokinetic studies to guide appropriate dosing of these agents [57], and their safety and efficacy for acute copper poisonings have not been established. In one case report of intentional copper and zinc sulfate ingestion, chelation therapy with dimercaprol and penicillamine was found to not be of clinical benefit [60]. The potential therapeutic benefit of other orally available chelating agents, such as DMSA, in acute copper toxicity has not been studied, thus would not be recommended at this time. The use of these chelators for other heavy metal poisonings is described in other chapters.

Indications for ICU Admission in Copper Compound Poisoning

Hematemesis

Shock

Signs of significant hepatic injury

Renal failure

Criteria for ICU Discharge in Copper Compound Poisoning

Resolution of gastrointestinal symptoms and signs

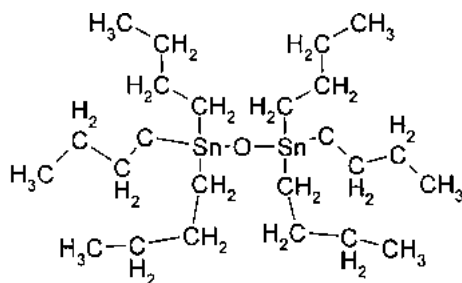
Hemodynamic stability

Common Misconception About Copper Compound Poisoning

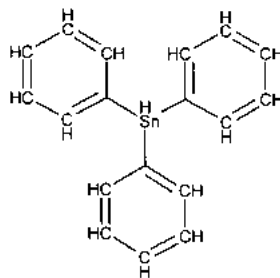
Chelation therapy is safe and effective for copper fungicide exposures.

Key Points in Copper Compound Poisoning

1. Corrosive gastrointestinal effects develop after ingestion.
2. Hepatic injury and necrosis may develop.
3. Oxidative injury and methemoglobinemia have been described.



Tributyltin oxide



Triphenyltin

Fig. 5 Chemical structures of organotin fungicides

Organotin Compounds

Organotin compounds are formulated as wettable and flowable powders and are used throughout the world as fungicides in a variety of agricultural and industrial settings. Tributyltin oxide (TBTO) had been registered for use as an anti-mildew control agent in interior and exterior paints, but it is now severely restricted in many countries due to its potent irritant properties. TBTO continues to be used as an antifouling agent in marine paints, due to its ability to prevent the growth of barnacles, algae, and marine organisms.

Biochemistry and Pharmacokinetics

In general, organotin compounds have low water solubility and are lipophilic (Fig. 5). Toxicokinetic data in humans are not available [61].

Pharmacokinetics of Organotin

Volume of distribution: >1 L/kg

Protein binding: 80%

Mechanism of clearance: biliary, fecal

Active metabolite: trimethyltin

Methods to enhance clearance: none

Pathophysiology

TBTO is a potent skin irritant and an extreme eye irritant [62]. Triphenyltin compounds have been shown to induce irreversible ocular lesions in animal studies [61]. Immunotoxicity (lymphopenia, decreased spleen and thymus weights) and immunosuppressive effects (altered humoral and cellular immunity) have been described following organotin compound exposure in short-term and long-term animal studies [62]. These immunotoxic effects may arise from cytoskeletal modification in addition to alterations in thymocyte calcium homeostasis.

Clinical Presentation

Symptoms from inhalational exposure to interior paints with TBTO additives include headache, nausea, mucosal irritation, watery eyes, and wheezing [63]. Dermal exposure from direct contact with TBTO compounds has resulted in severe skin irritation, contact folliculitis, and pruritic erythematous vesiculobullous rashes [64, 65].

Reports of other systemic effects from accidental or intentional ingestion of organotin compounds are rare, and limited clinical information is available. In one case of intentional ingestion of triphenyltin acetate [66], a 19-year-old woman developed symptoms of vomiting, weakness, and nausea, followed by the development of diplopia, vertigo, bidirectional nystagmus, and disorientation. Leukopenia was noted on the sixth day postingestion. No other hematologic, renal, or hepatic abnormalities were found, and functional and radiographic studies of the CNS (including single-photon emission computed tomography and magnetic resonance imaging) were unremarkable except for nonspecific electroencephalogram changes. A full recovery was described with supportive management. A mass poisoning involving three deaths and hundreds of hospitalizations was reported in association with the misuse of industrial lard contaminated with organotin compounds as cooking oil [67]. Gas chromatography and k coupled plasma-mass spectrometry were used to detect and measure organotin species in blood and urine of exposed persons. Trimethyltin and dimethyltin were detected in urine samples at ng/mL concentrations. This report did not provide information on the clinical presentation and hospital course of the patients, which limits the utility of the biomarker findings.

Diagnosis

With inhalational and dermal routes of exposure, physical examination findings consistent with organotin exposure include skin and

mucous membrane irritation. In cases of systemic intoxication, gas chromatography and inductively coupled plasma-mass spectrometry may be used to detect and quantify organotin species in blood and urine specimens, although reference ranges have not been established. A complete blood count with differential may reveal lymphopenia as an immunotoxic manifestation of systemic organotin toxicity.

Treatment

Identification and removal from exposure and supportive management are the mainstays of therapy after exposure to organotin compounds. No data are available on the efficacy of gastric decontamination methods after accidental or intentional human ingestions. There are no animal studies on the efficacy of chelating agents in enhancing the elimination of organotin compounds, and there are no data supporting their efficacy in humans.

Indications for ICU Admission in Organotin Poisoning

Respiratory distress
Central nervous system depression

Criterion for ICU Discharge in Organotin Poisoning

Hemodynamic stability

Key Points in Organotin Poisoning

1. Organotin compounds are potent skin and mucosal irritants.
2. Immunotoxic effects have been described after acute systemic exposure.

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Organophosphorus Insecticides

Organophosphorus (OP) insecticides are used widely in agriculture, horticulture, and veterinary medicine. These insecticides also are used domestically and in public hygiene to control vectors of disease. Some OP compounds (e.g., malathion) are used to treat human infestation with scabies, head lice, and crab lice.

As a result of the widespread use and availability of pesticides, each year 250,000–370,000 people die from their deliberate ingestion [1, 2]; these deaths are responsible for about a third of suicides globally [1]. The World Health Organization now recognizes pesticide poisoning to be the single most important means of suicide worldwide [3]. Many studies estimate that organophosphorus insecticides are responsible for around two-thirds of these deaths [4] – a total of some 200,000 a year [5].

Biochemistry and Clinical Toxicology

Biochemistry

Organophosphorus insecticides are usually esters, amides, or thiol derivatives of phosphoric acid (Fig. 1). The R¹ and R² moieties are usually alkyl or aryl groups, which may be linked via oxygen (this is termed a *phosphate*) (Fig. 1a) or a sulfur atom to phosphorus (when bonded via sulfur, the compound is called a *phosphorothiolate* or *S-substituted phosphorothioate*)

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(Fig. 1b). When the phosphorus is linked by a double bond to sulfur ($P = S$), this is known as a *phosphorothioate* (Fig. 1c). *Phosphoramidates* (Fig. 1d) have a carbon atom linked to the phosphorus atom through an NH group.

The X in Fig. 1 represents one of a wide range of substituted or branched aliphatic, aromatic, or heterocyclic groups linked to the phosphorus atom via an -O- or -S- to make it more labile. During the process of inhibition of the target enzyme, acetylcholinesterase (AChE), the phosphorus atom binds to an amino acid on the enzyme with X being eliminated; the group X often is referred to as the “leaving group.” The lability of the linkage between X and the phosphorus atom is critical with regard to the reactivity of the OP with the enzyme AChE.

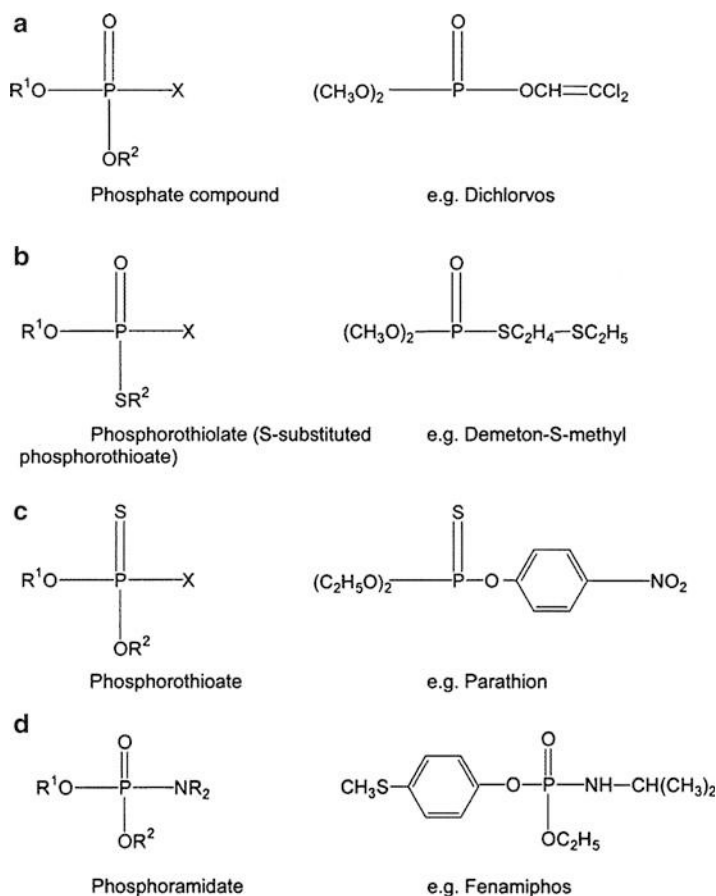
The $P = O$ -containing structure is often referred to as an *oxon*, and the $P = S$ structure is referred to

as a *thion*. The term *oxon* often is incorporated in the trivial name (e.g., parathion is the parent [$P = S$] compound of paraoxon [$P = O$]).

Clinical Toxicology

As most OP insecticides are lipophilic and not ionized, they are absorbed rapidly after inhalation or ingestion. Although dermal absorption of OP compounds tends to be slow, severe poisoning still may ensue if exposure is prolonged. The degree of absorption depends on the contact time with the skin, the lipophilicity of the agent involved, and the presence of solvents (e.g., xylene) and emulsifiers in the formulation, which can facilitate absorption. For powders, the finer the powder, the more rapid and complete is skin absorption. Other important factors include the volatility of the pesticide (e.g., dichlorvos is much more volatile than malathion, although both

Fig. 1 (a–d) Chemical structures of some organophosphorus insecticides



have relatively low vapor pressures), the permeability of clothing, the extent of coverage of the body surface, and personal hygiene. The rate of absorption also varies with the skin region affected. Parathion is absorbed more readily through the scrotal skin, axillae, and skin of the head and neck than it is through the skin of the hands and arms. Traumatized skin or the presence of dermatitis probably allows greater absorption of OP insecticides.

After absorption, OP compounds accumulate rapidly in the fat, liver, kidneys, and salivary glands. The phosphorothioates ($P = S$) (e.g., diazinon, parathion, and bromophos) are more lipophilic than phosphates ($P = O$) (e.g., dichlorvos) and are stored extensively in fat, which may account for the prolonged intoxication and clinical relapse after apparent recovery that has been observed in poisoning from these OP insecticides. This variable lipophilicity also explains why compounds vary in the ease with which they cross the blood–brain barrier.

Phosphates ($P = O$) are biologically active, whereas phosphorothioates ($P = S$) need bioactivation to the corresponding metabolite (oxon) to become biologically active. As a consequence, the features of intoxication may be delayed, unless aerial oxidation of the phosphorothioate ($P = S$) has occurred already to generate traces of oxon.

Organophosphorus compounds are metabolically activated to the corresponding oxon by oxidative desulfuration mediated by cytochrome P-450 isoforms [6], flavin-containing monooxygenase enzymes [7], *N*-oxidation, and *S*-oxidation [8]. The oxons that inhibit AChE can be deactivated by hydrolases, such as the carboxylesterases [9] and by A-esterases (e.g., paraoxonase). OP compounds undergo other transformations mediated by cytochrome P-450 that do not result in the production of an active metabolite, including oxidative dealkylation and dearylation [6]. OP compounds also may be transformed by enzymatic action on the side chains, including ring hydroxylation, thioether oxidation, deamination, alkyl and *N*-hydroxylation, *N*-oxide formation, and *N*-dealkylation [6]. The products of biotransformation may be

conjugated with glucuronide, sulfate, or glycine [10].

Elimination of metabolites occurs mostly in urine with lesser amounts in feces and expired air. Some OPs (e.g., dichlorvos, which is not stored in fat to any great extent) may be eliminated in hours, whereas the inhibitory oxon of chlorpyrifos or demeton-S-methyl may persist for days because of extensive storage in fat.

In summary, the chemical structure of the OP insecticides and the presence of other ingredients in the formulations may have an impact on the speed of onset of features of intoxication. In addition, the fact that many OP insecticides are lipophilic means that they are distributed to and stored in body fat, and elimination takes place slowly. The severity of intoxication may increase for 12–36 h after exposure, intoxication may be prolonged, or relapse may occur after apparent clinical recovery.

Pathophysiology of Toxic Effects

Acute Poisoning

The oxon phosphorylates the serine hydroxyl group located at the active site of AChE. Inhibition of AChE activity occurs in the blood, brain, and other tissues in a time-dependent manner. The extent of inhibition of AChE depends on the rate constant for the reaction and the time that the enzyme is exposed to the oxon. Inhibition of AChE results in accumulation of acetylcholine (ACh) at autonomic (both sympathetic and parasympathetic) preganglionic and some central synapses and at autonomic parasympathetic postganglionic and skeletal afferent nerve endings. Consequently, ACh binds to and stimulates muscarinic and nicotinic receptors. Phosphorylated enzyme may become “aged” by partial dealkylation of the serine group at the active site of AChE. “Aging” of the phosphorylated enzyme leads to an inactive enzyme, after which reactivation is no longer possible. The rate of aging depends on the structure of the OP compound. The activity of any aged, inhibited enzyme returns to normal only by resynthesis of new enzyme in the liver.

The rate of spontaneous reactivation of alkylphosphorylated AChE depends on the chemical structure of the OP compound. Most of the commonly used OP insecticides carry either two methyl (e.g., azinphos-methyl, demeton-S-methyl, dichlorvos, dimethoate, fenitrothion, malathion, oxydemeton-methyl, parathion-methyl) or two ethyl (e.g., chlorpyrifos, diazinon, disulfoton, ethion, parathion, quinalphos) ester groups attached to the phosphorus atom (see Fig. 1) so that dimethyl phosphorylated AChE or diethyl phosphorylated AChE is generated. The rate of spontaneous reactivation is faster for dimethoxyphosphoryl than diethoxyphosphoryl enzyme [11, 12], and this also appears to be true of oxime-induced reactivation [13]. Spontaneous reactivation of dimethoxyphosphorylated AChE proceeds quite rapidly so that the patient's condition should improve even without oxime therapy. Unless oximes are employed, however, there is no such expectation of rapid recovery for patients intoxicated with diethoxyphosphoryl insecticides.

OP-Induced Delayed Neuropathy

OP-induced delayed neuropathy is a rare complication of acute exposure to some OP insecticides [14–17]. It results from phosphorylation and subsequent aging of at least 70% of an esterase, neuropathy target esterase (NTE), in peripheral nerves that is distinct from AChE [18]; NTE is a 147 kDa membrane-bound protein of the patatin-like phospholipase family [19, 20]. After NTE becomes aged and as a result of loss of NTE activity, membrane phospholipid homeostasis and endoplasmic reticulum functions, including axonal transport and glial–axonal interactions, are disrupted [21]; axonal degeneration ensues and is followed by demyelination of nerve fibers [22]. Only a small number of marketed OP insecticides, for example, methamidophos [23], are capable of causing this syndrome, and most such OPs are banned. While there is compelling evidence of the involvement of NTE in the initiation of OP-induced delayed neuropathy, its role in axonal degradation remains obscure.

Intermediate Syndrome

Although the etiology of the syndrome is not clearly understood [24–30], it is generally believed to result from a persistent excess of ACh at the neuromuscular junction [31–39]. The intermediate syndrome can be regarded as a spectrum disorder affecting the neuromuscular junction: at one end of the spectrum, patients develop only the electrophysiological counterpart of neuromuscular transmission failure, while at the other end, patients develop weakness of three-fifths or less than three-fifths on the Medical Research Council grading of all three muscle groups and are at risk of developing respiratory failure [40]. The selective involvement of certain muscles remains unexplained.

Clinical Presentation and Life-Threatening Complications

Toxicity may occur after inhalation, after ingestion, or through skin contamination. Although dermal absorption of OP compounds tends to be slow, severe poisoning still may ensue if exposure is prolonged. Skin contact and subsequent absorption is the major route of exposure occupationally. Inhalation of OP insecticides, particularly during the manufacture of formulations (e.g., because of inefficiently operating ventilation equipment) or during spraying or mixing, is a recognized occupational hazard. Ingestion is uncommon in the workplace but can occur accidentally in workers with poor personal hygiene, such as those who do not remove contaminated clothing or fail to wash their hands. This exposure is likely to lead to only mild features, whereas the deliberate ingestion of an OP insecticide is likely to result in more severe features of intoxication.

The clinical presentation and severity of OP poisoning depends not only on the pesticide and the magnitude of exposure but also on several other factors, including the route of exposure, the age of the patient, whether exposure was a suicidal attempt (when a substantial ingestion is more likely), and the presence of a solvent in the formulation. Not only may skin absorption of the

Table 1 Systemic features of organophosphorus insecticide poisoning

Effect	Signs and symptoms
Muscarinic	Cough, wheeze, dyspnea, bronchorrhea, bronchoconstriction, pulmonary edema, cyanosis
	Rhinitis, increased salivation, rhinorrhea, increased lacrimation, diaphoresis, sweating
	Urinary and fecal incontinence
	Nausea, vomiting, abdominal cramps, diarrhea, tenesmus
	Bradycardia, hypotension
	Blurred vision, miosis
Nicotinic	Muscle fasciculation, including diaphragmatic muscle weakness
	Tachycardia, pallor
	Mydriasis
	Hyperglycemia
Central nervous system	Headaches, anxiety, dizziness, restlessness, insomnia, nightmares, drowsiness, confusion, tremor, ataxia, dysarthria, dystonic reactions
	Hypotension, respiratory depression
	Convulsions, coma

OP itself be enhanced by the presence of the solvent, but also ingestion of a solvent may induce vomiting with risk of aspiration; depressed consciousness may follow. There is increasing evidence that the solvents in formulations are responsible for the high morbidity and mortality [41, 42].

The onset and severity of toxicity depend on the speed and degree of depression of AChE activity. In addition, some OP compounds, such as the phosphorothioates, require biotransformation to become biologically active, and as a result, signs of intoxication may be delayed after exposure. Extensive occupational misuse of OP compounds may cause progressive depletion of AChE activity until toxic effects occur.

The typical features of OP poisoning are those of cholinergic excess and may be divided pharmacologically into muscarinic, nicotinic, and central nervous system effects (Table 1), though this classification is less relevant clinically except that it helps to explain the mechanisms of the features.

Table 2 Common *initial* features of OP insecticide poisoning by route of exposure

Route of exposure	Features
Inhalation	Chest tightness
	Rhinorrhea
	Increased salivation
Dermal	Bronchorrhea
	Localized sweating and muscle fasciculation
Ocular	Miosis
	Eye pain
Ingestion	Abdominal pain
	Nausea and vomiting
	Diarrhea
	Involuntary defecation

Note: systemic features may follow exposure by these routes

Symptoms can present within 5 min of massive ingestion and almost always occur within 12 h. Muscarinic symptoms rarely present more than 24 h after ingestion, although these features can reappear if therapy with oximes and atropine is discontinued too early. Muscarinic features appear first and characterize mild-to-moderate poisoning but are not always present. In one study, no single symptom was noted in more than 60% of cases [43]. Miosis, although the most prevalent specific sign, was found in only 44% of cases [43]. In other studies, miosis was observed in 82% of 61 cases [44] and in 83% of 23 cases [45].

The first symptoms of mild poisoning, particularly in individuals occupationally exposed, are often a feeling of exhaustion and weakness. Vomiting, cramping abdominal pain, sweating, and hypersalivation may follow (Table 2). Constriction of one or both pupils and a sensation of tightness in the chest during inspiration also may occur at an early stage, but these signs are not reliable indices of the severity of systemic poisoning because they may be caused by local anticholinesterase effects of spray mist on the eye or bronchi.

In cases of more severe poisoning, the nicotinic features tend to appear first, but a

combination of muscarinic, nicotinic, and central nervous system symptoms is apparent in many severe cases. This combination was found in 17% of patients in one series [43], although in a further study of more severely poisoned patients requiring ventilatory support, these features occurred in 60% [46].

Muscle twitching may affect the eyelids, tongue, face muscles, and calf muscles; respiratory muscles then become involved, and general muscle weakness ensues [47]. Convulsions may occur [45], though OPs vary in their potency to induce seizures [48]. Seizures may not be due entirely to AChE inhibition [49], considering that they are suppressed by benzodiazepines, which are known to act via 1-aminobutyric acidergic (GABAergic) mechanisms [50].

The respiratory complications of OP poisoning and their likely mechanisms have been reviewed [51, 52]. Bronchial hypersecretion/bronchorrhea with bronchoconstriction is followed in severe cases by cyanosis, respiratory depression, and coma. Death may follow from respiratory failure. Eddleston et al. [53] have proposed three mechanisms for respiratory failure occurring within a few hours of exposure during the acute cholinergic crisis: depression of the respiratory center in the ventrolateral medulla, respiratory muscle weakness, and direct pulmonary effects (bronchospasm, bronchorrhea). Bronchorrhea results from neuronal and nonneuronal cholinergic stimulation of the mucus glands, cilia, and cells producing periciliary fluid [52]. Bronchoconstriction results predominantly from bronchial smooth muscle contraction in response to muscarinic M3 receptor stimulation, with some involvement of nicotinic and M2 receptors (the latter also demonstrate negative feedback control); the nonspecific muscarinic antagonist atropine is highly effective in reversing bronchorrhea and bronchoconstriction. Respiratory failure may also occur later in conscious patients without cholinergic signs [53]. The mechanisms of late respiratory failure are uncertain, but some have suggested that the peripheral dysfunction results from sustained overstimulation of the neuromuscular junction by high synaptic concentrations of acetylcholine [54, 55]. Coma is usually due

Table 3 Cardiac manifestations of organophosphorus insecticide poisoning

Bradycardia, tachycardia
Ventricular arrhythmias
Torsades de pointes
Ventricular fibrillation
Asystole
<i>ECG changes</i>
ST-segment changes
Peaked T waves
Atrioventricular block
QTc interval prolongation
<i>Histopathological changes</i>
Lysis of myofibrils
Z-band abnormalities

to direct CNS depression by OPs and solvents in the commercial formulation, with EEGs show profound depression of cortical activity [56]. Aspiration pneumonia is common [57]. Other pulmonary function changes associated with OP poisoning include a decrease in dynamic lung compliance, an increase in total pulmonary resistance, and an alveolar–arterial oxygen gradient [58]. Respiratory effects generally are more severe in older patients with a history of respiratory disease.

Sinus tachycardia is likely to be present (although some patients may be bradycardic), but other cardiac effects (Table 3), including atrioventricular block, ST-segment changes, peaked T waves, and QT prolongation, have been observed. Ventricular arrhythmias are a common cause of death [59], and tachyarrhythmias of the torsades de pointes type [60, 61] may progress to ventricular fibrillation or asystole or both.

Mydriasis may be observed [62], particularly if atropine is given. Later effects may include diarrhea, tenesmus, incontinence, ataxia, and confusion.

Glycosuria and hyperglycemia [63, 64] have been reported. Leukocytosis and low-grade fever are noted frequently, even in the absence of infection. A low PaO₂ and metabolic acidosis are seen in severely poisoned patients, and creatine kinase activity may be high.

OP-Induced Delayed Neuropathy

Lotti and Moretto [14] have reviewed the features resulting from distal degeneration of some axons in both the peripheral and central nervous systems occurring 1–4 weeks after single or short-term exposures. Cramping muscle pain in the lower limbs, distal numbness, and paresthesias are followed by progressive weakness and depression of deep tendon reflexes in the lower limbs and, in severe cases, in the upper limbs. Signs include a high-stepping gait from bilateral foot drop and, in severe cases, quadriplegia with foot and wrist drop as well as pyramidal signs. In time, there might be significant recovery of peripheral nerve function, but, depending on the degree of pyramidal involvement, spastic ataxia may be permanent [14]. Human and experimental data indicate that recovery is usually complete in the young.

Intermediate Syndrome

Relapse after apparent resolution of cholinergic symptoms has been reported, particularly in patients who have ingested highly lipophilic OP insecticides, and is termed the intermediate syndrome. The syndrome was first described by Senanayake and Karalliedde [54] who reported the onset of muscle paralysis affecting particularly upper limb muscles, neck flexors, and cranial nerves some 24–96 h after OP exposure, though there are reports of paralysis occurring before 24 h and even after 96 h [31, 53, 65]. It is often associated with the development of respiratory failure, a major contributor to the high mortality of OP poisoning. Several recent reviews have described the syndrome in detail [40, 66–68].

Jayawardane et al. [40] have shown that subclinical electrophysiological abnormalities are common, progressive, and precede the onset of the clinical syndrome. Serial repetitive nerve stimulation studies have been most commonly used and are the most accessible for clinicians. Clinical and experimental studies demonstrate a progression through early initial decrement–increment patterns at high rates of stimulations, which correlate with moderate muscle weakness, to decrement–increment patterns at intermediate- and low-frequency stimulations. Progression to a

combination of decrement–increment and repetitive fade patterns correlates with clinical deterioration. Severe decrement pattern is usually observed immediately before the onset of respiratory failure. Although electrophysiological features closely parallel clinical severity during progression of the syndrome, the same is not true during recovery. Electrophysiological changes sometimes improve long before the patient recovers normal strength and respiratory function.

Delayed Neuropsychological Sequelae After OP Poisoning

Since acute poisoning with OP insecticides can cause major effects such as convulsions, respiratory failure, and cardiac arrhythmias, all of which can result in cerebral anoxia, it would not be surprising if severe acute OP poisoning was associated with long-term neurological sequelae. Moreover, there is now evidence that such complications can occur [69]. However, shortcomings in the methodology of these studies, including poor assessment of exposures and of the severity of poisoning, different timing of examination after poisoning, and choice of controls, do not allow a firm conclusion to be drawn that severe acute OP poisoning can produce subclinical damage to the central and peripheral nervous systems.

Rosenstock et al. [70] and McConnell et al. [71] investigated the neurophysiological effects and, as an index of delayed neuropathy, measured vibrotactile thresholds in 36 male agricultural workers in Nicaragua who had been admitted to hospital between 10 and 34 months earlier with occupationally related acute OP poisoning; 21 of 36 workers had been poisoned with methamidophos, a recognized peripheral neurotoxin. In a battery of neuropsychological tests, the exposed group performed significantly worse than the control group, and a significant decrease in vibrotactile sensitivity was also observed.

Steenland et al. [72] studied 128 men exposed to OP insecticides, the majority, occupationally, who had sought medical attention and of whom 28% had been admitted to hospital in California for more than one night. Neurobehavioral tests, nerve conduction tests, and vibrotactile threshold

responses were undertaken several years after exposure. The study group performed significantly worse in tests of sustained visual attention and mood, and those in the “definitely” poisoned subgroup also showed significantly worse vibrotactile sensitivity of the finger and toe, but had no neurological symptoms.

Savage et al. [73] investigated the presence of chronic neurological or neuropsychological abnormalities in 100 subjects who had experienced at least one episode of acute OP poisoning confirmed by a physician. The authors found significant deficits in a wide range of neuropsychological variables, including visuomotor, attention, and language function. Persistent abnormalities in affective behavior, especially anxiety, were also found, though no differences on EEG or neurological examination were identified.

Miranda et al. [74] studied a cohort of men who were exposed predominantly occupationally to an OP insecticide and who had been admitted for at least 1 day to two hospitals in Nicaragua for treatment of OP poisoning. Quantitative tactile vibration thresholds were measured in 56 subjects on the first occasion 1–24 days (median 7) after exposure and for the second time 24–128 days (median 50) after poisoning and compared to 39 nonexposed men. Big-toe vibrotactile thresholds increased markedly from the first to the second examinations in those with severe intentional poisoning (ingestion) due to neuropathic OPs (methamidophos, chlorpyrifos). No significant impairment of vibrotactile thresholds was detected in association with occupational poisonings or with less severe intentional poisonings with neuropathic or non-neuropathic OPs.

In a second study [75] of the same Nicaraguan population ($n = 59$), marked impairment of grip and pinch strength in the dominant hand was found, particularly among those with severe poisoning due either to neuropathic OPs or intentional ingestion.

In a third study [76], hand strength and vibration thresholds were performed in 48 men 2 years after admission for acute OP poisoning. In those exposed to non-neuropathic OPs, grip and strength had recovered and was not different from controls; pinch strength remained lower

than for controls. Those only moderately poisoned with neuropathic OPs poisoning showed an evolution similar to those exposed to non-neuropathic OPs, whereas those severely poisoned (notably as a result of intentional ingestion) still remained significantly weaker than controls. Index finger and toe vibration thresholds were slightly increased at the end of the 2-year period.

In a fourth study [77] in 53 individuals, changes in immediate verbal memory, visuomotor performance, and neuropsychiatric symptoms at the time of discharge, at 7 weeks post poisoning, and at 2 years were evaluated. Immediate verbal learning showed deficits in the high exposure group, particularly at the time of discharge. Visuomotor performance showed a deficit at 7 weeks but improved thereafter. A 2-year delayed excess of neuropsychiatric symptoms was present in those occupationally exposed. The authors concluded that visuomotor performance and possibly short-term verbal memory were affected early after severe acute OP poisoning and recover, either truly or by some compensatory mechanism. Neuropsychiatric symptoms seemed to increase after a longer latent period, particularly in the less severely exposed subjects.

Neuropsychological Effects Following Low-Level OP Exposure

There remains controversy as to whether low-level exposures to OP insecticides (without the features of acute poisoning or the cholinergic syndrome having occurred) can result in peripheral nerve dysfunction. However, we are still of the view [78], first proposed by Lotti [79], that a single pattern of subclinical disturbances that relates low-level OP exposure to human peripheral neuropathy has not been identified. The clinical characteristics of the mild neuropathies described point to a condition that differs from OP-induced delayed polyneuropathy. The distribution of involved peripheral nerves is unusual for a toxic polyneuropathy, including OP-induced delayed neuropathy, because both upper and lower limbs seem to be affected at once. In some studies, defects seem irreversible, because they were detected several months after cessation of exposure. Although OPs are rapidly cleared from

the body and peripheral nerves regenerate, it is not clear what mechanism would sustain a peripheral neuropathy for a sustained period of time after cessation of exposure. Therefore, in the absence of histopathology and follow-up studies, the significance of these changes remains unclear. These difficulties in interpretation are further amplified by the lack of an experimental model other than the classic OP-induced delayed polyneuropathy one. These mild, inconsistent and unexplained findings provide no evidence to support the proposal that low-level exposures to OPs caused peripheral neuropathy in humans, even among possibly hypersusceptible individuals.

As regards neurobehavioral function after low-level OP exposure, Mackenzie Ross et al. [80], having reviewed the available evidence by conducting a meta-analysis of 14 studies involving more than 1600 participants, claimed to have found a significant association between “low-level exposure to OPs and impaired neurobehavioral function which is consistent, small to moderate in magnitude and concerned primarily with cognitive functions such as psychomotor speed, executive function, visuospatial ability, working and visual memory.”

Diagnosis

The diagnosis of OP poisoning is based on the patient's history, clinical presentation, and laboratory tests. In a patient with a positive history, a typical odor on the breath, characteristic symptoms, and depressed erythrocyte and plasma cholinesterase activities, diagnosis is not difficult to make. The history is often unobtainable and in one study was missing in 36% of all cases [81]. The clinical features of OP poisoning may not be recognized as such if the patient presents, for example, with heart block, gastroenteritis, convulsions, or ketoacidosis. An awareness of this diversity of presentation is the first step toward accurate diagnosis. If there is a doubt regarding the diagnosis, consultation with a medical toxicologist or poison center should be considered.

The activity of two enzymes may be measured to confirm a diagnosis of OP poisoning. These are

red cell AChE and plasma butyrylcholinesterase (plasma cholinesterase, plasma pseudocholinesterase, BuChE). Both are surrogates for AChE activity in the central and peripheral nervous systems. The erythrocyte AChE activity is invariably more specific than plasma butyrylcholinesterase activity as a marker of OP insecticide exposure, though some OP insecticides (e.g., chlorpyrifos, demeton, malathion) depress plasma butyrylcholinesterase activity to a greater degree than erythrocyte cholinesterase activity. The diagnosis of OP poisoning can be confirmed by showing a significantly reduced cholinesterase activity in red blood cells or plasma, preferably the former. Difficulty often arises regarding the interpretation of results of plasma cholinesterase activities because individuals can vary widely in their normal complement of plasma cholinesterase. Low plasma cholinesterase activity should be confirmed by the measurement of red blood cell cholinesterase activity.

Usually a good correlation exists between the activity of erythrocyte AChE and the severity of symptoms in OP poisoning [82]. Hence, it is not necessary to wait for confirmation from the laboratory for the diagnosis of acute OP poisoning to be confirmed; specific treatment should be started immediately.

Few laboratories can determine quantitatively the insecticide responsible for the intoxication and measurement of the parent compound or metabolite in body fluids. Such measurement has little place in the immediate diagnosis or early management of poisoning. In many cases, rapid hydrolysis prevents the detection of the parent compound, although urinary metabolites may persist for several days. The measurement of metabolites is most helpful as a measure of low-level chronic exposure.

Treatment

All cases of OP poisoning should be dealt with as an emergency, and all patients with more than minor symptoms (grade 2 or greater, see Table 4) should be admitted to a critical care unit. Given the effects of OPs on the respiratory system,

Table 4 Assessment of severity and management of severe organophosphorus insecticide poisoning (After Johnson and Vale [98])

Grade 0	Suggestive history but no features of intoxication present
Grade 1	Patient is alert and awake and has
	Increased secretions
	Fasciculation +
Grade 2	Patient is drowsy and has
	Severe bronchorrhea
	Fasciculations + + +
	Crackles/wheezes on auscultation
	Hypotension (systolic BP <90 mm Hg)
Grade 3	Patient is comatose and has all the features of severe intoxication
	Increased FiO ₂ needed but not mechanical ventilation
Grade 4	Patient is comatose and has all the features of severe intoxication
	PaO ₂ < 8 kPa (60 mm Hg) despite FiO ₂ > 40%; PaCO ₂ > 6 kPa (45 mm Hg)
	Mechanical ventilation required
	Abnormal chest radiograph (circumscribed or diffuse opacities, pulmonary edema)

Note: all patients \geq grade 2 should be admitted to an intensive care unit

particular attention should be directed toward the patient's ventilatory status. Bronchorrhea requires prompt relief with intravenous atropine (see later), and supplemental oxygen should be given to maintain PaO₂ greater than 8 kPa (60 mm Hg). If these measures fail, the patient should be intubated, and mechanical ventilation (with positive end-expiratory pressure) should be instituted. Careful attention must be given to fluid and electrolyte balance and adjustments to infusion fluids made as necessary. Heart rate, blood pressure, electrocardiogram, and arterial blood gases should be monitored routinely.

Decontamination

During and after stabilization, thorough skin decontamination should be carried out, without caregivers themselves being contaminated. All contaminated clothing should be removed, and affected skin on all exposed areas should be washed thoroughly with soap and cold water (e.g., hands, arms, face, neck, and hair).

Gastric lavage has no routine role in management even after substantial ingestion of an OP insecticide as its value is unproven and its execution is potentially dangerous because hydrocarbons are present in many OP insecticide formulations.

The capacity of activated charcoal to adsorb most OP compounds has not been shown. While on theoretical grounds the use of activated charcoal might be considered, in a large study in Sri Lanka, involving OP and carbamate insecticide poisoning, no benefit from single- or multiple-dose charcoal was demonstrated [83]. Patients were randomized to receive no charcoal ($n = 1554$), one dose of charcoal 50 g ($n = 1545$), or six doses of charcoal 50 g at 4 h intervals ($n = 1533$); outcomes were available for 4629 patients. 2338 (51%) individuals had ingested pesticides (1310 had ingested OP and carbamate insecticides), whereas 1647 (36%) had ingested yellow oleander (*Thevetia peruviana*) seeds. Mortality did not differ between the groups: 109 (7.1%) of 1544 participants in the single-dose charcoal group died (adjusted odds ratio 1.05, 95% CI 0.79–1.40); 97 (6.3%) of 1531 participants in the multiple-dose charcoal group died (adjusted odds ratio 0.93, CI 0.69–1.25), compared with 105 (6.8%) of 1554 in the no charcoal group. No differences were noted for patients who took particular poisons, were severely ill on admission, or who presented early. Level of evidence for charcoal use in decontamination is therefore grade IV.

Supportive Care

In severely poisoned patients who are hypotensive, it may be necessary not only to expand plasma volume by administering a bolus of intravenous crystalloid but also to give inotropic support. Cardiac arrhythmias should be treated conventionally, and hypoxia must be considered as a possible etiology. The management of convulsions and muscle fasciculation is discussed later.

Antidotes

The evidence base for atropine, oximes, and diazepam has been reviewed [84–86]. While the

therapeutic combination of oxime and atropine is well established in experimental OP pesticide poisoning and is used routinely clinically, diazepam may also be of benefit by reducing anxiety, restlessness, and muscle fasciculation, suppressing seizures, and reducing morbidity and mortality when used in conjunction with an oxime and atropine.

Atropine

Atropine antagonizes the effects of accumulated ACh at muscarinic receptors. Atropine sulfate 2 mg (0.02–0.1 mg/kg in a child) intravenously should be given as soon as possible in moderately and severely poisoned adults and may be lifesaving in those with rhinorrhea and bronchorrhea (Grade I recommendation). The atropine dose should be titrated to control rhinorrhea and bronchorrhea, to raise the pulse rate above 80 bpm, and restore systolic blood pressure to more than 80 mmHg. In severe cases, several hundred milligram may be required, though in a study in Sri Lanka the mean dose was 23.4 mg (standard deviation 22.0, range 1–75 mg) [87]. If the initial dose produces only a partial response, it should be doubled and doubled again if there is only a limited clinical response [87].

An open-label randomized clinical trial was conducted in Chittagong Medical College Hospital, Chittagong, Bangladesh, on 156 hospitalized individuals with OP insecticide poisoning from June to September 2006 [88]. Group A consisted of 81 patients who received conventional bolus-dose atropine (increasing doses of intravenous atropine from 2 to 5 mg depending on severity, as assessed by the treating clinician, and repeated every 10–15 min until signs of atropinization were clinically evident); Group B consisted of 75 patients who received rapidly incremental doses of atropine (a first dose of 1.8–3.0 mg depending on severity as assessed by the treating clinician followed by another 5 min later at double this dose if needed. This was repeated every 5 min until all clinical signs of atropinization were clearly evident) followed by an atropine infusion (10% of the atropine required to load the patient was given per hour [e.g., if atropine required for atropinization was 18 mg, 1.8 mg was infused

each hour]). The mortality in Group A was 22.5% (18/80) and in Group B 8% (6/75) ($p < 0.05$). The mean duration of atropinization in Group A was 151.74 min compared to 23.90 min for Group B ($p < 0.001$). More patients in Group A experienced atropine toxicity than in Group B (28.4% vs. 12.0%, $p < 0.05$); intermediate syndrome was more common in Group A than in Group B (13.6% vs. 4%, $p < 0.05$), and respiratory support was required more often for patients in Group A than in Group B (24.7% vs. 8%, $p < 0.05$). In this study, rapid incremental dose atropinization followed by an atropine infusion reduced mortality and morbidity and shortened the length of hospital stay and recovery.

The peripheral antimuscarinic effects of atropine may not be the only antidotal property of the drug; it may also be of value in treating the acute dystonic reactions observed occasionally [89–92].

Oximes

The fundamental action of the pyridinium oximes is to reactivate AChE inhibited by OPs (see Fig. 52.3), thus allowing ACh to be hydrolyzed in the usual way and resumption of normal cholinergic neurotransmission (see also ► Chap. 52, “Hydantoin Anticonvulsants: Phenytoin and Fosphenytoin”). Pralidoxime does not pass readily into the central nervous system [93] because of its quaternary nitrogen structure. There are numerous contradictory reports of animal experiments showing occasionally detectable oxime concentrations in the brain and cerebrospinal fluid [94]. In the main, oxime doses far beyond those administered to humans were used, and the positive assays in the brain tissue may reflect damage to the blood–brain barrier rather than natural permeability to oximes [94]. All these data indicate that while the blood–brain barrier is not entirely impermeable to quaternary pyridinium compounds, it may become more permeable in stress situations, such as in severe intoxication [94].

It is generally held that the beneficial effects of pyridinium oximes in OP poisoning are confined to peripheral nicotinic sites and that peripheral muscarinic and central nervous effects are clinically insignificant. Thus, the beneficial effects of

oximes are mainly on neuromuscular transmission, and there is little action on muscarinic parasympathetic effects such as bronchorrhea, bronchoconstriction, and rhinorrhea. As atropine acts largely at peripheral muscarinic sites, the therapeutic combination of oxime and atropine is well established in the treatment of organophosphorus insecticide poisoning.

The reactivation of inhibited AChE and clinical improvement depend on:

- (i) The chemical form of inhibited AChE. While spontaneous reactivation of dimethyl phosphorylated AChE proceeds rapidly, in the case of diethyl phosphorylated AChE, it is very slow. Spontaneous reactivation of diethyl phosphorylated AChE can be accelerated by oximes.
- (ii) The plasma concentration of the OP insecticide [95, 96].
- (iii) Aging which results from monodealkylation of dialkoxylphosphorylated AChE [97]; aged enzyme reactivates neither spontaneously nor under the influence of oximes so that recovery depends on synthesis *de novo* of more enzyme.
- (iv) The plasma oxime concentration.
- (v) The duration of oxime therapy.

It is commonly but erroneously believed that within 1 day of intoxication, virtually all the inhibited AChE is in the “aged” form so that oxime therapy, if employed, would be useless. There are good biochemical reasons, however, for suggesting that as soon as an effective concentration of oxime is achieved *in vivo*, the balance of aging and reactivation reaction rate for inhibited AChE is altered in favor of the latter [98]. Progress toward complete inhibition may be slowed markedly. It is probable that benefit would ensue even if oxime therapy was started or continued several days after intoxication occurred [99].

There are consistent animal data supporting the effectiveness of oximes, when given early [100–107]. There are also some clinical studies which support the benefit of oxime therapy. Pawar et al. [108] administered two pralidoxime-dosing schedules in 200 patients who had moderately

severe OP insecticide poisoning. Patients ($n = 100$) who received the high-dose regimen (pralidoxime iodide 2 g loading dose over 30 min, then 1 g/h for 48 h, and then 1 g every 4 h until weaned from the ventilator) had a lower mortality (1% vs. 8%; $p = 0.03491$), less need of intubation ($p = 0.0001$), and a shorter time on ventilator support ($p < 0.0001$) than the 100 patients receiving a lower-dose regimen (pralidoxime iodide 2 g loading dose, then 1 g every 4 h until weaned). Those receiving high-dose pralidoxime also developed less muscle weakness and required less atropine (median 6 mg vs. 30 mg; $p = 0.0001$) during the first day and fewer developed pneumonia ($p < 0.0001$).

In contrast, de Silva and colleagues [109] concluded that nothing is to be gained in cases of severe acute OP insecticide poisoning by the addition of oxime reactivators to the standard regimen of atropine plus mechanical ventilation. This conclusion, which has been challenged [110], was based on a study in which 21 patients received atropine alone and 24 patients received atropine plus pralidoxime chloride (median doses, 4 g in the first 24 h and 1 g daily thereafter). The mortality in both groups was 29%, which is not dissimilar to that reported from other centers managing severe cases of OP insecticide poisoning.

Eddleston et al. [111] came to a similar conclusion after performing a double-blind, randomized, placebo-controlled trial comparing pralidoxime chloride (2 g loading dose, followed by a constant infusion of 0.5 g/h for up to 7 days) with saline. Despite clear reactivation of red cell AChE activity in diethyl OP pesticide-poisoned patients, there was no evidence of improved survival or reduced need for intubation [111].

The value of oximes has also been challenged in a Cochrane Review [86] which concluded that

Current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute OP pesticide poisoning. The World Health Organization recommended pralidoxime regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/h infusion) is not supported by outcomes to date. Lower doses have also shown worse outcomes in one RCT. Thus the published RCTs provide limited guidance for clinicians. Despite this there are consistent animal data supporting their

effectiveness, when given early. Based on our understanding of the mechanism, *in vitro* and animal data, benefit–risk ratio is more likely to be favorable when they are given early, to patients with serious poisoning by diethyl OPs. However, the RCTs have not defined effective doses or subgroups that are likely to benefit.

Specifically, the Cochrane Review [86] identified seven RCTs (845 people) in those poisoned with OP insecticides. Three of the RCTs (366 people), reported in four publications [111–114], compared pralidoxime treatment with placebo and the outcomes of mortality and ventilation requirement. Reporting of methods in the RCTs was poor. The review noted that many studies did not account for factors that would affect outcomes. In some studies, characteristics of participants in different groups were not balanced at baseline. Only one RCT [111], comparing pralidoxime treatment with placebo, used doses of pralidoxime recommended by the World Health Organization (at least 30 mg/kg loading dose, then 8 mg/kg/h intravenous infusion) [115, 116].

In the three RCTs, oximes were given either as a dose of 4–12 g infused daily over 3 days without a loading dose or as a 2 g loading dose over 20 min followed by a constant infusion of 0.5 g/h for a maximum of 7 days. The review found no significant difference between treatment with an oxime and placebo in mortality (3 RCTs = 366 people; 47/186 [25%] with oxime treatment vs. 22/180 [12%] with placebo; OR 2.68, 95% CI 0.93–7.72) or need for ventilation (3 RCTs = 70/186 [38%] with oxime treatment vs. 50/180 [28%] with placebo; OR 2.00, 95% CI 0.81–4.95). The review authors noted that the different oxime doses used in the studies and differences in the types of organophosphate poison meant that meta-analysis might not produce a true estimate of effect. One of the RCTs (110 people) identified by the review also reported the proportion of people developing intermediate syndrome [113, 114]. It found that an infusion of pralidoxime 12 g over 3 days significantly increased the proportion of people developing intermediate syndrome compared with placebo (36/55 [65%] with pralidoxime vs. 19/55 [35%] with placebo; OR 3.59, 95% CI 1.64–7.88). However, baseline differences in this RCT suggested that people

allocated to treatment with an oxime might have been more severely poisoned compared with those allocated to placebo [86].

Why is there this discrepancy between the experimental and clinical data? In an important study performed in mini pigs using orally administered clinically relevant doses of dimethoate EC (agricultural emulsifiable concentrate), dimethoate active ingredient alone, or solvents, Eddleston et al. [42] found that administration of agricultural dimethoate EC, but not saline, caused respiratory arrest within 30 min, severe distributive shock, and NMJ dysfunction, that was similar to human poisoning. Moderate toxicity resulted from poisoning with dimethoate active ingredient alone or the major solvent cyclohexanone. Combining dimethoate with cyclohexanone reproduced severe poisoning characteristic of agricultural dimethoate EC poisoning. A formulation without cyclohexanone showed less mammalian toxicity. These results indicate that solvents play a crucial role in OP (and specifically dimethoate) toxicity, which could explain why oximes seem to be less effective clinically than in experimental studies where pure OP insecticide rather than marketed formulations is often employed.

Pralidoxime

Pralidoxime chloride 30 mg/kg by intravenous injection should be administered as soon as possible in any severe or progressive case of intoxication and repeated at 4–6-h interval; alternatively an intravenous infusion of 8–10 mg/kg/h in an adult may be employed. These regimens are based on reported clinical studies [95, 117, 118] and have been recommended by WHO [115] and ourselves [119]; these are Level III recommendations. Administration of pralidoxime should continue for as long as atropine is required, that is, until clear, irreversible clinical improvement is achieved, which may take many days, while residual insecticide is cleared from the body stores.

Obidoxime

Based on pharmacokinetic data of obidoxime in healthy human volunteers [120], Thiermann et al. [121] considered that a bolus dose of obidoxime 250 mg IV, followed by a continuous

infusion at 30 mg/h, is an appropriate therapeutic regimen, which they employed in single patients [122, 123]; this is a Level III recommendation. The efficacy and safety of this regimen was evaluated in an observational study [124, 125]. These authors further investigated this regimen in 34 severely poisoned patients [121]. The mean (\pm SD) total dose of obidoxime infused over 65 (\pm 55) h was 2,269 (\pm 1,726) mg, which resulted in a mean steady-state plasma concentration of 5.2 (\pm 2.6) mg/L. Reactivation of inhibited erythrocyte AChE was achieved in 23 of 34 patients, while in seven patients, aging was complete before the commencement of obidoxime. In four patients high OP insecticide load prevented significant reactivation, and complete aging ensued in spite of this obidoxime regimen.

Thiermann et al. [123] reported that in parathion poisoning, obidoxime 250 mg IV as a bolus followed by 750 mg/day by infusion was effective but that in severe poisoning AChE reactivation did not occur until the concentration of inhibitor in the plasma had declined. The same dosage regimen was ineffective with oxydemeton-methyl when oxime therapy was delayed more than 1 day after poisoning. In another series, Thiermann et al. [126] reported that in parathion poisoning, reactivation was possible 7 days after poisoning, whereas with oxydemeton-methyl, a response was only seen when obidoxime therapy was instituted soon after poisoning. Similarly, Zilker et al. [127] found that obidoxime (750 mg/day by infusion) reduced the need for atropine in parathion poisoning but that demeton-S-methyl poisoning only responded if obidoxime therapy was instituted shortly after intoxication.

Adverse Effects of Oximes

Male volunteers were given obidoxime 1.84–3.58 g as a single dose, or 7.36 g divided into 4 equal doses. Over half the subjects complained of one or more side effects: pallor, nausea, burning sensation, headache, generalized weakness, sore throat, and paresthesia of the face. However, activities of blood cholinesterase, alanine, and aspartate aminotransferases, as well as hematocrit values, heart rate, and blood pressure were not affected [128].

In human volunteer studies, Jager and Stagg [129] found that medical students given pralidoxime iodide developed dizziness, blurred vision, diplopia, impairment of accommodation, and headache. Dizziness, blurred vision, and occasionally diplopia have been reported in human volunteer studies after intravenous or intramuscular administration of pralidoxime chloride [130].

Reversible fatty change has been observed in the liver of rats dosed with obidoxime [131], and impaired liver function has been seen in humans after treatment of parathion poisoning treated with obidoxime [132, 133]. Finkelstein et al. [46] have shown an association between liver dysfunction and the cumulative dose of obidoxime. The liver damage usually manifests as an increase in hepatic enzyme activities and hyperbilirubinemia [123].

Diazepam

Diazepam may be of benefit in OP-poisoned patients by:

1. Reducing anxiety and restlessness
2. Reducing muscle fasciculation
3. Treating seizures
4. Reducing morbidity and mortality when used in conjunction with pralidoxime and atropine

Diazepam 10 mg intravenously reduces anxiety, restlessness, and visible motor activity. Midazolam has been employed as an alternative benzodiazepine but offers no advantages over diazepam in this regard. Short-term diazepam, 10–20 mg (or midazolam 10 mg, then 10 mg after 10 min if required) in an adult, is also an effective anticonvulsant and may prevent chronic OP-induced seizures if administered immediately [134]. Potentially, respiratory depression may result from the repeated use of a benzodiazepine, although this is unlikely to be a significant clinical problem, unless OP-induced respiratory impairment also is present and the patient is breathing spontaneously. If repeated doses of a benzodiazepine are required to suppress seizure activity, phenytoin is an appropriate second-line agent as it has been shown *in vitro* to be an effective anticonvulsant (suppression of epileptiform bursting in

guinea-pig hippocampal slices induced by the OP nerve agent, soman) [135]. Phenytoin 20 mg/kg (max. per dose 2 g) should be given at a rate not exceeding 1 mg/kg/min (max. 50 mg/min), with blood pressure and ECG monitoring.

Prevention and Treatment of Intermediate Syndrome

If intermediate syndrome is a consequence of ACh accumulation at the neuromuscular junction, oximes should protect against its development. It is noteworthy, and possibly relevant, that pralidoxime methylsulfate protected against development of muscle fiber necrosis [136]. Johnson et al. [137] reported a prospective trial with two treatment regimens of pralidoxime in the treatment of patients with OP poisoning. Seventy-two adults with a history of consumption of these compounds and requiring intensive care were entered into the trial. They were then randomized using a block randomization to receive either a single bolus of pralidoxime 1 g at admission followed by placebo infusion over the next 4 days or a single placebo bolus at admission followed by pralidoxime 12 g as a continuous infusion over the next 4 days. A higher prevalence of intermediate syndrome was observed in the latter group. Comparison of patients who received at least pralidoxime 1 g within 12 h of ingestion of the OP poison with those who received pralidoxime after 12 h suggested that the time of administration of pralidoxime was important, the first group being less likely to develop the syndrome.

However, other case reports have suggested that high dose of oxime may not avert intermediate syndrome. In a case of severe malathion self-poisoning, pralidoxime 1 g was administered intravenously approximately 7 h after poisoning, and at 12 h, an infusion of pralidoxime 400 mg/h was given. The patient developed intermediate syndrome on hospital day 3 [138].

Carbamate Insecticides

Carbamate insecticides were developed in the 1950s in response to a search for insecticides with anticholinesterase activity but with greater

specificity and lower mammalian toxicity than OP insecticides. Carbamates are used widely in many countries where agriculture is a major industry and pest control essential and are employed frequently as alternatives to OP insecticides. Carbamate insecticides include carbaryl, aldicarb, methomyl, carbofuran, bendiocarb, benfuracarb, butoxycarboxim, carbosulfan, ethiofencarb, methiocarb, oxamyl, pirimicarb, propoxur, thiodicarb, and thiofanox.

Poisoning with carbamates almost always involves commercial formulations, not isolated active ingredients, and the additional chemicals they contain not infrequently contribute to toxicity [139–142]. Carbamate poisoning occurs predominantly in countries where agriculture is the primary industry, and pesticide ingestion is an important means of suicide. Among 228 confirmed fatal poisonings in Northern Greece between 1990 and 1995, carbamates were implicated in 24 of 85 cases of pesticide poisoning [143]. There have been occasional outbreaks of carbamate poisoning after consumption of contaminated food [144, 145] or illegal use as a rodenticide [146] and as the poison in attempted murder [147].

Biochemistry and Clinical Pharmacology

Carbamate insecticides are derivatives of *N*-methyl carbamic acid and have the general formula $\text{CH}_3\text{NHC(O)OR}$, where R is an aromatic or aliphatic moiety. Carbamate insecticides are susceptible to hydrolysis in alkalis, a property that is used in decontamination and cleanup after carbamate spillages.

Clinical Pharmacology

Carbamate insecticides are lipophilic and absorbed readily by dermal and inhalational exposure and after ingestion. The use of these agents in conditions of high temperature and humidity enhances dermal absorption because of increased exposed skin surface area and peripheral vasodilation. In addition, in high ambient temperatures, some carbamate aerosols (e.g., propoxur) are

susceptible to revolatilization with increased likelihood of absorption by inhalation.

When absorbed, carbamate esters undergo rapid biotransformation via phase I and phase II detoxification reactions. Phase I detoxification involves either hydrolysis of the carbamate ester by nonspecific tissue carboxylesterases (to form a phenol or alcohol, carbon dioxide, and an amine) or oxidation by monooxygenase P-450 enzymes. Oxidative reactions predominantly involve either direct ring hydroxylation or side-chain oxidation reactions (e.g., *N*-dealkylation or *O*-dealkylation or *N*-methyl hydroxylation). Phase II conjugative reactions produce sulfates, glucuronides, and mercapturates of the hydrolysis products. These species are eliminated predominantly by the kidneys. Based on the limited data available, the plasma half-life of carbamate insecticides is of the order of a few hours [148]. A woman who ingested 10 g of aldicarb developed severe poisoning with a peak serum aldicarb concentration at 3 h. The aldicarb plasma half-life in this case was 5.75 h [149].

Pathophysiology of Toxic Effects

Carbamates inhibit AChE by carbamylation of a serine hydroxyl residue at the active site of the enzyme. This process involves cleavage of the carbamate molecule, which in effect is treated by the enzyme as an alternative substrate to ACh [150]. The AChE–carbamate interaction is not truly reversible because the carbamate does not depart the encounter intact, but rather as the products of hydrolysis. AChE activity is restored when spontaneous hydrolysis of the carbamylated enzyme occurs. This spontaneous reactivation of carbamylated enzyme, expressed as half-life, varies between 2 and 240 min depending on the carbamate and in part explains some of the observed differences between carbamates as regards their toxicity [148]. The rate of regeneration of the carbamylated enzyme to AChE is relatively rapid compared with that of an OP-phosphorylated enzyme, and aging does not occur. Many carbamates do not cross the blood–brain barrier readily, so the impact on

cerebral AChE is considerably less than that caused by OP insecticides. For all these reasons, human exposure to carbamate insecticides is potentially less dangerous than exposure to an OP insecticide.

Clinical Presentation and Life-Threatening Complications

Toxicity may occur after inhalation, ingestion, or skin contamination. Inhalational and topical exposures typically are occupational. Life-threatening poisoning in these circumstances is rare, although cholinergic symptoms have occurred after equipment malfunction or inadequate protective measures [151–153]. In these cases, the rapid (often within 30 min) onset of mild cholinergic features, including nausea, headache, sweating, lacrimation, salivation, chest tightness, coughing, bronchorrhea, and constriction of one or both pupils causing blurred vision, serves to alert affected individuals to remove themselves from exposure [151, 152, 154]. Resolution of symptoms occurs typically within hours [154], often without the need for atropinization [152]. If exposure continues, vomiting, diarrhea, abdominal pain, muscle fasciculation, and weakness develop [152]. Hypotension, sinus tachycardia or bradycardia, and dyspnea also may occur [152]. Electrocardiogram T-wave changes, including inversion, are recognized [155]. Severe sequelae after occupational carbamate exposure are rare, often involve methomyl, and include several cases involving pilots of crop-spraying aircraft exposed to carbamates in the cockpit [156–158]. One of these cases [157] proved fatal as a result of the pilot crashing the plane.

Most cases of severe carbamate poisoning occur after ingestion, which may be accidental [146, 159] or deliberate [146, 160, 161]. These patients usually develop cholinergic symptoms within a few minutes [161], and in most severe cases, muscle twitching, profound weakness, profuse sweating, incontinence, mental confusion, and progressive cardiac and respiratory failure may ensue [159, 161]. Seizures are relatively uncommon [162] as a primary complication in

severe carbamate poisoning because their penetration into the central nervous system is limited. Seizures may occur secondary to hypoxia, however. Death has occurred within a few hours in untreated cases and is usually due to respiratory failure [159, 163]; pulmonary edema and evidence of cerebral hypoxia are the main findings at autopsy [159, 161]. In patients who survive, coma may persist for 18–24 h [161].

In less substantial ingestions, cholinergic symptoms are evident within 2 h in most cases and typically resolve within 24 h [164]. There is some evidence that central nervous system depression in moderate carbamate poisoning is more common in infants than in adults, possibly as a result of a greater blood–brain barrier permeability [164]. Acute pancreatitis is reported rarely after ingestion [165, 166]. Klys and colleagues [167] reported a case of deliberate carbofuran ingestion in a young pregnant woman, which resulted in fatal carbamate poisoning in the fetus, although the mother survived. At autopsy, the fetal liver contained 2.5 µg/g of carbofuran, which was comparable to the maternal blood carbofuran concentration of 2.6 µg/g.

Although most carbamate insecticides are less toxic than OP insecticides, they should not be considered toxicologically benign. Severe cholinergic effects may ensue after ingestion, and unless supportive care, often with atropinization, is instituted promptly, significant morbidity may ensue. Deaths have been reported [162].

Delayed Neurological Sequelae

Carbamate poisoning is generally held not to be associated with delayed polyneuropathy such as is seen with some OP insecticides, but three cases have been reported involving ingestion of carbaryl [168], m-tolyl methylcarbamate [169], and carbofuran [170]. The first developed a sensory–motor neuropathy [168], while the second had loss of large myelinated fibers and axonal degeneration on sural nerve biopsy [169]. The third [170] developed arm and foot sensory symptoms and muscle weakness on the sixth day after hospitalization; the sensory component resolved rapidly, but motor features accompanied by abnormal electrophysiological studies persisted

for several months. Lotti and Moretto [171] concluded that high doses of carbamate may cause a sensorimotor polyneuropathy in humans similar to OP insecticide-induced delayed polyneuropathy. Moreover, carbamates may exacerbate polyneuropathy initiated by prior dosing with an OP insecticide or by underlying subclinical axonal damage.

Peripheral neuropathy was also seen in 3 out of 36 patients aged 14–70 years poisoned with carbamates, 80% of exposures involved carbofuran [172]. Though it is not clear whether this finding was carbamate induced or predated the poisoning, other common causes of neuropathy, especially ethanol, were carefully excluded leaving carbamates as the probable explanation [172].

Diagnosis

Measurement of cholinesterase activity is unlikely to be helpful clinically because of the rapid course of the intoxication. Most laboratories are not acquainted with the special procedure required to assay red blood cell cholinesterase activity in the presence of carbamates. Samples must be kept on ice or frozen at –20 °C during transportation to the laboratory before analysis. Spontaneous reversal of the inhibition is rapid and is accelerated by the time interval between sampling and analysis; the dilution of the sample; the addition of substrate, usually acetylcholine, at high concentration (which competes successfully for the enzymatic active site); and duration of assay time. Laboratory assay should take less than 3 min and employ minimal dilution and minimal amounts of substrate [173].

Treatment

All cases of carbamate poisoning should be dealt with as an emergency, and the patient should be admitted to hospital as quickly as possible. Gastric lavage has no routine role in management even after substantial ingestion of a carbamate insecticide as its value is unproven and its execution is potentially dangerous because hydrocarbons are

present in many formulations. The capacity of activated charcoal to adsorb most carbamates has not been shown. While on theoretical grounds, the use of activated charcoal might be considered; in a large study in Sri Lanka, involving OP and carbamate insecticide poisoning, no benefit from single- or multiple-dose charcoal was demonstrated [83]. Patients were randomized to receive no charcoal ($n = 1554$), one dose of charcoal 50 g ($n = 1545$), or six doses of charcoal 50 g at 4 h intervals ($n = 1533$); outcomes were available for 4629 patients. 2338 (51%) individuals had ingested pesticides (1310 had ingested OP and carbamate insecticides), whereas 1647 (36%) had ingested yellow oleander (*Thevetia peruviana*) seeds. Mortality did not differ between the groups: 109 (7.1%) of 1544 participants in the single-dose charcoal group died (adjusted odd ratio 1.05, 95% CI 0.79–1.40) and 97 (6.3%) of 1531 participants in the multiple-dose charcoal group died (adjusted odd ratio 0.93, CI 0.69–1.25), compared with 105 (6.8%) of 1554 in the no charcoal group. No differences were noted for patients who took particular poisons, were severely ill on admission, or who presented early. Level of evidence for charcoal use in decontamination is therefore grade IV.

Bronchorrhea requires removal of secretions by suction and prompt relief with intravenous atropine (see below). Supplemental oxygen should be given to maintain arterial PaO_2 greater than 8 kPa (>60 mm Hg). If these measures fail, the patient should be intubated and mechanical ventilation instituted. Heart rate, blood pressure, electrocardiogram, and arterial oxygen saturation or blood gas tensions should be monitored.

Atropine

Atropine antagonizes the effects of accumulated ACh at muscarinic receptors. Atropine sulfate 2 mg (0.02–0.1 mg/kg in a child) intravenously should be given as soon as possible in moderately and severely poisoned adults and may be lifesaving in those with rhinorrhea and bronchorrhea (Grade I recommendation). The atropine dose should be titrated to control rhinorrhea and

bronchorrhea, to raise the pulse rate above 80 bpm, and to restore systolic blood pressure to more than 80 mmHg. In severe cases, several hundred milligrams may be required, though in a study in Sri Lanka, the mean dose was 23.4 mg (standard deviation 22.0, range 1–75 mg) [87].

If the initial dose produces only a partial response, it should be doubled and doubled again if there is only a limited clinical response [87].

An open-label randomized clinical trial was conducted in Chittagong Medical College Hospital, Chittagong, Bangladesh, on 156 hospitalized individuals with OP insecticide poisoning from June to September 2006 [88]. Group A consisted of 81 patients who received conventional bolus-dose atropine (increasing doses of intravenous atropine from 2 to 5 mg depending on severity, as assessed by the treating clinician, and repeated every 10–15 min until signs of atropinization were clinically evident); Group B consisted of 75 patients who received rapidly incremental doses of atropine (a first dose of 1.8–3.0 mg depending on severity as assessed by the treating clinician followed by another 5 min later at double this dose if needed. This was repeated every 5 min until all clinical signs of atropinization were clearly evident) followed by an atropine infusion (10% of the atropine required to load the patient was given per hour [e.g., if atropine required for atropinization was 18 mg, 1.8 mg was infused each hour]). The mortality in Group A was 22.5% (18/80) and in Group B 8% (6/75) ($p < 0.05$). The mean duration of atropinization in Group A was 151.74 min compared to 23.90 min for Group B ($p < 0.001$). More patients in Group A experienced atropine toxicity than in Group B (28.4% vs. 12.0%, $p < 0.05$); intermediate syndrome was more common in Group A than in Group B (13.6% vs. 4%, $p < 0.05$), and respiratory support was required more often for patients in Group A than in Group B (24.7% vs. 8%, $p < 0.05$). In this study, rapid incremental dose atropinization followed by an atropine infusion reduced mortality and morbidity and shortened the length of hospital stay and recovery.

Oximes

Eckert et al. [174] demonstrated in in vitro studies that HI-6, and to a lesser extent obidoxime, could accelerate the rate of decarbamylation of human erythrocyte AChE inhibited by physostigmine or pyridostigmine. In some animal studies [175–179], pralidoxime increased the toxicity of carbaryl, while in others [180] it protected against poisoning. More importantly, some human carbamate poisonings [181–185] have benefitted from pralidoxime though there has been at least one death despite its use [186]. At present there is insufficient evidence to either recommend or prohibit the use of pralidoxime in severe poisoning with carbamate insecticides (Level III evidence). Pralidoxime seldom should need to be administered in less severe cases since carbamates have a shorter duration of action than OP compounds. However, if intoxication is life threatening and unresponsive to atropine and supportive measures, pralidoxime chloride 30 mg/kg body weight by intravenous injection over 5–10 min should be given. Cases of mixed OP and carbamate poisoning should be treated as for OP poisoning.

Indications for ICU Admission in Organophosphorus Insecticide Poisoning

All cases of ingestion or substantial dermal or inhalational exposure
All patients with symptoms or signs of cholinergic excess (see Table 1)

Criteria for ICU Discharge in Organophosphorus Insecticide Poisoning

Absence of symptoms or signs of cholinergic excess >12 h after ingestion or substantial dermal or inhalational exposure; normal erythrocyte or plasma cholinesterase activity after organophosphorus insecticide exposure
No recurrence of symptoms or signs of cholinergic excess 24 h after discontinuation of oxime therapy

Common Misconceptions About Organophosphorus Insecticide Poisoning

1. Oximes are of no benefit in organophosphorus insecticide poisoning.
2. Oximes are of no benefit if started >24 h after the onset of organophosphorus poisoning.

Key Points in Organophosphorus Insecticide Poisoning

1. Depending on the organophosphorus insecticide, features of cholinesterase inhibition may be delayed for 12 h, particularly after dermal exposure.
2. The rate of spontaneous reactivation of organophosphorus-inhibited acetylcholinesterase depends on the chemical structure of the insecticide.
3. Oximes are indicated particularly in the management of poisoning due to diethyl organophosphorus insecticides.
4. Oximes must be administered in sufficient dose to reactivate inhibited acetylcholinesterase and be continued for as long as atropine is required.

Key Point in Carbamate Insecticide Poisoning

1. Severe cholinesterase inhibition after carbamate insecticide exposure usually occurs only after ingestion and typically resolves within 24 h.

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Bipyridyl (or bipyridinium) herbicides are quaternary ammonium compounds marketed as contact herbicides and desiccants in over 90 countries [1]. Paraquat is produced by a large number of companies across the world and is very widely used; however, it has been the subject of regulatory action and bans due to its degree of toxicity to humans. Diquat is much less widely used and often formulated in combination with paraquat or other herbicides. Bipyridyl herbicides that are little used or no longer marketed include cyperquat, diethamquat, difenzoquat, and morfamquat.

Bipyridyl herbicides are rapidly acting and nonselective, being toxic to a wide range of grasses and broad-leaved weeds when applied topically in the presence of sunlight. They exert their herbicidal activity by interfering with the electron transfer system, inhibiting the reduction of nicotinamide adenine dinucleotide phosphate to reduced nicotinamide adenine dinucleotide phosphate (NADPH) during photosynthesis [3]. In contrast to many other herbicides, they have no residual environmental activity because they are inactivated almost immediately on contact with most naturally occurring soils, forming an inert complex with clay minerals in the soil. This complex is harmless to both plant and animal life [4].

This chapter builds upon the chapter by Alan Talbot in the 1st edition and the paper on diquat by Jones & Vale, *Clinical Toxicology* 2000, 38, 123–128.

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Chemistry

Paraquat (1,1'-dimethyl-4,4'-bipyridinium) and diquat (1,1'-ethylene-2,2'-bipyridinium) are bis-quaternary ammonium compounds, with molecular formulae of $C_{12}H_{14}N_2$ and $C_{12}H_{12}N_2$, respectively (Fig. 1). Both contain a bipyridyl ring structure and exist as divalent cations associated with anions such as bromide and chloride. Paraquat and diquat have molecular weights of 186.2 g/mol (cation) and 257.2 g/mol (dichloride) and of 184.2 g/mol (cation) and 344.0 g/mol (dibromide), respectively. Both are nonvolatile, freely soluble in water, sparingly soluble in lower alcohols, and insoluble in hydrocarbons. They are corrosive to metals and stable when stored in the original plastic container. They are strongly adsorbed to and inactivated rapidly by clay soils and anionic surfactants and can be decomposed by exposure to ultraviolet light [2].

Formulation

Paraquat is available for agricultural use as soluble liquid concentrate (SL), emulsifiable concentrate (EC), and soluble granule (SG) formulations. The SL and EC formulations typically contain 20–24% w/w paraquat ion, although novel generic formulations with higher concentrations have been developed. Granular formulations often

contain 5% or more paraquat ion with 50% formulations available.

The original SL product was an odorless red-brown liquid, which led to many cases of mistaken identification and unintentional fatal poisoning in the 1960s and 1970s [3, 4]. To reduce these poisonings, the formulation was changed in 1977 with the addition of a blue coloring agent, a stenching agent, and an emetic (phosphodiesterase inhibitor PP796). These additions are now part of the United Nations Food and Agriculture Organization's specifications for the herbicide. Unfortunately, there is little evidence that these measures improved outcome after ingestion, with vomiting being a common feature of fatal poisoning, although the coloring and stenching agents may have reduced the incidence of accidental poisoning [5].

There have been other more localized attempts to improve safety by changing formulations. The large number of fatal poisonings prompted Japanese authorities to replace the 24% SL paraquat product with a combined 5% paraquat/7% diquat SL product in 1986. Although this approach was intended to reduce the number of deaths [6], recent studies have shown no evidence that this change reduced fatality [7]. Instead, the number of deaths appears to have fallen in parallel with reduced importation [7]. A similar situation was observed in Samoa [8].

In 2004, Syngenta introduced a new Gramoxone INTEON formulation into Sri Lankan agricultural use. This product still contained 20% paraquat ion but also included an increased emetic concentration, a purgative, and an alginate that formed a gel under the acid conditions of the stomach, potentially slowing the absorption of paraquat and giving the emetic more time to be effective [9]. Unfortunately, the benefit after self-poisoning was modest with case fatality at 3 months falling from 73% to 63% in a large study of 586 patients (difference 9.5%; 95% confidence interval 2.0–17.1%; $p = 0.002$, log rank test) [10]. A further change in the INTEON formulation was introduced into Sri Lanka in 2006, with the active paraquat ingredient and surfactant sold in separate sachets. An ecological study reported the case fatality falling from 73% with the original formulation (297 patients from Dec 2003 to Sep 2004) to 65% with the first

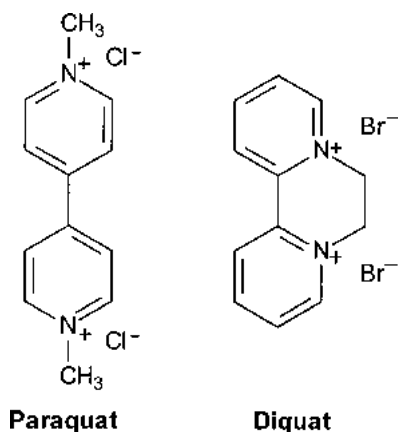


Fig. 1 Chemical structures of paraquat dichloride and diquat dibromide

INTEON formulation (398 patients from Oct 2004 to Jan 2006; $p = 0.008$, Kaplan-Meier) to 55% with the second INTEON formulation (533 patients from Sep 2006 to Sep 2008, $p = 0.001$, Kaplan-Meier) [11].

Diquat is formulated as an aqueous SL concentrate, containing 20% diquat dibromide, or as an SG product, containing 2.5–5% diquat. However, it is often co-formulated with other herbicides, especially paraquat, in areas where the latter is permitted.

Both paraquat and diquat can be purchased for home garden use in some countries as 0.2% liquid formulations.

Incidence of Human Poisoning

Far fewer reports of human poisoning and death due to diquat poisoning have been reported than due to paraquat poisoning [12, 13]. Paraquat is modestly more toxic than diquat; their respective acute rat oral LD50 values are 150 mg/kg (paraquat) and 231 mg/kg (diquat). Both compounds are classified as WHO Class II “moderately hazardous” pesticides [14].

The epidemiology of paraquat poisoning has changed markedly over the last 50 years. However, precise numbers are not known, in part because of the lack of a specific International Classification of Diseases (ICD) code for bipyridyl poisoning, the lack of standardized data collection by poison control centers, and the lack of national databases in countries where the problem is large [5].

The first reports of fatal paraquat poisoning occurred in industrialized countries following accidental ingestion of concentrated products decanted into drinking containers [3, 15, 16]. These incidents became much less common in industrialized countries after enforcement of legislation to prevent decanting of herbicide and changes in formulation to stop confusion with soft drinks. Nearly all deaths in industrialized countries now occur from intentional ingestion [5, 17, 18].

The introduction of pesticides into rural developing world homes with the Green Revolution resulted in a massive increase in pesticide-related suicides as nonfatal self-harm with low toxicity poisons was converted into lethal poisoning with the highly hazardous pesticides recently

introduced into agricultural practice [19]. Paraquat has one of the highest case fatalities of any pesticide after ingestion, with deaths occurring in over 60% of patients presenting to hospital [20] and practically all patients ingesting more than 20 mL of the 20% formulation [10]. Although in some locations, such as the Caribbean and South Pacific [8, 21, 22], paraquat became the main cause of pesticide-induced suicide throughout the 1980s and 1990s, the highly hazardous WHO Class I toxicity organophosphorus (OP) insecticides were probably responsible for the great majority of pesticide suicides globally [23, 24].

The situation may now be changing with ongoing bans of highly hazardous OP insecticides in the developing world, where they cannot practically be used or stored safely, and the increased manufacture, export, and use of paraquat in China [25–27] and India [28]. An increasing number of paraquat poisoning deaths in China [27] resulted in 20% aqueous SL formulations being withdrawn in 2012 with a complete ban planned for 2016. A ban of paraquat in South Korea in 2011 has resulted in a 37% reduction in pesticide-related suicides [29].

Occupational exposure has resulted in death as well as less-severe injury from sustained dermal exposure, especially due to leaking backpack sprayers [30, 31]. Accidental poisonings after drinking water from discarded paraquat bottles still occur [32].

Most cases of diquat poisoning have resulted from the intentional ingestion of concentrated solutions [13, 33], although deaths have occurred after ingestion of 1.2% dilute products [34] and 5% granular products. Accidental ingestion has occurred as a consequence of decanting diquat concentrates into soft drink bottles [35]. There have been no large case series of diquat-poisoned patients with which to accurately estimate case fatality. However, it is likely to be similar to related paraquat formulations, given the similar mechanism of action, animal data, and human case studies.

Level of Evidence

Much of the evidence for diagnosis and management comes from case reports and case series

(Level 3). Prediction of outcome based on plasma paraquat concentration has been derived from large case series [36–38] and the different formulae tested in a large independent data set ($n = 451$) [39]. There have been several RCTs of immunosuppression to prevent paraquat-induced lung fibrosis [40–42] and large prospective studies of the effects of introducing a new formulation [10]. Assessment of literature reports requires information on the plasma paraquat concentration, which is unfortunately often lacking, particularly with cases encountered prior to the mid-1970s [43].

Pharmacokinetics

There are few data on the pharmacokinetics of paraquat and diquat in humans. However, a population analysis for paraquat was recently performed in a cohort of 78 Sri Lankan patients [44]. This showed a two-compartment toxicokinetic model with first-order absorption and elimination. The apparent clearance, volume of distribution, and elimination half-life of paraquat were calculated as 1.17 L/h, 2.4 L/kg, and 87 h, respectively. Creatinine clearance was the most significant covariate to explain between-patient variability in clearance [44].

In rats, both herbicides are absorbed poorly from the gastrointestinal tract; approximately 1–5% of an oral dose is absorbed systemically, with most being excreted in the feces [12, 13, 45]. Paraquat appears to be absorbed poorly from the stomach, but facilitated absorption takes place in the small intestine. A linear relationship was noted between the plasma concentration of paraquat and the paraquat content of the rat small intestine, but not the stomach [46].

Of note, in dogs, a greater proportion of paraquat – about 45–65% – is absorbed, consistent with the greater susceptibility of dogs to oral paraquat poisoning [47]. Slowing passage from the stomach to the small bowel slowed absorption, indicating the lack of absorption from the stomach. Only modestly greater amounts of diquat were absorbed in dogs (10–20%) [47] compared to rats (1–5%).

The absorbed fraction of an oral paraquat or diquat dose absorbed by humans is not known. Although initially proposed to be similar to the small amounts absorbed in rat [48], Davies argued that human paraquat absorption in humans is more likely to be similar to dogs, with around 40% of the dose absorbed by 6 h [49]. There is little information regarding diquat absorption; however, the blood concentrations of paraquat and diquat were similar after ingestion of a combined product, suggesting similar absorption [50, 51].

Liquid formulations enter the small intestine rapidly, particularly if the stomach is empty. The time at which the plasma paraquat concentration peaks is not known in humans, but is 60–75 min in dogs [47]. The few studies performed in humans suggest that peak plasma concentrations are attained well within 4 h [36, 52].

When absorbed, paraquat and diquat distribute to most organs. The highest concentrations are found initially in the kidney and liver, and, for paraquat, the lungs [51, 52]. Several organs, including the lung and skeletal muscle, provide reservoirs for paraquat, which then slowly redistributes into the bloodstream. Neither herbicide is bound by plasma proteins.

Large amounts of absorbed paraquat and diquat are eliminated in the first few hours after ingestion via glomerular filtration, with some contribution from renal secretion [53, 54]. Most of the absorbed dose is excreted unchanged in the urine within the first 24 h of ingestion, even in patients who develop renal failure. As renal function deteriorates, clearance decreases, resulting in a dramatic slowing in the rate of decline of plasma concentrations. The terminal plasma half-life of both bipyridyls can then increase from less than 12 h to 120 h or longer. In the Sri Lankan toxicokinetic study of patients with moderate-severe paraquat poisoning described above, the apparent elimination half-life was estimated as 87 h [44]. Paraquat has been detected in the urine up to 3 months after ingestion, possibly from a deep body compartment reservoir (see above) [52].

A study of eight patients poisoned by a combined paraquat (5%) and diquat (7%) product showed lower serum diquat concentrations after 24 h, despite similar concentrations at 24 h after ingestion, indicating more rapid elimination of

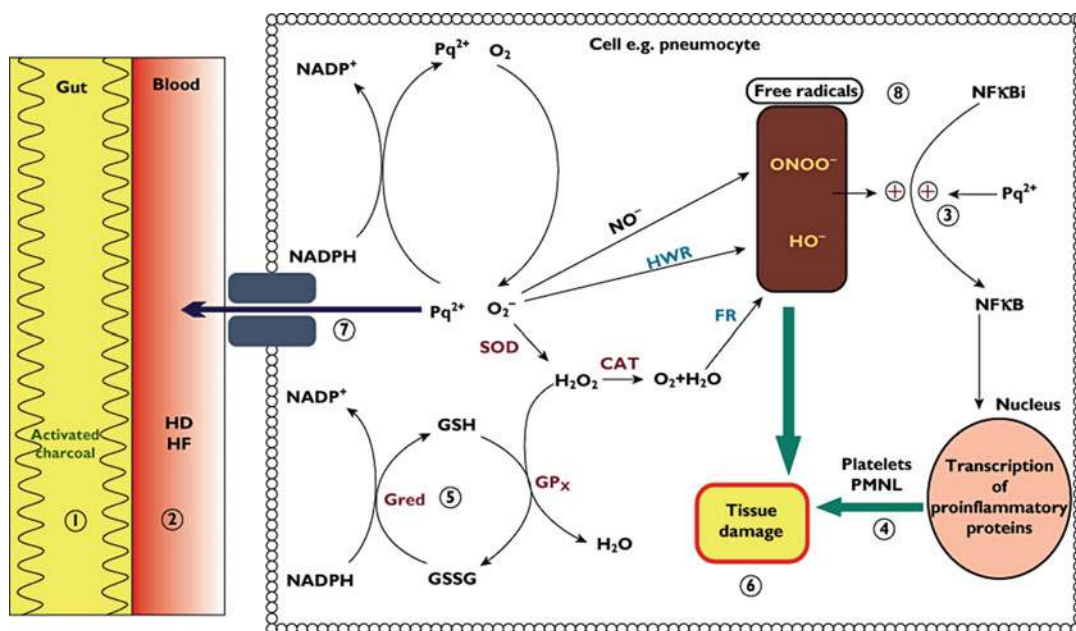


Fig. 2 Graphical representation of paraquat toxicity inside a pneumocyte and potential sites of antidotal therapy. *SOD* superoxide dismutase, *CAT* catalase, *Gred* glutathione reductase, *Gpx* glutathione peroxidase, *FR* Fenton reaction, *HWR* Haber-Weiss reaction. 1–8: potential sites

of action by available treatment options. 1, activated charcoal and Fuller's earth; 2, dialysis; 3, 4, 6 and 8, salicylates; 5 and 8, *N*-acetylcysteine; 7 (P-glycoprotein induction), dexamethasone; 4, immunosuppression (Taken with permission from Ref. [104])

diquat [51] (or alternatively metabolism of diquat to monopyridone and dipyridone [13]). Absorbed paraquat and, at a higher concentration, diquat have been detected in the bile, suggesting the presence of an enterohepatic circulation that may be of greater relevance in the elimination of diquat considering its more rapid elimination [51, 55].

Pathophysiology

Bipyridyl herbicide toxicity is associated with NADPH depletion [56] and lipid peroxidation [57]. Flavoenzymes, such as NADPH-cytochrome P-450 reductase, xanthine oxidase, and mitochondrial NADH-quinone oxidoreductase, initiate the single electron reduction of paraquat or diquat to form the free paraquat/diquat radical (Fig. 2) [58, 59]. This radical is unstable, transferring an electron to molecular oxygen to form a superoxide anion radical, which causes the observed systemic toxicity [12]. The resulting superoxide anion radicals

react with one another, forming hydrogen peroxide and molecular oxygen, a reaction that may occur spontaneously or via the enzyme superoxide dismutase. Under normal circumstances, hydrogen peroxide is detoxified by catalase and glutathione peroxidase. However, when these protective mechanisms are overwhelmed, cellular toxicity ensues. Paraquat, and to a lesser extent, diquat toxicity is enhanced by the administration of oxygen in a rat model [60]. Animal studies indicate that the bipyridyl herbicides may also exhibit direct mitochondrial toxicity [61].

The lung is the primary target organ of paraquat toxicity in humans and several animal species because of selective uptake and accumulation of paraquat by type I and type II alveolar epithelial cells and Clara cells [62]. In contrast, animal studies indicate that diquat does not accumulate in the lung and has a half-life in the lung five times shorter than that of paraquat [63]. Paraquat uptake into the lung occurs by a slow, energy-dependent active transport process, reaching concentrations that may be 50 times greater than those in plasma

[64, 65]. Animal studies indicate that pulmonary uptake is virtually complete by 6 h [66]. Human studies suggest that there may be efflux of paraquat from the lung back into the circulation [67].

Paraquat uptake occurs via a transporter for endogenous polyamines, including putrescine [65, 68]. The transport process appears to require the structural feature of two positively charged quaternary nitrogen ions separated by a distance of 0.6–0.7 nm. Paraquat and the polyamines, but not diquat, share these features. This may be reflected in the relative lack of pulmonary uptake of diquat [69].

Paraquat produces degenerative lesions in the lungs accompanied by biochemical and ultrastructural changes of the pulmonary capillary endothelium and damage to the alveolar epithelium [62, 70]. In rat models, paraquat stimulates the infiltration of profibroblasts, which mature into basophilic fibroblasts. The coalescence of fibroblast clumps and the destruction of alveolar walls destroy the architecture of the lung parenchyma, resulting in diffuse intra-alveolar fibrosis [71, 72].

Clinical Presentation

Local Toxicity

Skin. The surface epithelium of the skin is normally an effective barrier to these herbicides. Diluted for spraying, they are unlikely to cause serious poisoning via the skin [73, 74], unless soaked clothing is worn for prolonged periods, the spray apparatus leaks, or protective clothing is not worn [31, 75–78].

However, concentrated formulations are strong irritants, causing dermal erythema, blistering, ulceration, and dermatitis [12, 13, 79]. Systemic absorption can then occur causing respiratory and renal failure and death [79–82]. Full thickness burns of the feet, requiring skin grafting, followed leakage of diquat from a backpack sprayer into the applicator's boots [83]. Nail damage occurs after contact with concentrated diquat or paraquat [84–86].

Inhalation. Aerosolized droplets have diameters exceeding 5 μm and therefore do not reach the alveolar membrane to cause either direct or systemic toxicity via inhalation. The vapor pressure of paraquat and diquat is low, making vapor inhalation unlikely and inhalational exposure rarely lethal [74]. However, excessive inhalation of the spray during formulation, mixing, or application can cause epistaxis, stomatitis, headache, and sore throat [87, 88].

Eyes. Severe ocular inflammation may develop if the eyes are exposed to concentrated solutions [89–92]. Inflammation develops gradually, reaching a maximum after 12–24 h, and may progress to ulceration of the conjunctiva and cornea. Healing is slow, although recovery is typically complete.

Mucosa. Corrosive damage to the oral mucosa, leading to burning in the mouth and painful hemorrhagic ulceration of the oropharynx and esophagus, is a common early feature following ingestion of concentrated paraquat and diquat solutions [93, 94]. Extensive local damage, as well as severe systemic effects, have followed intravaginal application of diquat and paraquat solutions [95, 96].

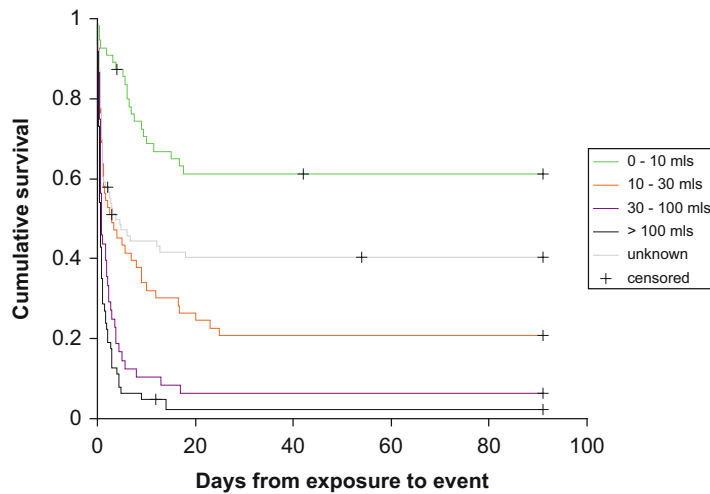
Systemic Toxicity

The severity of systemic toxicity is determined by the amount of diquat or paraquat absorbed. The vast majority of severe systemic poisonings and fatal cases have occurred after ingestion, although death has occurred after administration by parenteral injection [97, 98]. A dose-effect after ingestion is readily apparent (Fig. 3)

A grading system has been developed based on the amount of paraquat or diquat ingested (Box 1), separating toxicity into mild (grade 1), moderate-to-severe (grade 2), and acute fulminant poisoning (grade 3). Within 24 h of ingestion, patients with systemic poisoning develop lethargy, a widespread burning sensation, generalized weakness and myalgia, giddiness, headache, anorexia, and

Fig. 3 Effect of self-reported dose on outcome after paraquat poisoning.

Kaplan-Meier survival curves by ingestion amount in 297 patients who ingested the standard formulation of paraquat. A similar dose response was noted with the Inteon formulation (Taken with permission from Ref. [10])



fever. Fear and apprehension are prominent features, and restlessness is sometimes observed.

Box 1 Grading System for Toxicity Resulting from Ingestion of Bipyridyl Herbicides [13, 99, 100]	
Grade 1 Mild poisoning	After ingestion of <20 mg/kg paraquat ion or <50 mg/kg diquat ion In addition to gastrointestinal symptoms, acute kidney injury may occur together with, in paraquat poisoning, a transient decline in the gas transfer factor and vital capacity. Recovery is usual
Grade 2 Moderate-to-severe poisoning	After ingestion of 20–40 mg/kg paraquat ion or 50–200 mg/kg diquat ion Vomiting and diarrhea plus systemic features are seen. Multiple organ dysfunction is frequent, and acute renal failure in particular is common, but recovery may occur. Pulmonary fibrosis develops in all paraquat poisoning cases, but may resolve
Grade 3 Acute fulminant poisoning	After ingestion of >40 mg/kg paraquat ion or >200 mg/kg diquat ion Multiple organ failure develops and death occurs in most cases within 24–48 h

Gastrointestinal tract. Patients develop nausea, vomiting, abdominal pain, and diarrhea soon after ingestion as a result of local irritant action on the gut. In moderate-to-severe poisoning, a burning sensation, soreness, and pain in the mouth, throat, retrosternal area, and abdomen (usually epigastric, sometimes associated with guarding) are common [93, 99]. Severe and extensive inflammation and ulceration occur in the mouth, esophagus, stomach, and small intestine, with sloughing of the oropharyngeal mucosa, an inability to swallow saliva, dysphagia, and aphonia. Prominent pharyngeal membranes (“pseudodiphtheria”) occur [101]. Perforation of the esophagus may result in mediastinitis, surgical emphysema, and pneumothorax or pleural effusion in association with pleuritis [102, 103]. Ulceration usually heals in patients who survive.

Jaundice, hepatomegaly, and central abdominal pain due to pancreatitis are frequent complications [104]. At postmortem examination, centrilobular hepatic necrosis, bile duct injury, and cholestasis were observed [105, 106]. Raised serum transaminase and pancreatic enzyme activity is correlated with poor outcome [107, 108]; however, these rises can be mild and resolve spontaneously in less-severe poisoning [109].

Renal. Oliguric or nonoliguric renal failure may occur, usually due to acute tubular necrosis,

becoming evident after about 24 h [110–112]. Rarely, glomerular and tubular hemorrhage may be found [94]. In other cases, proximal tubular dysfunction may develop within 2–6 days and may progress to anuria. Hypovolemia, after sequestration of fluid in the gut, may also cause renal failure by reducing renal perfusion. Renal dysfunction commonly results in proteinuria, microscopic hematuria, glycosuria, aminoaciduria, phosphaturia, and excessive leaking of sodium and urate [111].

Pulmonary. Many patients develop a cough, which may be productive and blood-stained. Dyspnea is a prominent feature and occurs early in patients who have ingested substantial doses, particularly of paraquat, due to the development of adult respiratory distress syndrome and/or bronchopneumonia. Occasionally, pneumothorax (in association with mediastinitis), pleural effusion, and iatrogenic pulmonary edema may precipitate dyspnea [113]. In addition to a declining gas transfer factor and vital capacity, severely poisoned patients have a low and declining PO_2 with resultant central cyanosis. Radiologic changes do not always parallel the severity of clinical symptoms. The chest x-ray may be normal, particularly in patients dying early from multiple organ failure. Respiratory failure with need for mechanical ventilation may occur.

In patients less-severely poisoned by paraquat, the onset of dyspnea may occur later and be caused by pulmonary fibrosis. Patchy infiltration occurs on x-ray, which may progress to an opacification of one or both lung fields. Survivors of paraquat poisoning may recover normal pulmonary function or be left with a restrictive type of pulmonary dysfunction [114–116]. Such fibrosis has not been reported in diquat-poisoned patients.

Cardiovascular. Except for sinus tachycardia, cardiovascular complications are usually not observed until the terminal phase of poisoning. Ventricular tachycardia, intraventricular conduction disturbances, and nonspecific T-wave changes on electrocardiogram occur in the terminal phase. Sinus bradycardia, hypotension, and cardiac arrest may supervene. Chest x-ray may

show massive cardiomegaly, and at postmortem examination, toxic myocarditis and subendocardial hemorrhages have been found histologically [106].

Neurologic. Coma is a common terminal event in bipyridyl herbicide poisoning. Coma has been observed in association with brain stem infarction and pontine hemorrhage in diquat-poisoned patients [35, 117]. Convulsions and status epilepticus may occur in the terminal phase [118, 119] but are not common. Postmortem histology shows generalized brain oedema and hemorrhage [120]. A peripheral burning sensation has been reported to be a marker of poor prognosis and of higher plasma paraquat concentrations after paraquat poisoning [121].

Endocrine. At postmortem examination, adrenal cortical necrosis has been observed in patients who died with fulminant poisoning [122, 123]. Raised pancreatic enzymes are common in moderate-to-severe paraquat poisoning and are associated with poor outcome [108, 124].

Diagnosis

The diagnosis can usually be made based on the history, the local mucosal damage seen in the mouth after ingestion, and the ensuing characteristic organ damage. However, occult paraquat poisoning may present with only lung fibrosis [125].

The diagnosis of paraquat or diquat poisoning should be confirmed with laboratory analyses of urine or serum. A qualitative urine test should be performed with alkaline sodium dithionite (Box 2) [126–129]. The presence of paraquat turns the mixture blue while diquat turns it blue-green or yellow-green. It is important to ensure that negative and positive controls are analyzed with each patient specimen. There are no common false positives in these patients. Failure of the test is usually due to the use of sodium dithionite that has oxidized on storage [129]. The test has some prognostic value: in urine taken within 24 h of poisoning, concentrations less than 1 mg/L (no color to light blue) generally predict survival,

while those >1 mg/L (navy blue to dark blue) generally predict a poor outcome [38]. A negative test does not exclude the possibility of bipyridyl ingestion; repeated urine tests are suggested over the next 6 h. Plasma can also be tested for paraquat using sodium dithionite [130].

Quantitative methods of analysis in biologic fluids include spectrophotometry, ion-exchange chromatography, gas chromatography, and radioimmunoassay [129]. The serum paraquat concentration can be compared against a nomogram to predict outcome with good accuracy, especially for death (Fig. 4) [36, 37]. At serum paraquat concentrations expected in overdose (i.e., up to 10 mg/L), little interference occurs with laboratory tests. At higher serum paraquat concentrations, false elevations of creatinine and lactate dehydrogenase may occur when analyzed with the Jaffe reaction [131, 132].

At present, there are insufficient data to allow accurate determination of prognosis based on the admission plasma concentration following diquat poisoning [13]. A diquat-poisoning nomogram has not been developed.

Box 2

Ten mL of urine should be added to 1 mL of a 1% solution of 2 N sodium dithionite in 1 N sodium hydroxide. A blue color (λ maximum 603 nm) indicates paraquat while a blue-green color (λ maximum 603 nm) suggests diquat [126, 129]. The presence of both paraquat and diquat complicates measurement the concentration of either.

Prognosis

The quantity of paraquat in the specific herbicidal preparation and the volume ingested (one mouthful of a 20% solution is life-threatening) should be confirmed by examination of the container and contents if possible. There is a direct correlation

between the quantity of paraquat ingested and outcome (Fig. 3) [10]. In patients who claim to have had only dermal, inhalational, or ocular contact, it is important to determine whether ingestion has also occurred, as this affects exposure dose and, therefore, prognosis.

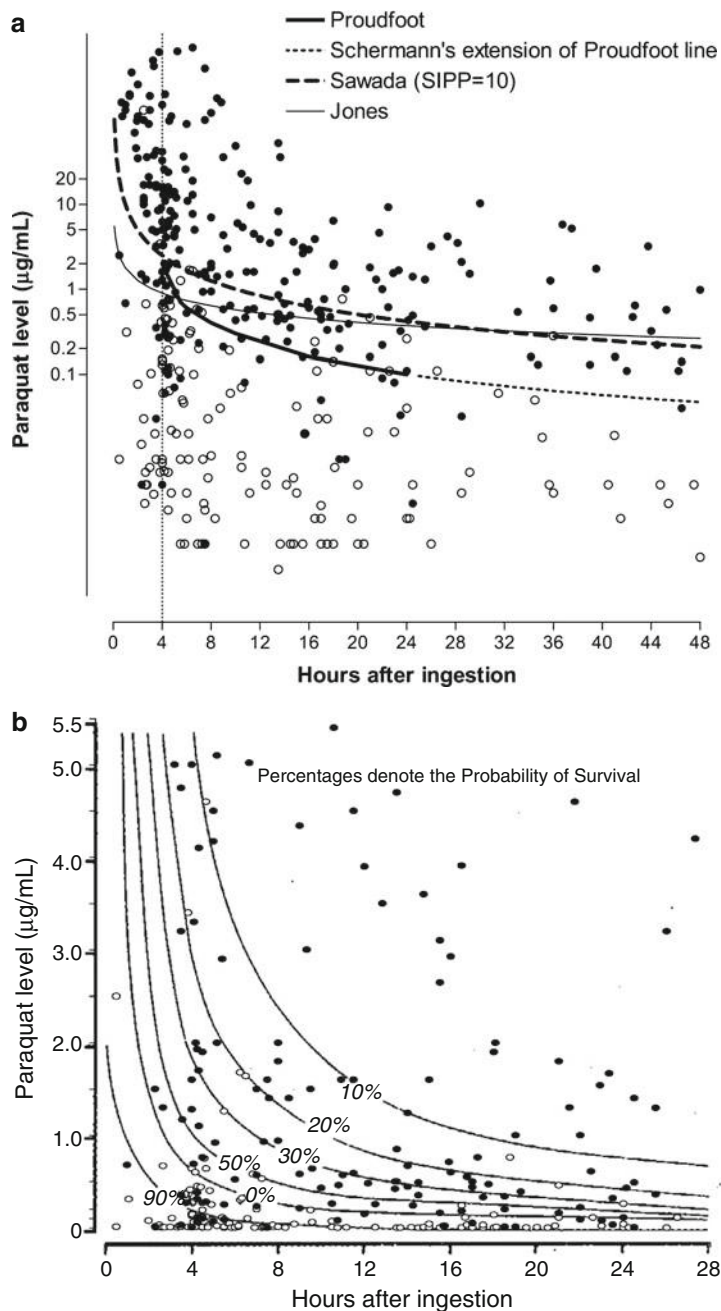
Bismuth and colleagues first identified several factors that predict severe toxicity. In particular, it was noted that the ingestion of concentrated solution on an empty stomach, the occurrence of esophageal and gastric mucosal lesions, and the development of renal failure were predictive of poor outcome [93]. There have since been multiple reports proposing markers of poor prognosis. Many of these have been based on plasma paraquat concentrations and therefore need time and a high-level analytical laboratory [41]. Others have proposed the use of relatively simple laboratory tests, such as serum creatinine or transaminase [74, 107, 133], pancreatic enzymes [108], arterial blood gases [134, 135], lactate [136–138], or critical care scores such as APACHE and MSAPS II [139, 140] to predict prognosis. Unfortunately, none of these systems have been systematically validated or compared in large prospective cohorts.

Measurement of plasma paraquat concentration correlates well with outcome within 24 h of exposure [36, 37, 38]. Prognosis can be determined from a nomogram which relates the initial plasma paraquat concentration and the time after ingestion to the probability of survival. Five different prediction methods had been published by 2009 [36–38, 135, 141], but none had been validated or compared with another in an independent prospective cohort. These methods were then compared using data from a prospective cohort of 451 Sri Lankan patients for whom admission plasma paraquat concentrations and outcome were obtained (Fig. 4) [39]. All methods showed comparable performance, with positive predictive values of 0.92–0.96 but lower negative predictive values between 0.59 and 0.73. All five published methods better predicted death than survival [39].

Concentrations of paraquat in urine obtained within the first 24 h of ingestion have also been used to determine prognosis [39]. Of 53 patients

Fig. 4 Paraquat nomograms and outcome.

(a) Paraquat concentrations and outcome of patients with paraquat poisoning using Jones, Proudfoot, Scherrmann, and Sawada prediction lines. All methods predicted that those patients with plasma paraquat concentrations above the lines were more likely to die than survive (*filled bullet* = fatality, *empty bullet* = survivor). (b) Paraquat concentrations and outcome from 277 patients with paraquat poisoning compared with the probability of survival estimated by Hart's nomogram (Taken with permission from Ref. [39])



with urinary concentrations of paraquat of less than 1 mg/L within the first 24 h, 15 survived. In patients who died within 24 h, the urinary paraquat concentrations were 10–10,000 mg/L, and in patients who died later from pulmonary fibrosis, the urinary paraquat concentrations were 1–1000 mg/L.

Treatment

Current treatment of paraquat or diquat intoxication is largely ineffective [43, 99, 104, 142]. In addition to providing supportive care, management involves attempting to remove the chemicals

from the gastrointestinal tract before absorption, increasing their excretion from the blood, and decreasing subsequent tissue damage (Fig. 2). Patients topically exposed to paraquat via the skin or eyes should have all sites of contact extensively irrigated with water.

Resuscitation and Supportive Care

With currently available treatments, the prognosis for critically ill paraquat-poisoned patients is extremely poor. Once the diagnosis is confirmed, management should focus on keeping patients comfortable and providing pain relief. Intensive care will not change the outcome; there is no indication for intubation in the acute situation, unless coma and respiratory failure might be due to a co-ingestion. However, due to the absence of pulmonary lesions, some critically ill diquat poisoned patients have been successfully managed with intensive care measures.

Hypoxemia should be treated conservatively due to animal studies suggesting that a high FiO_2 can exacerbate formation of oxygen-free radicals and thereby extend lung injury [60]. Standard practice is to reserve oxygen for patients with distressing hypoxia and dyspnea [104].

Patients are often dehydrated due to gastrointestinal fluid losses. This should be corrected with fluid resuscitation to maximize elimination before the development of tubular necrosis.

The severe pain of local ulceration is difficult to treat. Mouthwashes, ice-cold fluids and ice cream, local anesthetic sprays, and lozenges have been used with some success. Opiates, sometimes with benzodiazepines, are required in many patients to relieve general and local pain.

Gastric Lavage or Emesis

Early vomiting is common after significant bipyridyl ingestion [93, 142], meaning that the stomach is likely to be empty by the time a patient presents to hospital. Absorption of the herbicides from the small bowel is also rapid. This suggests that neither gastric lavage nor

forced emesis on presentation to hospital is likely to offer benefit.

There is no evidence that gastric lavage is clinically effective [99, 142]. Paraquat's corrosive effects risk esophageal perforation during passage of a lavage tube [143], especially if it is delayed more than 1–2 h. Large-bore lavage tubes are therefore contraindicated. There is no evidence that induced emesis after paraquat or diquat ingestion offers clinical benefit [142].

Oral Adsorbents

There is no clear evidence for clinical benefit from the use of oral adsorbents.

Investigation of a range of soils in the 1960s showed that montmorillonite bound strongly to paraquat and that bentonite (sodium montmorillonite) and Fuller's Earth (calcium montmorillonite) were particularly effective [144]. Single [145] or repeated [46] doses reduced mortality in rats even if given after a potentially lethal dose of paraquat.

Smith and colleagues recommended the use of these soils for treating patients [46]. Fuller's Earth is preferred, and still widely used, because it can be administered as a 15% (w/v) suspension, whereas bentonite swells in water and can be used only as a 7% solution. However, the use of these soils in poisoned patients has not met with the success of animal experiments. In two studies, Fuller's Earth was used for 72 patients [146, 147]; however, survivors had generally taken a nonlethal dose and neither publication reported any benefit. Although the initial 1971 study by Clark suggested that activated charcoal was ineffective [145], this has been disputed [148]. Activated charcoal is now also widely recommended for bipyridinium-poisoned patients.

A single dose of adsorbent should be administered to all patients at first presentation to medical care. (Grade III recommendation). It is possible that a small number of patients may benefit from a resulting modest decrease in absorbed dose.

Extracorporeal Removal

Hemoperfusion is used routinely in many East Asian centers for treatment of paraquat poisoning [149–151]. Paraquat clearance is similar for the kidney and hemoperfusion; the latter becomes comparatively more effective as renal function fails after several hours [152]. Hemoperfusion is more efficacious than hemodialysis [153]. However, no large-scale, high-quality RCTs have been performed to assess the effectiveness of hemoperfusion versus no extracorporeal removal. In all large series, hemoperfusion, with or without the addition of hemodialysis, did not improve the prognosis of paraquat poisoning when plasma concentrations were above the nomogram. There is a negative correlation between the amount of paraquat eliminated and the time of death: the larger the body burden of paraquat, the larger the amount of paraquat removed from the blood, and the greater the probability of early death [154].

Two studies have compared hemoperfusion alone with hemoperfusion followed by continuous veno-venous hemofiltration (CVVH) [155, 156]. Both found that the addition of hemofiltration increased the time until death (from 2.5 to 5 days, and from 5.1 to 8.6 days); however, the absolute mortality did not differ between groups since patients seemed to be shifted from the fulminant group to the still often fatal moderate-to-severe group (grade II evidence).

Gawarammana and Buckley [104] have argued that hemoperfusion or CVVH cannot reduce mortality since dog studies [157] indicate that it needs to be started within 2 h of ingestion to reduce uptake into the lung and prevent lung fibrosis (Fig. 5). In addition, paraquat renal clearance is excellent in the first 6 h post-ingestion, making it unlikely that a modest contribution from hemoperfusion will be clinically significant.

Diquat is cleared from the blood by hemoperfusion at similar rates to paraquat [153]. However, there remains a lack of evidence for effectiveness and a theoretical need to initiate treatment before distribution to tissues. The potential for cerebral hemorrhage dictates the cautious use of heparin during hemoperfusion.

Antidotes and Specific Treatments

Pharmacologic intervention in paraquat poisoning has not been successful [158]. Many agents reduce paraquat uptake into lung in vitro but fail to show protection in vivo [159, 160]. Antioxidants such as superoxide dismutase, selenium, salicylate, acetylcysteine, and vitamin C have been studied in animals and human cases without any clear evidence of benefit [104, 158, 161].

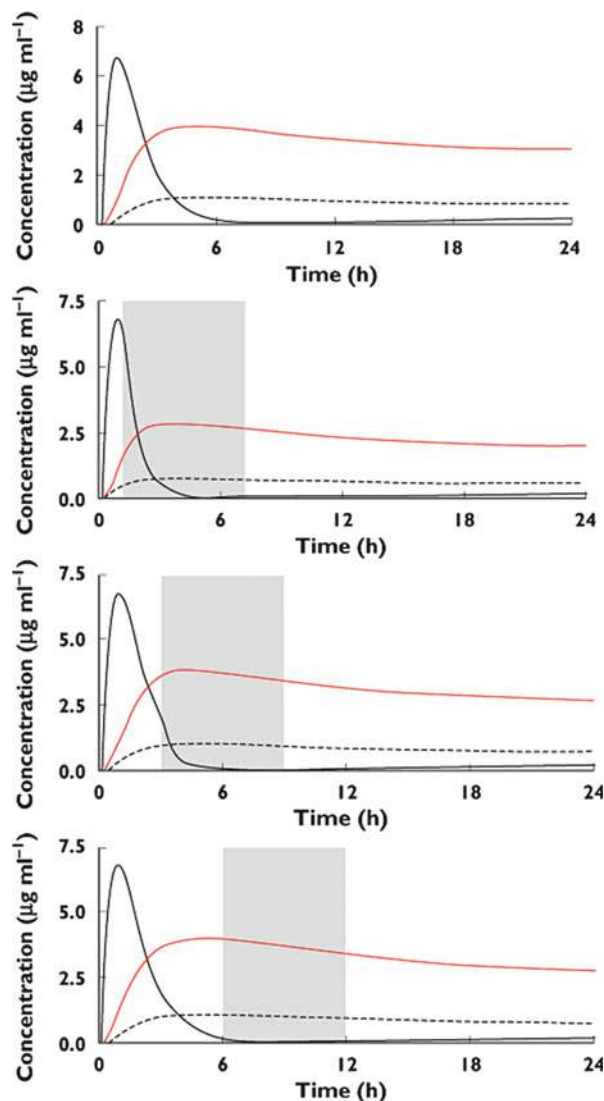
There is no antidote for diquat or paraquat poisoning [43]. Immunotherapy with paraquat specific antibodies or Fab fragments has been proposed and tested in animals. These tests showed that although the antibodies increased the concentration of paraquat in the plasma, they did not reduce tissue accumulation and were therefore unlikely to affect mortality [162, 163].

Prevention of Lung Fibrosis

The use of immunosuppressive therapy to prevent lung fibrosis was first proposed in 1971 [16]. Since then multiple immunosuppressive and anti-inflammatory drugs, such as azathioprine, beclomethasone, bleomycin, cyclophosphamide, and fluorouracil and fibrinolytics, such as potassium aminobenzoate, have been used with no clear evidence of benefit [158].

A regimen of intravenous cyclophosphamide followed by dexamethasone was advocated by Malone [16] then by Addo [143], although review of the data does not suggest clear benefit [41]. A Taiwanese group then combined intravenous cyclophosphamide with methylprednisolone, followed by oral dexamethasone. A small RCT reported benefit in moderate-to-severe paraquat poisoning (survival 43% [12/28] with standard care versus 72% [18/22; $p = 0.008$] with the immunosuppression) [40, 164]. However, the study was not analyzed on an intention-to-treat basis – such an intention-to-treat analysis did not show effectiveness [165]. Additional small trials have been performed; a Cochrane review of three studies including 164 patients reported that cyclophosphamide and corticosteroids might benefit patients [166]. A retrospective observational

Fig. 5 Modeling of hemodialysis efficacy by time post-ingestion. A model of the time-dependent effect of hemodialysis on plasma (black line), tissue (dashed line), and lung (red line) paraquat concentrations. It should be noted that there is minimal reduction in lung concentrations when instituted at 3 or 6 h post-ingestion (parameters from model developed by Pond et al. [157]) (Taken with permission from Ref. [104])



national study from Taiwan using insurance data has suggested that introduction of combined immunosuppression and hemoperfusion into clinical practice resulted in increased survival [167].

A Sri Lankan RCT directly compared intravenous cyclophosphamide and methylprednisolone, followed by oral dexamethasone, with placebo ($n = 299$ patients) and found no difference in mortality (Grade 1 evidence) [42]. Of interest, a post hoc analysis did suggest a small benefit during the 2-week course of dexamethasone that needs to be tested in a further RCT.

Treatment to inhibit fibroblastic proliferation such as lung irradiation [168–171] or drug therapy, with, for example, colchicine or collagen synthesis inhibitors, has been proposed without evidence of clinical benefit [172, 173]. Lung transplantation has been performed to treat fibrosis. However, the persistence of paraquat in the body often results in fatal redevelopment of paraquat toxicity in the transplanted lung; fatal complications of transplantation have also been reported [174–177].

Special Populations

Pediatric Patients

The clinical picture in paraquat-poisoned children [4, 15, 178–182] is similar to that in adults with early vomiting, corrosive effects on the oropharynx, and multi-organ failure or lung fibrosis, depending on dose. There are few reports of diquat poisoning in children [35, 183]. Children rarely provide a history of ingestion or are unable to identify of the liquid ingested (sometimes concentrated solution decanted into unmarked containers [4, 15, 184]), making diagnosis difficult [184]. The diagnosis may also be delayed because of a relatively symptom-free period that occurs after the initial vomiting. This delay can be avoided if a method for rapid detection of paraquat and diquat in gastric aspirate and urine is employed when the nature of the ingested fluid is not known [129].

Pregnant Patients

Maternal and fetal deaths have occurred after ingestion of concentrated paraquat [185–187]. Even emergent cesarean section did not save the fetus [187]. In two cases, the fetuses died while the mothers survived; one survivor later had a normal pregnancy, showing no evidence of teratogenicity from the earlier exposure [187]. There have been cases of survival of pregnant women after paraquat ingestion with delivery of a normal child at term [188–190]. In one case, the child developed acute lung injury from paraquat that remained present at 10 months of age [191]. Maternal, fetal, and cord blood paraquat concentrations in one fatal case showed that paraquat crossed the placenta and was concentrated in fetal blood to levels four to six times greater than in maternal blood [187]. Amniocentesis revealed amniotic fluid paraquat concentrations nearly twice that of maternal blood in a second case [187], while breast milk contained paraquat in a third case [192].

Elderly Patients

There is no published scientific experience specifically with paraquat poisoning in the elderly.

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Pesticides and grain fumigants play an important part in the development of agriculture and enhance grain production in the world. Their use has led to improved quantity and better quality of crops, resulting in better availability of food grains to the population. Despite these benefits, the increased availability of pesticides and grain fumigants has led to them being misused as agents of self-harm [1, 2].

Pesticides are compounds used to control pests. Fumigants are pesticides mainly used to control rodents, insects, weed seeds, and fungi, typically where the grain is stored, as in silos or stores [3]. They are extensively used to protect grain during the transport in ships, containers, or railcars. Fumigants comprise a diverse group of compounds and exist in solid (aluminum phosphide), liquid (formaldehyde), and gaseous (ethylene oxide) forms [4]. Exposure to grain fumigants is generally accidental or suicidal. Being heavier than air, the gaseous forms tend to settle near the surface of the ground, resulting in potential exposure of unprotected workers walking in the store or silo. This chapter summarizes the potential adverse effects of phosphine and metal phosphides.

Phosphides (aluminum, zinc, calcium, and magnesium) are used worldwide as grain fumigants and rodenticides. These agents are highly efficacious in killing rodents and insects. They are inexpensive and simple to manufacture. Major advantages of metal phosphides are that they do not leave behind any toxic residue, and have no

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adverse effect on the seed viability [4]. Phosphides are mixed with grains during storage in prefixed ratios. The moisture in the grain reacts with phosphides to release phosphine (PH_3) gas. Phosphine acts rapidly and kills the pests without leaving toxic traces on the grain. Any remaining residues are easily washed away with water before the grain is used for consumption.

History

The majority of deaths attributed to phosphides in the first 50 years of the twentieth century were due to accidental exposure to phosphine. Prior to 1980, aluminum phosphide (ALP) was not registered in India as a major self-harm agent. The first large series describing the human health hazards of toxic exposure to aluminum phosphide came from Northern India in 1985 [1, 5]. Following this, there was an explosion of reports from different areas of India, predominantly the northwest and central areas of the country [5–10]. Cases are now reported with increasing frequency from other parts of the world, especially Sri Lanka, Iran, Jordan, and Morocco [11–13]. Reports of poisonings from developed countries are uncommon and are mostly accidental [14, 15]. Recently, accidental exposure to phosphine gas has been reported from Middle Eastern countries due to inadvertent use of metal phosphides as pest control agents in the home [16]. There is also potential of these agents being used as chemical warfare agents or in terrorist attacks [17].

Physical Properties

Aluminum phosphide is available as greenish-gray tablet of 3 g which contains 56% aluminum phosphide and 44% ammonium carbonate. Some preparations such as Sanphos contain 5% ammonium carbonate and 40% inert ingredients. It is also formulated as pellets, granules, and as dust. Since late 1990s, ALP has been marketed in India mainly as granulated powder in plastic pouches [10 g] as Celphos. This has resulted in marked decrease in the mortality of ALP ingestion [1].

The toxicity of ALP is due to the release of phosphine (PH_3) when it comes in contact with moisture or gastric hydrochloric acid. Pure phosphine is a colorless and odorless gas. Authors have reported a “decaying fishlike” odor at phosphine concentrations of only two parts per million (ppm) [18, 19]. Zaebs et al. reported olfactory fatigue in workers habituated to working in an environment with phosphine concentrations as high as 50 ppm for several minutes [20]. Garlic-like odor is attributed to impurities such as substituted phosphines, diphosphines, and arsine.

Phosphine is flammable and spontaneous ignition of some tablet forms in air has been attributed to aluminum oxide and diphosphine gas [21–23]. There has been one published case report of spontaneous ignition of phosphine during gastric lavage [24]. However, cases of spontaneous ignition or illness in health-care workers due to secondary exposure to phosphine while managing patients in emergency departments of intensive care units has not been reported from other centers.

Zinc phosphide, widely used as rodenticide in Southeast Asia, is available as a dark gray powder or crystals with a rotting fishlike odor [4]. It is commonly mixed with wheat flour and made into small pellets for use as rodent bait. Calcium phosphide is available as a reddish-brown powder [25]. It is not readily available from commercial sources.

A standard 3 g tablet of ALP liberates approximately 1 g of phosphine gas. The remaining aluminum hydroxide residue is nontoxic [25, 26]. The release of phosphine from these tablets is even more vigorous when they come in contact with an aqueous acid, such as the hydrochloric acid present in the stomach [4].

Toxicokinetics

The majority of reported exposures between 1900 and 1960 were accidental, with inhalation being the most common exposure route [27]. The most common route of exposure today is ingestion when the phosphides are used as agents for self-harm. Some phosphine is liberated the moment

the phosphide contacts moisture in the oral cavity. However, the majority of phosphine is released upon reaching the acidic stomach juices [26, 28].

Granules or the powder form of aluminum phosphide is usually ingested in suicide attempts after dissolving in water or other liquid. This results in immediate release of phosphine to the atmosphere leaving very little in the liquid. This may be an important factor in the apparently decreased toxicity of powder and granular formulations [1].

Once released, phosphine is rapidly absorbed from the mucous membranes in the gastrointestinal tract. The highly soluble compound is widely distributed to all organs [25]. When inhaled, it is readily absorbed from the respiratory mucosa. Dermal and ocular absorption has also been reported, though to a much smaller extent [25]. After ingestion, phosphine is readily exhaled and can be detected on the breath. It can also be detected in the blood and liver [29, 30]. In an autopsy study, phosphine was detected in the lungs and gastrointestinal tract at autopsy [31].

If gastric lavage is performed on suicide victims, phosphine gas may escape and may not be detected in a lavage sample. One may be able to detect nontoxic aluminum hydroxide as a clue to the ingested agent, though aluminum hydroxide is also present in some antacid preparations. In urine, hypophosphite, phosphate, and phosphite may be detected as phosphine degradation products [32].

Pathophysiology and Toxicodynamics

Phosphine is a cellular toxin, not unlike cyanide. The exact mechanism by which phosphine acts is not clear. Nakakita et al. [33] found that oxygen uptake in isolated rat liver mitochondria was inhibited by the presence of phosphine. Phosphine also inhibited adenosine diphosphate uncoupler and ion-stimulated respiration, but the exact target site was not identified. In a later detailed study [34], phosphine was found to be strong inhibitor of mitochondrial respiration in both the active (state-3) and resting (state-4) states in mouse liver, housefly flight muscles, granary weevils,

and beef heart. It was found to inhibit uncoupled site and ion pumping state affecting pyruvate, malate, succinate, glycerophosphate, and ascorbate cytochrome substrates. The effect was maximal on liver mitochondria, but intermediate in beef heart. This inhibition could not be reversed, suggesting that it is due to a direct effect on electron transport, which is the electrochemical link between respiration and oxidative phosphorylation in mitochondria. The spectral and dichroism studies revealed an interaction with the heme moiety of cytochrome oxidase (cytochrome c), but it has not yet been determined whether it interacts with either cytochrome a, a₃, or both (Fig. 1). In a study [35] involving three species of stored beetles, insect catalase, and not the cytochrome c oxidase system, was found to be inhibited. In an experimental study where parameters of energy metabolism and oxidative stress were measured in rat brain and liver after administration of ALP at the LD₅₀ dose (i.e., 10 mg/kg body weight), it was found that cytochrome c oxidase activity in platelets was inhibited in a concentration-dependant manner. Adenosine triphosphate (ATP) synthesis was found to be decreased, with a corresponding marked decrease in ATP concentrations in both the liver and brain. The activity of succinic dehydrogenase and NADH dehydrogenase were markedly lower. Liver glycogen content was depleted and the activity of glycolytic enzymes was increased. The activity of glucose-6-phosphate dehydrogenase was decreased in both organs. The results suggest that inhibition of cytochrome oxidase disturbs electron transport, leading to impaired energy production [36, 37]. The noncompetitive inhibition of cytochrome c oxidase results in tissue hypoxia and metabolic acidosis [36, 38].

Phosphine causes generation of highly reactive free radicals by inhibiting catalases, inducing superoxide dismutase, and decreasing glutathione concentration. The result is widespread damage to cellular membranes due to lipid peroxidation and protein denaturation [39, 40]. This damage then interferes with protein synthesis and enzymatic function leading to organ failure [5].

Recent studies indicate that various organs are affected in different ways [41]. When inhaled,

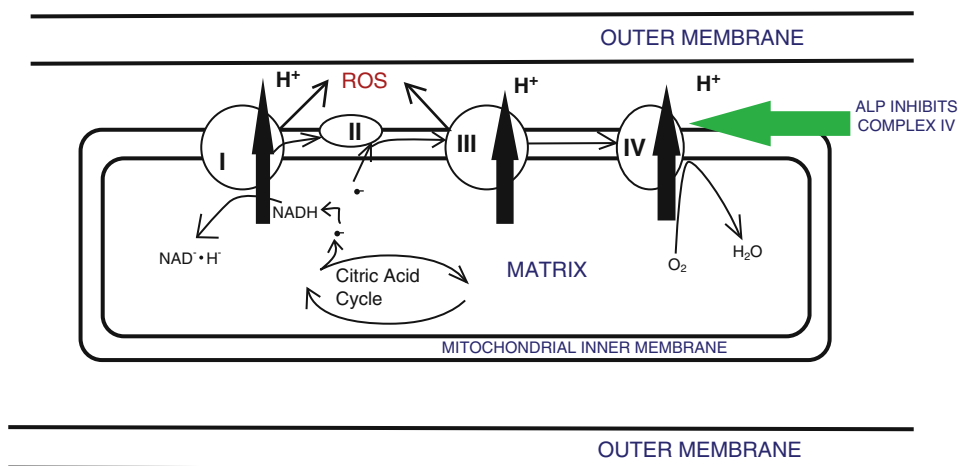


Fig. 1 Inhibition of mitochondrial respiration by ALP (From [http://medcraveonline.com/JACCOA/images\(Figure/JACCOA-02-00068-g001.png](http://medcraveonline.com/JACCOA/images(Figure/JACCOA-02-00068-g001.png) under a Creative Commons licence)

phosphine causes direct alveolar damage resulting in acute respiratory distress syndrome (ARDS) [5, 32]. There is also evidence suggesting diffuse endothelial dysfunction leading to systemic capillary leak characterized by ascites, as well as pleural and pericardial effusion [42].

Toxic Dose

Significant toxicity can result from relatively small doses of phosphine gas. The US National Institute of Occupational Safety and Health recommended safe level of occupational exposure to phosphine gas at the workplace is less than 0.3 ppm for up to 10 h per day [43]. At a concentration of 50 ppm there is an immediate threat to life, and exposure to 600 ppm for 30 min could be lethal [44].

Death has been reported following ingestion of as little as 4 g of zinc phosphide or 500 mg of aluminum phosphide [45].

Clinical Presentation

The clinical features of toxic metal phosphide exposure depend on the route, the dose, and the interval between ingestion and presentation [5, 45]. In many countries such as India,

attempting to harm oneself is illegal, leading to concealment of information about dose, the nature of the ingestion, and the elapsed time since exposure. Since most suicidal victims are adolescent females, it is necessary to maintain a high index of suspicion with this demographic [1].

Inhalation of phosphine is a difficult clinical diagnosis, although the smell of rotten eggs or a garlic-like odor may be an important clue [15]. However, these findings are frequently either absent or missed in a busy emergency department. Patients commonly report cough and breathlessness secondary to airway irritation [26], gastrointestinal symptoms, chest tightness, dizziness, diplopia, weakness, paresthesias, and tremors [2, 26].

The clinical effects of metal phosphide ingestion are summarized in Table 1. Almost all patients develop nausea, vomiting, retrosternal burning, and epigastric discomfort, which are also the most common clinical manifestations after inhalation. In significant poisoning, gastrointestinal manifestations are severe, and refractory hypotension, tachypnea, and shock invariably develop within 30 min to 2 h [4–8, 10]. Signs of sympathetic excess, such as sweating and tachycardia, are commonly observed. Cardiac dysrhythmias are a hallmark of metal phosphide poisoning and are typically fatal. Several electrocardiographic abnormalities have been reported

Table 1 Clinical features of phosphide poisoning

Following ingestion
Gastrointestinal: nausea, vomiting, epigastric discomfort, retrosternal burning, diarrhea
Cardiovascular: hypotension, shock, arrhythmias
Respiratory: tachypnea, cyanosis, adult respiratory distress syndrome
Hepatic: tender hepatomegaly, jaundice, elevated transaminases
Renal: oliguria, acute renal failure
Central nervous system: altered sensorium, restlessness, coma
Metabolic: metabolic acidosis, hypomagnesemia, hypermagnesemia, hypokalemia
Following inhalation
Chest tightness, cough, shortness of breath, and pulmonary edema if severe exposure

Table 2 Electrocardiographic changes in phosphide poisoning

Arrhythmias: sinus tachycardia, bradycardia, supraventricular ectopics, ventricular ectopics, atrial fibrillation, ventricular fibrillation
Conduction defects: wide QRS complex, A-V conduction defects, bundle branch block, complete heart block
ST-T changes: ST depression, ST elevation, T-wave changes

(Table 2). Oliguria develops in approximately half of metal phosphide poisoning cases. Adult respiratory distress syndrome commonly develops in severely hypotensive patients.

Following poisoning by a phosphide, restlessness, anxiety, and dizziness are expected, but sensory symptoms (e.g., paresthesias, numbness) and ataxia are not commonly reported. The sensorium is initially normal in most patients, until hypoxia supervenes resulting in altered mentation and delirium [5–7]. Seizures and deep coma are usually secondary to severe hypoxia. Acute kidney injury is caused by severe hypotension and typically presents clinically with a prerenal picture [5].

If the patient survives the shock phase, signs of capillary leak including ascites, pleural effusion, and ARDS may develop [42]. Other complications include disseminated intravascular coagulation, intravascular hemolysis, gastrointestinal

bleeding, fulminant hepatic failure, congestive heart failure, and, rarely, pericarditis [7, 26].

The outcome of patients poisoned by phosphides correlates best with the number of vomiting episodes after ingestion and severity of the patient’s hypotension and acidosis [46]. Theoretically, removal of as much of the tablets/granules as possible may help in reducing the toxic after ingestion. However, there is no data to support or refute the improved outcomes after gastric lavage in patients with phosphide ingestion.

The majority of deaths occur within the first 12–24 h after ingestion and are usually due to refractory hypotension and dysrhythmias. Deaths occurring more than 24 h after exposure are likely related to ARDS, liver failure, renal failure, or other complications [46].

Prolonged hypotension and hypoxia result in diffuse cellular damage in various organs. Reported autopsy findings include diffuse congestion of the liver, spleen, kidneys, adrenal glands, gastrointestinal tract, and brain, which correlate with the severity of hypotension. No specific changes are observed on histopathologic examination beyond visceral congestion, patchy liver necrosis, and neuronal injury in the brain [46].

Diagnosis

The following features, either alone or in combination, are of assistance in the diagnosis of metal phosphide toxicity:

1. History of ingestion
2. Symptoms and signs compatible with aluminum phosphide ingestion
 - (a) Mainly emesis with vomitus smelling like decaying fish or garlic
 - (b) Severe hypotension or shock
 - (c) Metabolic acidosis
 - (d) Abnormalities in cardiac rate or rhythm

The triad of hypotension, severe metabolic acidosis, and a garlicky odor on the breath should put this diagnosis high on the differential. Although the patient may be mentally clear immediately after ingestion, delay in accessing a health-care

facility may result in altered mental status by the time of presentation. Thus, mental status alone cannot be relied upon as an important clue for clinical diagnosis.

The diagnosis of phosphide exposure can be confirmed through detection of phosphine in exhaled air or stomach aspirate using the silver nitrate test. In this test, diluted gastric contents are heated in a flask and a strip of filter paper impregnated with freshly prepared silver nitrate is held near the flask mouth. The presence of phosphine in the fume turns the filter paper black [47]. While this test can also be performed by having the patient exhale into the silver nitrate paper, the results are not reliable. A false-negative result may occur in patients receiving supplemental oxygen due to phosphine being converted to phosphorus pentoxide; a false-positive result may occur in the presence of hydrogen sulfide in the air [48, 49].

Neither phosphine nor its metabolites can be reliably detected in urine or blood [49]. While breath phosphine can be detected using phosphine detector tubes, gas chromatography with nitrogen–phosphorus detection (GC-NPD) is usually recommended [50, 51]. The gold standard for phosphine detection is GC-NPD, but performing this analysis is often cost prohibitive in developing countries [51].

For spot sampling of phosphine in air, detector tubes and bulbs can be used and are important tools for the investigation of air quality at the site of accident/incident.

In a suspected case of poisoning, initial investigations should also be aimed at detecting organ system dysfunction. Chest X-ray and electrocardiogram are done to rule out dysrhythmias, aspiration, and ARDS. Electrocardiographic abnormalities are varied and nonspecific. They range from tachycardia, nonspecific ST and T-wave changes, and conduction abnormalities [7, 52, 53]. Atrial flutter and fibrillation and ventricular tachycardia and fibrillation are commonly observed dysrhythmias [54].

Echocardiography may reveal hypo- or akinesia of the left ventricle (LV), LV dilatation, and systolic dysfunction [13, 55, 56].

Arterial blood gas analysis is important in order to diagnose hypoxia and metabolic acidosis.

The most common finding is metabolic acidosis with respiratory alkalosis [57]. Serum electrolytes, blood sugar, liver, and kidney function tests are done to get the baseline data at presentation so that remedial measures can be taken. These tests can be repeated to evaluate declining organ function.

Magnesium levels in aluminum phosphide poisoning are variable and do not help in guiding the clinical management [4, 5, 26, 27, 58–61]. Both hypo- and hyperglycemia have been reported, and these conditions should be managed in standard fashion [62–64].

Treatment

Early recognition and management of phosphide poisoning is essential. Young patients presenting with severe metabolic acidosis and hypotension having raised jugular venous pressure/high central venous pressure should be suspected of phosphide poisoning if coronary artery disease and sepsis can be ruled out and one is an area where phosphide poisoning is common. It is important to take a detailed history and find out the exact nature/formulation of the compound ingested. Preparations made with large-sized tablets may lodge in the esophagus. Phosphine is rapidly absorbed from the mucous membranes and has a significant cutaneous absorption. Rapid mucosal absorption can lead to significant systemic symptoms even in the absence of the tablet reaching the stomach. Decontamination can be simultaneously carried out while examining the patient in the emergency [46].

Removing clothes soiled with patient's vomitus and washing the skin with water is sufficient. Induction of emesis is contraindicated, though spontaneous vomiting often occurs.

Although gastric lavage is no longer routinely used for most poisonings, lavage with potassium permanganate (1:10,000), which is known to oxidize phosphine, may be beneficial if done within the first hour of ingestion and if available [65, 66]. However, there is no evidence that gastric lavage improves outcome in poisoned patients, and it can be associated with

complications including aspiration, hypoxia, and tachycardia in an agitated, obtunded patient. Alternatively, the potassium permanganate can be administered through a nasogastric tube (Grade III recommendation).

Sodium bicarbonate has been tried as a neutralizing agent for gastric acid, but there is no definitive evidence of its utility [4, 26, 65]. Moreover, many patients present late in the course of illness when phosphine has already been absorbed.

Intragastric administration of a slurry of activated charcoal (adult 50–100 g, infant 1 g/kg, child 1–12 years 25–50 g) has been advocated in the past; however, no studies are available in literature that shows that it benefits patients. Therefore activated charcoal cannot be recommended [65].

There is experimental evidence of inhibition of phosphine release when vegetable oil (e.g., coconut oil) or liquid paraffin has been used after ingestion of aluminum phosphide tablet [67]. This practice was shown to benefit a patient in a single case report [68]. Since administration of any kind of oil/paraffin may be associated with a risk of aspiration in an agitated/comatose patient, it cannot be recommended and has not been used routinely in centers across the world [4].

Since phosphine can be released from the nasogastric or urogastric tube, while gastric lavage is being performed, there is a concern regarding secondary exposure to health-care workers. It is advisable to use universal precautions while handling these cases even though there is no documented evidence of any significant illness/poisoning in health-care workers taking care of metal phosphide poisoned patients [69, 70]. Phosphine is known to be flammable, but there are only two cases of autoignition that have been reported [22, 23].

The management of phosphide poisoning is supportive as there is no specific antidote. Ventilation for respiratory distress syndrome, replacement of electrolyte abnormalities, and early recognition/management of hypoglycemia are important [57, 62, 63]. Severe metabolic acidosis results in tissue hypoxia and can lead to significant myocardial depression. Early and effective

management of metabolic acidosis can be accomplished with the administration of sodium bicarbonate infusion or hemodialysis [32]. Management of metabolic acidosis can be difficult as high central venous pressure may preclude the use of large amounts of sodium bicarbonate and severe hypotension/shock may make hemodialysis life-threatening in these patients.

The primary aim of the management of phosphide poisoning is early recognition and aggressive treatment of shock [4]. Intravenous fluids are indicated as leakage of fluids from the intravascular to the extravascular space occurs as a result of capillary dysfunction [29]. However, these patients generally have high central venous pressures. Administration of excessive amounts of fluids has not improved outcomes and should be avoided [29]. Intravenous fluids should thus be judiciously administered and only after measuring central venous pressure or inferior vena cava (IVC) diameter. Bedside echocardiography may help guide management. A rapidly contracting left ventricle with a collapsing inferior vena cava would indicate fluid deficit, whereas a poorly contractile left ventricle with a full/dilated IVC would indicate a significant myocardial dysfunction [71]. Judicious administration of norepinephrine and vasopressin may help maintain blood pressure and improve peripheral perfusion [4]. Administration of dopamine or dobutamine is not recommended for hypotension as it may induce cardiac dysrhythmias [32].

Magnesium sulfate has been used in an attempt to prevent dysrhythmias from phosphide poisoning [58, 59] (Grade III evidence). In addition, it also has antioxidant effects suspected to combat free radical mediated injury. Although an improvement in dysrhythmia was noted, mortality was not affected. Amiodarone has been tried, but it can lead to hypotension and should therefore be used carefully [72]. The use of digoxin in these patients is controversial and has been limited to experimental studies only [73, 74].

In severe cases compromised adrenal function has been reported, but administration of steroids does not result in improved mortality [75]. Corticosteroid administration is not therefore routinely recommended by the author.

N-Acetylcysteine (NAC) has shown to benefit in experimental animal studies of phosphide poisoning [76]. The benefit may, however, be attributed to the fact that NAC was administered before the animals were exposed to phosphine. Two human studies reported conflicting results. One has shown some beneficial effects on mortality but has not taken into consideration the severity of poisoning [77]. The other study has failed to show any benefit in patients with refractory hypotension [78]. Therefore, NAC cannot be recommended as standard of care till more data are available. Some studies have shown inhibition of acetylcholinesterase [79–81] by aluminum phosphide and phosphine poisoning, but there have not been any studies to confirm the usefulness of oximes.

Glucose, insulin, and potassium (GIK) infusion administered to produce hyperinsulinemic euglycemia has been shown to benefit poisoned patients by providing energy, restoring calcium influx, and increasing myocardial contractility in patients with aluminum phosphide poisoning [82]. Most of the data has come from one center and needs to be reproduced at other centers before this can be advocated as standard of care (Grade III evidence). Because the efficacy of GIK has not been ruled out, in a patient with refractory cardiovascular decompensation, an attempt at its use cannot be faulted.

Hemodialysis/hemoperfusion does not remove phosphine but can help in management of metabolic acidosis or a fluid overload state [32]. Performing hemodialysis in a patient with severe shock can be detrimental and should only be done carefully.

Hemodynamic support with an intra-aortic balloon pump [83] and extracorporeal membrane oxygenation (ECMO) has shown to improve mortality [84], but the reports are from a limited number of centers. These therapies have significant drawbacks, including high cost, poor availability, and lack of expertise hampering larger clinical trials.

In the case of an inhalational exposure to phosphine gas, removal from the source and administration of oxygen has been sufficient therapy in the majority of the cases [32, 57]. The remainder of treatment is guided by the clinical condition of the

patient. Hyperbaric oxygen has been found to be of some survival benefit in animal trials but its usefulness in humans has not been studied [85].

Esophageal ulceration and erosions leading to bleeding have been reported after ingestion of aluminum phosphide tablets [86, 87]. It has been postulated that the large pill may result in exothermic damage to the esophageal mucosa and if it gets stuck, it may cause pressure necrosis [87, 88]. Although pressure necrosis has been ascribed as a cause of bleeding and esophageal strictures, yet, there has been no documented case of a stuck pill needing endoscopic removal in the series of cases published to date [86–88].

After the acute phase is over, this may result in esophageal strictures in survivors of aluminum phosphide pill ingestion [87, 88]. This complication has not been reported since granule formulations were made available. Patients developing upper gastrointestinal bleeding following aluminum phosphide tablet ingestion should be followed up carefully with endoscopy to look for development of strictures [88].

Prognosis

A large number of parameters [89] and critical care scoring systems [90, 91] have been evaluated as predictors of mortality in aluminum phosphide poisoning. However, low arterial pH, low sodium bicarbonate levels, hypotension (SBP < 90 mmHg), and altered mental status have been observed by many authors as predictors of poor prognosis [91, 92].

Prevention

An important preventive measure lies in better regulated supply of ALP. When properly used, it is an excellent and safe fumigant as it leaves little residue on grain. Legislative and administrative measures have been suggested to restrict and modify its supply. Unfortunately, there has been a failure in their application, except for the ALP's largest producer, in changes in formulation to granules, which has helped in reducing human mortality [1].

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Rodenticides are utilized worldwide. Specific types of rodenticide exposures critical care physicians commonly encounter vary regionally. In the USA, before 1976, anticoagulant rodenticides contained warfarin. However, rodents developed resistance to warfarin, leading to the manufacture of more potent, longer lasting superwarfarins, also known as second-generation anticoagulants or long-acting anticoagulant rodenticides (LAAR). In the USA, the most common rodenticides involved in human poisonings are anticoagulant agents, specifically superwarfarin products. Annual reports of the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) reported ten deaths involving LAAR from 2002 to 2013. Superwarfarins are commonly present in homes throughout the United States, and exposure to them occurs frequently in the pediatric population [1–3]. The amount ingested is usually limited, and coagulopathy from single pediatric ingestions is rare [1–4].

Availability of various rodenticides within each country influences the likelihood of exposure. In the USA, rodenticides with high potential toxicity are available mostly to professional licensed exterminators as restrictions on production and distribution have become more stringent. In 2008, the US Food and Drug Administration (FDA) took steps to limit availability of ten active ingredients in rodenticides: brodifacoum, bromadiolone, bromethalin, chlorophacinone, cholecalciferol, difenacoum, difethialone, diphacinone (and its sodium salt), warfarin (and its sodium salt), and zinc phosphide. In 2015, one of the major producers of rodenticides Reckitt Benckiser Inc in the USA stopped distribution of 12 of their d-CON mouse and rat poison products [5].

Other rodenticides of higher order toxicity are available, but their use has been restricted or prohibited in many countries, including the USA. For example, *N*-3-pyridylmethyl-*N*-p-nitrophenylurea (PNU, VacorTM) was on the US market only a few years (1975–1979) before distribution was voluntarily halted owing to many

successful suicides with this product. Survivors developed insulin-dependent diabetes. Other highly toxic compounds used by commercial applicators in sheep collars for predator control are sodium monofluoroacetate and its metabolically related fluoroacetamide which inhibit a specific step in the tricarboxylic acid (Krebs) cycle. Though restricted in the USA, these agents remain readily available in many Southeast Asian countries.

Aluminum phosphide remains a common choice for suicide in a number of countries, such as Iran and India [6, 7]. It is far less commonly used for this purpose in the USA, with four deaths involving this agent in the 2002–2013 AAPCC TESS. Occupationally, phosphine (formed from phosphide) exposures and toxicity occur during grain fumigation in transport and storage areas [8–11]. Aluminum phosphide is discussed in greater detail in the chapter on phosphides and phosphine.

Bromethalin, which became available for use in the USA in 1986, has been involved in multiple exposures given its availability. Three deaths were attributed to bromethalin in the USA from 2002 to 2013.

Most of the remaining rodenticides that are discussed in this chapter are primarily of historical interest, particularly in developed countries where they are not commonly still used. However, in some parts of the world substantial numbers of exposures may still occur. For example, barium carbonate no longer is widely available as a rodenticide. It was sold as a water-soluble white powder. Many epidemics occurred when this rat poison was mistaken for flour [12–16]. Historically, many commercially available products contained strychnine, which at one time accounted for 30 deaths per year in the USA [17]. Four deaths attributable to strychnine were reported in the 2002–2013 Annual Reports of the American Association of Poison Control Centers Toxic Exposure Surveillance System [18–29]. Most human exposures to strychnine resulted from its prescription as an analeptic, analgesic, aphrodisiac, appetite suppressant,



Image 1 Anticoagulants (Courtesy of Nguyen Trung MD Poison control center, Bach Mai Hospital, Hanoi, Vietnam)

cathartic, circulatory stimulant, emetic, and tonic. Tetramine, still available in Southeast Asia, is often involved in multiple human exposures and deaths from refractory seizures [29]. Vitamin D exposures have occurred but in general do not cause critical illness. Other rodenticides of significance to the critical care physician are discussed in other chapters (i.e., arsenic, phosphorus, and thallium).

Biochemistry

Anticoagulants

Anticoagulant rodenticides are often combined with cornmeal, oats, or grain to increase palatability (Image 1). They can be tasteless, odorless, or foul smelling pending upon the agent. Most exposures are oral; however, they have been reported through the dermal and inhalational routes [3]. Specifically, brodifacoum is lipid soluble, concentrated in the liver, is approximately 100 times more potent than warfarin, and long lasting with clinical effects that can range from days to months (Table 1) [3].

α -Naphthylthiourea ANTU

ANTU (molecular weight 202) (Fig. 1) is a colorless to white-gray powder or crystal substance. It is odorless and bitter tasting. It has been a component of a number of rodenticide products (see Table 2).

Barium

Barium rodenticides no longer are available for sale in many countries, including the United States, but old product may remain. Barium carbonate is a white powder usually prepared of one part barium carbonate and four parts of a protein carbonate rich food such as rolled oats or fish meal mixed with milk or water [30]. Barium carbonate as a powder may be inhaled and cause acute paralysis [31].

Bromethalin

Bromethalin is odorless and crystalline yellow or white in color. It is commonly packaged into green pellets of approximately 7.5% concentrate

Table 1 Available forms of long-acting anticoagulant rodenticides

Rodenticide	Concentrations (%)	Forms	Brand names
4-Hydroxycoumarins			
Brodifacoum	0.005	Bait	D-Con Mouse Prufe II
			Talon, Talon G, Havoc
Bromadiolone	0.005	Bait	Bromone, Super-Caid
			Ratimus, Maki
Difenacoum	0.005	Bait	Ratak
Coumatetralyl			Endox, Endrocid
			Endrocode, Racumin
			Racumin 57, Rodentin
Indanediones			
Chlorphacinone	0.005	Bait	Caid, Drat, Ramucide
	0.25	Solution	Liphadione, Ratomet
	2.5	Concentrate	Microzul, Rozol
			Topitox, Raviac
Diphacinone	0.005	Cake	Diphacin
	0.05, 0.1, 0.2	Bait	Promar
	2	Concentrate	Ramik
Pindone	0.025, 0.1, 0.2, 0.5	Powder	Pival, Pivacin
	0.5, 1.5, 2	Concentrate	Pivalyn, Tri-Ban

α -Naphthylthiourea (From [124])

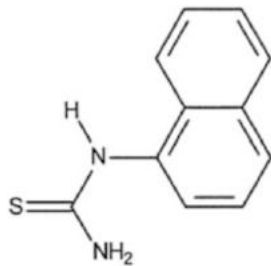


Fig. 1 Chemical structure of ANTU

[32]. Its major metabolite is desmethyl bromethalin formed by *N*-demethylation in the rat [32]. It acts as an uncoupler of oxidative phosphorylation and interrupts nerve impulse conduction.

Phosphides

Phosphides usually are found as powders or pellets and may have a rotten-fish odor (Image 2). Zinc and aluminum phosphide are the most

Table 2 Examples of α -naphthylthiourea-containing products

Bontu prep rat baits
Bontu rat powder
Brown rat poison
College brand rodenticide
Dr. Hess anturat
Nott's rat paste
Pied piper for rats and mice
Ratsalt
Rat stop
Rat tox
Rat-X
Rateraser

Noninclusive list

commonly available products. Calcium and magnesium phosphides also are available. In the presence of water and gastric acid, the metal is released, and phosphine gas (PH₃) is produced. This gas may have a garlic odor. Examples of reactions generating phosphine from phosphides are as follows:



Image 2 Phosphides (Courtesy of Nguyen Trung MD Poison control center, Bach Mai Hospital, Hanoi, Vietnam)

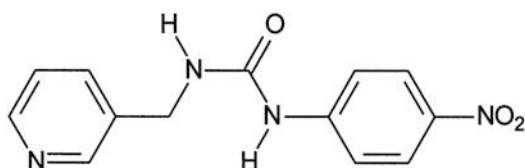
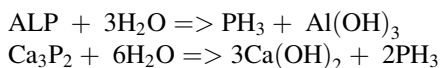


Fig. 2 Chemical structure of PNU



N-3-pyridylmethyl-N-p-nitrophenylurea (PNU)

PNU (Fig. 2) was sold as a yellow-green powder or cornmeal. A peanut odor may be evident. Examples of brand names in the USA have included Vacor Rat Killer, DLP-787 2% Bait, and DLP-787 10% House Mouse Tracking Powder.

Sodium Monofluoroacetate and Fluoroacetamide

Sodium monofluoroacetate is a white, odorless and tasteless salt that is added to grain baits (Image 3). It is absorbable by the gastrointestinal and pulmonary routes but not dermal routes, unless the skin is broken [33]. This product is isolated from African and Australian plants [34, 35].

Strychnine

Strychnine is an extract from the seed of Asian and Australian trees, including *Strychnos nux-vomica*. It is a bitter-tasting, odorless white powder. Table 3 lists strychnine-containing rodenticides [17]. Most products contain 0.5% strychnine.

Tetramine (tetramethylene disulfotetramine, TETS, TEM)

Tetramine is a white powder (Image 4). Its production has been banned in the USA since 1980. The dose of tetramine which kills 50% of mammals (LD50) is 0.1–0.3 mg/kg and doses of 7.0–10.0 mg are considered lethal in humans. Tetramine is approximately 100 times more toxic to humans than potassium cyanide and might be a more powerful human convulsant than strychnine [36].

Pathophysiology

Anticoagulants

Warfarin and warfarin-like anticoagulants disrupt enzymes in the liver (Fig. 3). These rodenticides inhibit liver vitamin K reductases, which are

Image 3 Fluoroacetates, fluoroacetamides (Courtesy of Nguyen Trung MD Poison control center, Bach Mai Hospital, Hanoi, Vietnam)



Table 3 Strychnine-containing products^a

Arab mouse lure
Dolco mouse cereal
El Roy mouse bait
Farmite orchard mouse bait
Gopher death
Gopher go
Hot springs buttons
Kilmice
Mice doom pellets
Mole death
Mole-nots
Mouse lure
Mouse seed
Mouse-nots
Mouse-rid
Mouse-tox
Pied piper mouse seed
Rat seed
Saraseed mouse seed
Senco poison oar kernels
Senco special poison canary seed
Sweeney's poison wheat

^aExamples of brand names used in the USA. Other countries may use similar, or different, brand names

crucial to endogenous activation of hepatically synthesized clotting factors II, VII, IX, and X and proteins C, S, and Z. These coagulation proteins are activated by carboxylation of terminal glutamic acid groups. Vitamin K is oxidized to an epoxide during this reduction reaction. Vitamin K₁ 2,3-epoxide reductase converts the epoxide to its quinone form, whereas vitamin K₁ quinone reductase changes the quinone into the active quinol form of vitamin K₁. In human overdoses, this inhibition is evident by an increased ratio of the epoxide to the quinol form [37]. Bleeding from the coagulopathy may occur when factor concentrations decline to less than 25–30% of baseline levels. Factor VII has the shortest half-life (approximately 5 h). After three to four half-lives (or 15–24 h), prothrombin time elevations can be seen. Bleeding complications usually manifest days after ingestion. The period of clinically significant anticoagulation for warfarin rodenticides typically lasts less than 1 week, whereas that induced by the long-acting agent brodifacoum may be months to longer than a year [3, 38–41].



Image 4 Tetramine (Courtesy of Nguyen Trung MD Poison control center, Bach Mai Hospital, Hanoi, Vietnam)

ANTU

The toxicity of ANTU results from its active metabolites. Lung reduced nicotinamide adenine dinucleotide phosphate-dependent cytochrome P-450 enzymes seem to generate these injurious metabolites [42]. The thiocarbonyl group ($>C = S$) is most likely the site where a reactive intermediate is generated that subsequently binds pulmonary macromolecules and produces pulmonary injury [42, 43]. Glutathione depletion seems to exacerbate the toxicity [43]. Pulmonary edema may result from the injury. Rats also may metabolize ANTU [42]. It is not known why the lung is more susceptible to this compound than the liver.

Barium

Life-threatening barium toxicity results from actions on the neuromuscular and cardiovascular systems [44, 45]. Barium, after stimulating muscle, produces a depolarizing neuromuscular blockade [44, 46]. Potassium is shifted

intracellularly along with blockage of cellular potassium channel efflux [44, 46]. Profound weakness and partial paralysis result.

Bromethalin

Bromethalin uncouples oxidative phosphorylation and interrupts nerve impulse conduction. Toxicity is primarily related to the central nervous system manifesting as muscle tremors, myoclonic jerks, ataxia, seizure, and coma [32].

Phosphine

The mechanisms of phosphine toxicity are not completely understood; however, it may block cytochrome *c* and *a* oxidases [46]. Free radical generation and lipid peroxidation also seem to have a role [47, 48, 49]. Pulmonary edema is common and may develop over days. The toxicity of phosphine is discussed in greater detail in ► Chap. 94, “Phosphate and Phosphine.”

PNU

PNU is related structurally to alloxan, streptozotocin, and 1-methyl-1-nitrosourea. These antineoplastic compounds damage pancreatic beta cells [50–52]. Because of structural similarities, these compounds may be substituted for nucleotides. A substitution for nicotinamide in the generation of nicotinamide adenine dinucleotide and possibly nicotinamide adenine dinucleotide phosphate is a proposed mechanism. Nicotinamide adenine dinucleotide depletion has been documented after streptozotocin administration [50]. Cofactors no longer can function as hydrogen carriers for enzymatic redox reactions, including oxidative phosphorylation. The pancreas is especially susceptible because β cells are destroyed. The nervous system also may be affected, and neuropathies and encephalopathy may develop [53–55].

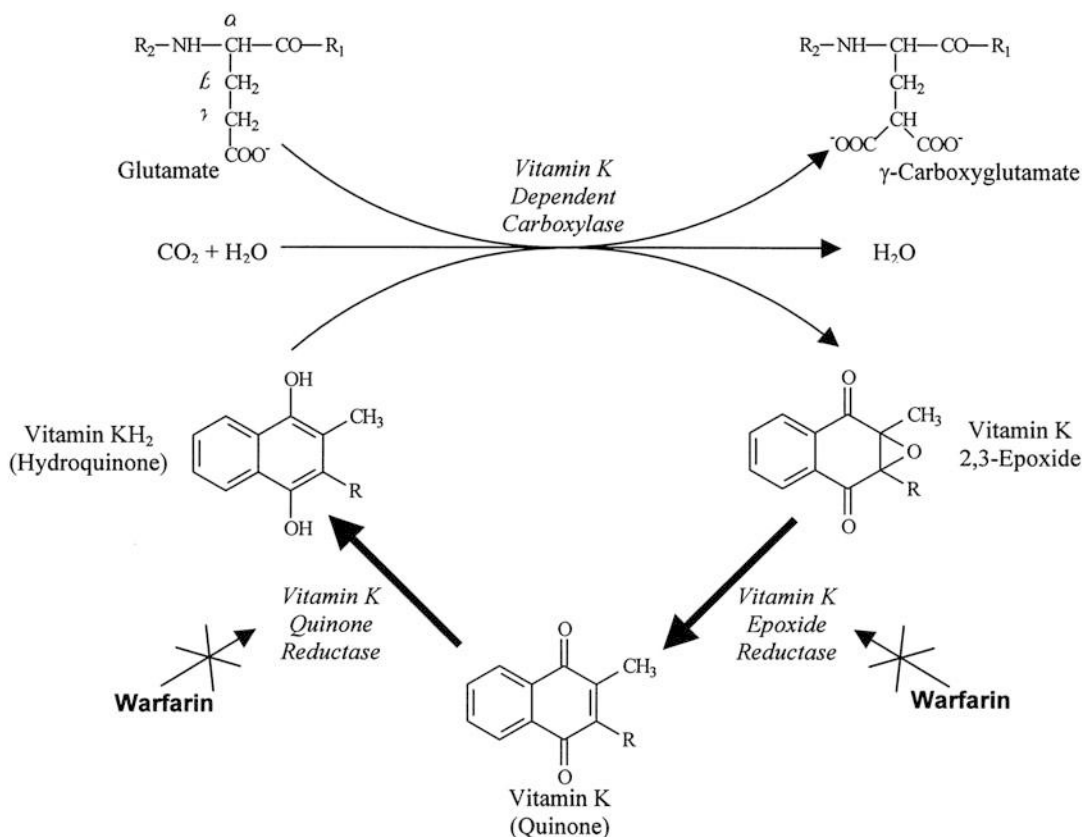


Fig. 3 Graphic depiction of the actions of warfarin on the vitamin K cycle

Sodium Monofluoroacetate and Fluoroacetamide

Sodium monofluoroacetate blocks the tricarboxylic acid (Krebs) cycle [34]. Fluorocitrate, its metabolite, accumulates and inhibits aconitate hydratase (Fig. 4) [56]. This inhibition disrupts cellular respiration, depleting adenosine triphosphate energy stores. The absorption, conversion, and inhibition lead to a delay of hours before effects appear [57]. This delay may be longer for fluoroacetamide because it is converted to fluoroacetate.

Strychnine

Strychnine acts on the central nervous system as a competitive antagonist at glycine receptors.

Although structurally dissimilar from glycine, its charge and surface configuration seem to allow binding at the glycine receptor site [58]. Glycine is the predominant inhibitory neurotransmitter in the brainstem and spinal cord. It acts by increasing chloride conduction in postsynaptic cells, causing them to be hyperpolarized. Strychnine blocks the postsynaptic binding of glycine. Strychnine also seems to block the action of γ-aminobutyric acid (GABA) in spinal interneurons, although this inhibition is not as potent as that with glycine [59, 60]. The GABAergic system provides the major neuroinhibitory pathways in the central nervous system. Benzodiazepines that are used to treat strychnine poisoning bind glycine and GABA receptor sites and increase chloride conductance [61, 62]. Barbiturates also enhance chloride conductance and have been reported to be effective in the treatment of strychnine poisoning [8, 63, 64].

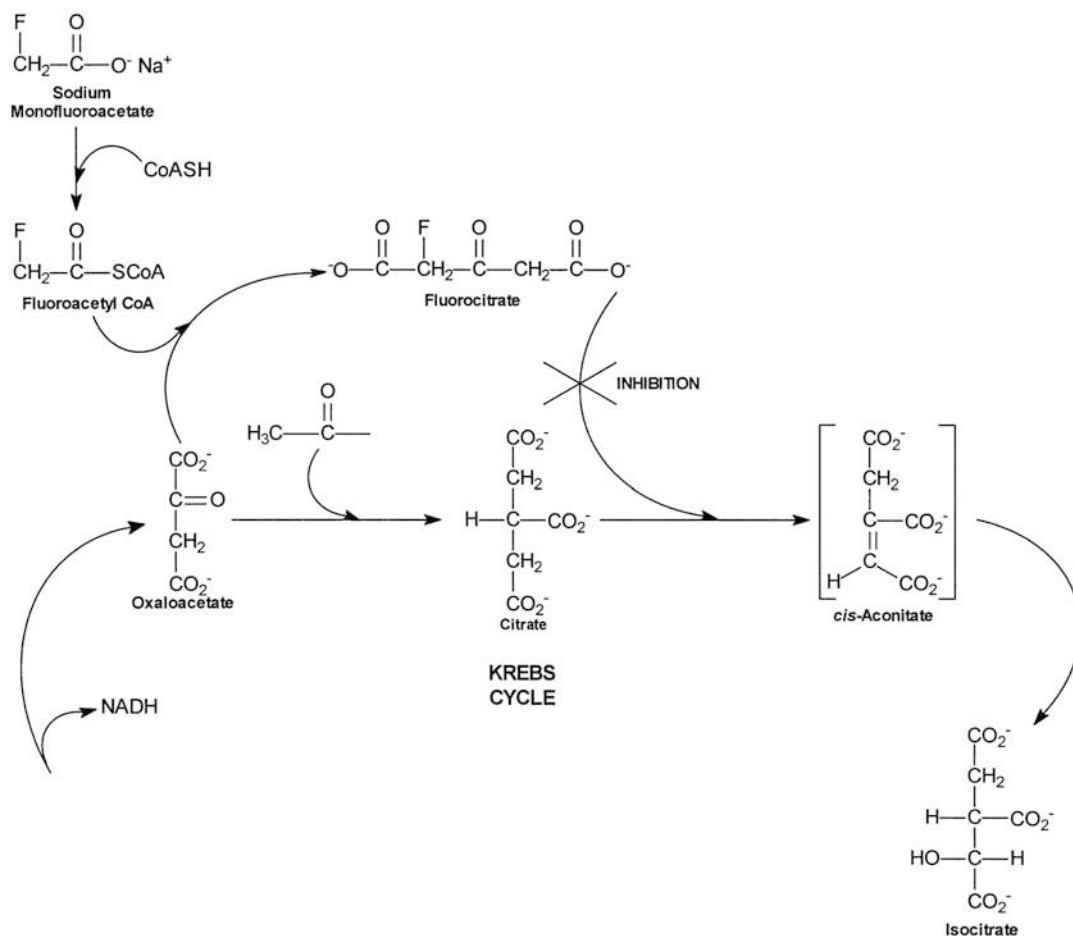


Fig. 4 Interference of monofluoroacetate with the Krebs cycle

Tetramine

Tetramine is a noncompetitive GABA antagonist that acts by direct blockade of the chloride ionophore complex, blocking chloride channels in a fashion similar to picrotoxin [20].

Clinical Presentation

Anticoagulants

Patients with superwarfarin poisoning, may present with serious hemorrhagic complications. Most fatalities have occurred after intracranial

hemorrhages. Subdural, subarachnoid, retroperitoneal, and intracerebral hemorrhages have also been reported [3, 65–67]. These patients typically have bleeding from other sites or organ systems. Pulmonary hemorrhage may require ventilatory support [40, 41, 68]. Vaginal bleeding also has caused a fatal outcome [69]. Compartment syndromes have been reported [40, 41, 68]. Gastrointestinal bleeding and epistaxis should be anticipated and may be life-threatening. Clinical effects are often delayed as the onset of symptoms may be days or weeks after exposure, with one case report having a patient present to a health care facility 9 days after his overdose and another with presentation 3 weeks post exposure [67, 68].

ANTU

ANTU poisoning may have the potential for serious pulmonary toxicity in humans manifesting as the acute respiratory distress syndrome. Infrequent reports of significant toxicity simply may reflect that ingestions have not been large enough to produce serious poisoning. Brewer and Haggerty [17] suggested an oral mean lethal dose of 4 g/kg in primates. Shortness of breath and rales were noted after a large ingestion of 80 g of a 30% bait pack [70].

Barium

Facial paresthesias may be the first symptoms of barium toxicity [12]. These paresthesias may spread to the extremities [12]. Gastrointestinal symptoms usually follow and may include salivation, nausea, vomiting, abdominal pain, and diarrhea [12, 13, 71]. Gastrointestinal hemorrhage has been reported [12, 13]. In association with progressive hypokalemia, profound weakness develops and may progress to paralysis. Presentation may include ptosis, monoplegia, hemiplegia, and quadriplegia [12]. Most importantly, respiratory paralysis and respiratory failure characterize severe poisoning [45, 72]. Hypokalemia is also associated with cardiac conduction disturbances and dysrhythmias [70]. Electrocardiogram changes typically include QRS prolongation and flattened T waves and U waves [13, 71]. Ventricular extrasystoles, hypertension, and tachycardia may follow [45].

Ventilatory support may be needed for the respiratory paralysis [45]. Arterial blood gases may show respiratory acidosis as respiratory failure progresses. Cardiac monitoring is required to identify and treat any dysrhythmias that result from the intracellular potassium shifts and severe hypokalemia.

Bromethalin

Onset of toxicity is often immediate and manifests in central nervous system as muscle tremor,

myoclonic jerks, muscle flexion, ataxia, seizure, and coma [32].

Phosphine

Signs and symptoms of phosphide toxicity often develop within 15–30 min, and death may occur in less than 6 h [73]. Potency is highest when fresh, previously unopened tablets are ingested [74]. Open packages allow atmospheric moisture to react with tablets and decrease their potency. Banjaj and Wasir [75] stated that ingestions of 500 mg are usually fatal. Phosphides are potent gastric irritants; profuse vomiting and abdominal pain are often the first symptoms [74]. Tachypnea, hyperpnea, dyspnea, cough, and chest tightness usually follow. Tachycardia, hypotension, and arrhythmias may develop [76–79]. Central nervous system toxicity may include coma and delirium [73, 76].

Phosphides react with water to form phosphine gas. Though illegal in most first world countries, they are still quite available in many parts of the world. Recent media reports have implicated phosphine in the deaths of tourists in Thailand and two small children in Edmonton, Alberta, whose parents imported aluminum phosphide tablets from Pakistan to kill bed bugs [80, 81]. There have been many deaths reported in India and Iran [6, 7]. Phosphine is discussed in greater detail in ► Chap. 94, “Phosphate and Phosphine.”

PNU

PNU toxicity may manifest within hours or be delayed for days [82]. Anyone with a history of PNU ingestion should be observed, even if there are no manifestations of toxicity. Patients who develop signs of major toxicity should be admitted to an intensive care unit. Hyperglycemia or diabetic ketoacidosis follows the insulin deficiency from beta cell destruction, although hypoglycemia may precede these symptoms [83]. The onset of diabetes mellitus has been detected 4 h to 7 days after exposure [82, 84]. Autonomic and peripheral neuropathies causing postural

hypotension, diminished gastrointestinal and bladder motility, and motor and sensory loss may develop. The onset is often acute, manifesting in the first few hours, although in some cases manifestations can be delayed for days [84, 85]. These neuropathies may be reversible or irreversible [83, 84]. An acute cerebral encephalopathy also may develop [83, 85]. Other signs and symptoms may include delirium, confusion, lethargy, coma, memory impairment, dyskinesias, tremor, seizures, myoclonus, abdominal pain, chest pain, palpitations, and hypothermia [83–85]. On autopsy, pancreatic beta cell destruction and neuropathic lesions of the sensory spinal roots have been documented [85].

Sodium Monofluoroacetate and Fluoroacetamide

Neurologic and cardiovascular toxicity from sodium monofluoroacetate and fluoroacetamide has caused many fatalities, and intensive care unit admission is warranted in an exposed patient manifesting any signs of toxicity. Epigastric pain and vomiting may be the first symptoms to develop [86]. Mental status changes may include confusion, irritability, agitation, and coma [33, 87, 88]. Neuromuscular irritability may include muscle twitching, muscle spasms, and seizures [87, 88]. Electrocardiogram monitoring shows nonspecific ST wave changes, prolonged QT_c intervals, ventricular ectopy and tachycardia, and rapid atrial fibrillation. Hypocalcemia and possibly hypokalemia are common manifestations that may contribute to the aforementioned life-threatening conditions [56, 87]. Patients who survive beyond 24 h may develop renal failure [87, 88].

Gastrointestinal effects precede the life-threatening effects on the heart (ventricular dysrhythmias) and the central nervous system (coma and seizures) [33, 87, 88]. One report suggested that subacute exposure may result in sudden death [35]. Parkin and associates described a rabbit who developed chronic toxicity with renal, hepatic, neurologic, and thyroid dysfunction. Symptoms can be prolonged [89].

Strychnine

Initially a patient's apprehension may produce hyperventilation and respiratory alkalosis. When spasms compromise effective gas exchange, hypercarbia and respiratory acidosis may be seen [90, 91]. Finally, the spasms can produce a severe metabolic lactic acidosis with or without a respiratory acidosis. Often the pH can become significantly less than 7.1. Severe acidosis can precipitate multiorgan dysfunction and failure. Bradycardia and hypotension may precede cardiac arrest [92]. Lactic acidosis and hypoxia also may result in central nervous system depression. By the gastrointestinal route, signs and symptoms typically occur within 15–30 min. Nasal insufflation or intravenous injection can occur when strychnine is used as a substitute for drugs of abuse. In these cases, effects can occur within 5 min [90, 93]. Stimulation of the patient should be kept to a minimum. Loss of motor neuron inhibition causes hyperexcitability in affected muscles. The stimulation produces muscle twitching or spasms of extensor muscle groups, and trismus or opisthotonos has been seen [90, 93–96]. A unique manifestation of strychnine poisoning is an awake and alert patient with convulsions. Such patients may manifest seizure-like activity based on spinal hyperexcitability with relative noninvolvement of the brain. Stimulation may precipitate these effects [90]. In between spasms or after recovery, patients often describe severe pain during these episodes [94]. Between these events, the patient may be awake and relaxed. Respiratory compromise may occur secondary to spasms of the diaphragm and chest wall musculature [90]. Other complications may include rhabdomyolysis, hyperthermia, lactic acidosis, and multiorgan failure [90, 91, 97]. Severe spasms in addition to rhabdomyolysis may cause compartment syndrome [90]. Because strychnine poisoned patients are heavily sedated during the course of treatment, frequent examinations are required to assess distal extremity temperature, capillary refill, and firmness of the compartments. If there is any question of developing compartment syndrome, compartment pressures should be measured. The patient must be well hydrated to

avoid acute myoglobinuric renal failure. Central venous pressure monitoring should be considered if urine output decreases after appropriate volume expansion. Close monitoring of electrolytes is required. Derangements of potassium, calcium, phosphate, and magnesium may occur [91, 92, 96]. Hepatic and renal function should be followed in severely poisoned patients.

Tetramine

The most common routes of exposure are by ingestion and inhalation. Tetramine poisoning manifests primarily as refractory seizure, coma and myocardial ischemia. Clinical effects may occur approximately 30 min after exposure and last up to 13 h [36].

Diagnosis

Anticoagulants

Confirming the diagnosis requires a detailed history and laboratory analyses. Many patients who present with bleeding complications do not provide the history of exposure to anticoagulant rodenticides. Minor bleeding often occurs before a life-threatening bleed. When taking the history, search for liver disease or a possible cause of vitamin K deficiency in addition to other bleeding disorders, such as hemophilia, von Willebrand's disease, or coagulation factor deficiencies. Hepatotoxic liver disease (e.g., from acetaminophen, hepatotoxic mushrooms, or chronic alcoholism) could present with a bleeding complication although distinguishing features will be present. The various hepatotoxins are discussed in their respective chapters in this book. A prolonged prothrombin time or international normalized ratio (INR) may be a laboratory clue to the diagnosis. Coagulation factor levels should be measured and usually confirm the clinician's suspicion. These tests should be obtained before any blood products are administered. To assess quickly for coagulation factor depletion, the patient's plasma can be mixed with known normal

plasma. A 50:50 mixing of the two should correct the prothrombin time or INR if the cause of prolongation is factor deficiency.

Patients with severe hemorrhage may develop factor depletion or disseminated intravascular coagulation. D-dimer, fibrin split products, and fibrinogen levels help assess these diagnoses. Transfusions may be required. Liver function tests should be measured to rule out toxin-induced or other hepatic diseases, as mentioned earlier. Measurement of brodifacoum and other superwarfarin levels clarifies the diagnosis. However, concentrations of these rodenticides are frequently under the limits of detection of reference laboratories. Often this degree of testing is required if confirmation is desired because anticoagulant self-poisoned patients deny the ingestion of these products. However, a negative test does not rule out the diagnosis. Pediatric cases with serious bleeding complications are rare [98]. Most of these pediatric case reports are suspected to be Munchausen syndrome by proxy. In these cases, laboratory confirmation should be attempted for medicolegal reasons.

ANTU

The diagnosis of ANTU poisoning mostly relies on the history. Care must be taken to identify the product properly when possible. This diagnosis also should be in the differential diagnosis of a patient with a history of rodenticide ingestion who presents with pulmonary edema. Laboratory studies are of little help in the acute management of these patients.

Barium

The diagnosis of barium intoxication is typically made by history. Paralysis coupled with hypokalemia should confirm the diagnosis. Although barium can be measured in many matrices, including blood, serum/plasma, tissue, hair, and urine, obtaining barium levels do not enhance patient management. Although serum levels have been shown to correlate with toxicity, the patients

have been and can be managed appropriately without them [72, 99, 100].

Bromethalin

The diagnosis of bromethalin exposure is primarily made by history of exposure and clinical presentation consistent with neuromuscular hyperactivity. Levels and specific laboratory values are of little help in the acute management of these patients.

Phosphine

The clinical history coupled with the patient's clinical course make the diagnosis of phosphide poisoning. A rotten-fish odor can be an important clinical sign. One must be careful because off-gassing of the emesis can expose health care workers to phosphine fumes [6]. Laboratory tests are of limited diagnostic utility.

PNU

The diagnosis of PNU toxicity should be considered in patients with a history of rodenticide exposure and a presentation of diabetic ketoacidosis, especially with concomitant signs of neuropathy. Laboratory tests have only a confirmatory role and are not important to the acute critical care management of the patient and testing would be especially challenging given lack of availability of this agent.

Sodium Monofluoroacetate and Fluoroacetamide

The correlation of a clinical history of exposure with the onset of the clinical picture (initial gastrointestinal symptoms followed by mental status changes and cardiac toxicity) within hours of exposure is important to obtain the diagnosis. Fluoroacetate concentrations can be measured in serum, tissues, vomitus, and baits, but these

usually are not readily available. Laboratory consultation may provide confirmatory testing. In addition, in the correct clinical setting, elevated citric acid serum levels may support the diagnosis [101].

Strychnine

The history of exposure and rapid onset of symptoms, especially awake convulsions, often in less than 30 min, is expected in strychnine poisoning. Strychnine blood concentrations can be obtained but are not clinically useful, only confirmatory.

Tetramine

Acute refractory seizures lasting an extended period of time should heighten concern regarding exposure to tetramine, especially in the setting of a rodenticide exposure. Laboratory identification, though not clinically useful in an acute exposure, may be accomplished by several methods: including gas chromatography (GC) with nitrogen-phosphorous detection, GC with flame photometric detection, and GC-mass spectrometry [36].

Treatment

Anticoagulants

Gastrointestinal decontamination is of limited, if any, value in the management of the critically ill anticoagulant-poisoned patient. These patients present well after absorption and subsequent hepatic enzyme inhibition has developed. In the rare case of a patient presenting very soon after ingestion, activated charcoal may be warranted. However, in one case, multiple doses of charcoal did not seem to alter the outcome [3, 100]. There is no evidence that the administration of activated charcoal affects the outcome in these patients [102].

Critical care management decisions are based first on the bleeding complications the patient may develop and the severity of the coagulation defect. Control of hemorrhage should respond rapidly to the administration of whole blood, fresh frozen plasma, or factor concentrates. These blood products contain coagulation factors that stop ongoing bleeding (Level of Evidence [LoE] III). Whole blood reverses severe anemias that may develop. Prothrombin complex concentrates containing factors II, VII, IX, X, C and S may also be used in patients who cannot tolerate large volumes of Fresh Frozen Plasma (FFP) or whole blood (LoE III).

Indications for ICU Admission in Rodenticide Poisoning

Agent	Indication
Long-acting anticoagulants	Life-threatening hemorrhage
ANTU	Pulmonary edema
Barium Bromethalin	Ventilatory management, severe hypokalemia Refractory seizure
Phosphides	Hypotension, cardiac arrhythmias, coma, status epilepticus
PNU	Autonomic neuropathy with hypotension, encephalopathy, ketoacidosis
Fluoroacetates, fluoroacetamide	Cardiac dysrhythmias, coma, status epilepticus
Strychnine Tetramine	Status epilepticus or severe muscle spasms with ventilatory support, cardiac dysrhythmias, severe acidosis Myocardial ischemia, status seizure

Vitamin K therapy administration allows for the conversion of the coagulation factors into their active carboxylated forms. Vitamin K₁ is the only effective form (LoE III). For example, Aquamephyton is the parenteral brand available in the United States. Care must be taken with its administration because of the risk for anaphylactoid or possibly anaphylactic reactions from polyoxyethylated castor oil in its formulation [103]. To avoid these reactions, the rate of intravenous administration should not exceed 1 mg/min (LoE III). The use of a dilute solution also is

recommended because this step also may prevent anaphylactoid reactions (LoE III). The American College of Chest Physicians published consensus guidelines for parenteral vitamin K therapy in coumadin toxicity based on the INR. For patients with critical bleeding, 10 mg is recommended. If bleeding is not evident, INR results and recommended vitamin K doses are 6–10 (0.5–1.0 mg), 10–20 (3–5 mg), and greater than 20 (10 mg) [104]. Some medical toxicologists believe that the subcutaneous route is safer than the intravenous route and that the efficacy may be similar (LoE III). In either case, the benefits from vitamin K therapy are delayed for the approximately 6 h it takes for the hepatic elevation of active coagulation factor levels. If indicated, oral vitamin K therapy also should be initiated as soon as possible. Although the relatively slower oral absorption delays vitamin K’s effect, this route can be used to maintain elevated factor levels. Oral vitamin K doses of 100 mg to several hundred milligrams have been used [105]. Vitamin K has a half-life of less than 3 h [106, 107]. Without continued vitamin K administration, the coagulopathy may recur within 1–2 days. If the coagulopathy does not recur within 2 days of discontinuing therapy, vitamin K no longer should be required. When the bleeding complications are controlled, these patients can be transferred out of the intensive care unit.

ANTU

Most ANTU-exposed patients require close observation. Gastrointestinal decontamination with activated charcoal may decrease ANTU absorption in massive ingestions. Standard management protocols for pulmonary edema should be used for patients who manifest toxicity. Experimentally, and based on human case reports, fructose-1,6-diphosphate has been shown to protect the lung from ANTU-induced injury [108]. Fructose-1,6-diphosphate is an inhibitor of oxygen free radical production by neutrophils. Additionally, the preadministration of phorone produces an elevation of glutathione levels that protects against ANTU toxicity in rat models

[109]. Given this, *N*-acetylcysteine warrants testing as an antidote.

Barium

Barium carbonate is less soluble than other barium salts and may have a slower onset to effect. Activated charcoal binding of barium has not been studied but is not expected to offer significant benefit [107]. Although unproven, the administration of 30–60 g of magnesium sulfate or sodium sulfate has been recommended based on the theory of converting some barium into the insoluble salt barium sulfate, which would pass through the gastrointestinal tract without absorption [110, 111]. If larger doses are used, frequent measurement of sodium and magnesium levels must be done, especially if renal insufficiency develops. Despite oral sulfates, there are cases in which patients' conditions continued to deteriorate [112]. Intravenous sulfates are not recommended because these may induce barium sulfate precipitates in the renal tubules and lead to renal failure [72].

Potassium replacement is crucial (LoE III). Resolution of hypokalemia reportedly has coincided with recovery from the paralysis [99, 113]. Some authors believe that lowering the barium concentration is more important, however [72, 100]. Intravenous routes, including central lines using rates greater than 30 mEq/h, have been effective in elevating potassium levels in many cases [44, 71]. If emesis is controlled, one could administer potassium orally, and in critically ill patients this could be done via a nasogastric or orogastric tube [113]. However, hemodialysis may be more effective treatment as it directly removes barium [71, 72, 99, 100]. The addition of a high concentration of potassium (e.g., 4 or 4.5 mEq/L) to the dialysis bath elevates the serum potassium concentration. One patient 3 h into dialysis recovered from paralysis and was extubated successfully [99]. Hemodialysis should be the first line therapy in patients who have persistent paralysis despite adequate potassium replacement therapy, especially in patients with renal insufficiency (LoE III). Hemofiltration also has been used with success [114].

Bromethalin

Symptomatic and supportive care is the mainstay of treatment for this agent. Neuromuscular findings are probably best treated with appropriate agents such as benzodiazepines for seizures (LoE III). There is no available antidote for this agent.

Phosphine

Gastrointestinal decontamination after exposure to phosphides has not been studied. Patients develop nausea and vomiting from the irritant effects and [56] health care workers should protect themselves from the emesis because it theoretically may off-gas phosphine [74]. Jayaraman reported a physician who became symptomatic when the stomach of a suicide victim was exposed [6]. Though activated charcoal may be recommended, it is not known how well activated charcoal binds phosphides and has not been shown to alter outcome in these patients. Historically, dilution with bicarbonate solution has been recommended, although this treatment is based on theory and unproven [115]. The bicarbonate is believed to decrease the gastric hydrochloric acid concentration, which enhances the conversion of phosphides to phosphine gas. Another unproven recommendation is the use of diluted potassium permanganate to remove and oxidize the phosphides [115]. Duenas and colleagues [79] described the use of trimetazidine for the treatment of cardiac toxicity. They suggested that trimetazidine (an antianginal medication) may help mitigate the oxidant stress caused by phosphine [47]. However, trimetazidine is not widely available. Aggressive supportive care is the only approach that can be recommended at this time. This may include the use of extracorporeal membrane oxygenation.

PNU

Gastrointestinal decontamination using activated charcoal, particularly if it can be administered

very early, may be useful. However, it has not been shown to alter outcome in these patients. Management decisions depend on serum glucose determination and hemodynamic monitoring. Hypotension should be treated with volume expansion. If there is no response, a trial of fludrocortisone is warranted (LoE III) [82].

Nicotinamide (vitamin B₃) is a specific antidote for PNU poisoning. Animal models document nicotinamide's early benefits in treating streptozotocin and *N*-nitrosomethylurea toxicity [50, 51, 116]. However, the parenteral formulation is no longer widely available. Historical recommendations were to give 500 mg as a loading dose followed by 100–200 mg every 4 h for 2 days, not to exceed 3 g/day (LoE III). Children were to receive 50% of this dose (LoE III). The subsequent recommended oral dose was 100 mg three to five times per day for 2 weeks (LoE III). In animal models, protection was provided only when the antidote was given before or within hours of exposure [51]. The reported experience with delayed therapy in humans is disappointing [84]. Nicotinic acid was less effective than nicotinamide in a rodent model [117]. Nicotinic acid may not be a safe alternative because its vasodilatory effects may complicate the further treatment of hypotension [85].

Sodium Monofluoroacetate and Fluoroacetamide

Treatment of toxicity from sodium monofluoroacetate and fluoroacetamide consists of the stabilization of any cardiovascular or neurologic effects. If it is able to be given within the first hour postingestion, the administration of activated charcoal may decrease absorption. Theoretical recommendations for lavage with sodium bicarbonate or magnesium sulfate are unproven and most likely would not be of benefit. There are no proven antidotes for the management of these poisonings. Glycerol monoacetate, 0.1–0.5 mL/kg/h, as a Krebs cycle substrate replacement, has prolonged survival in a primate model, but it also

may aggravate toxicity and seems to be effective only early in the course [34, 118]. Ethanol, metabolized to acetate, also has been studied, with inconclusive results. In a more recent mouse model, simultaneous sodium succinate and calcium gluconate, but not calcium gluconate alone, reduced mortality [119]. Therefore, the mainstay of treatment remains critical care life support.

Strychnine

Signs and symptoms of strychnine poisoning can be seen within minutes depending on the route of exposure. Universal precautions should be maintained. Strychnine is absorbed rapidly through the gastrointestinal tract and mucous membranes. Strychnine is cleared by hepatic elimination via cytochrome P-450 system-mediated metabolism [92, 120, 121]. Very little strychnine is excreted unchanged in the urine. Attempts to enhance urinary elimination are of no benefit. Half-lives of 10–16 h have been reported [92, 122, 123]. Recovery within 12–24 h is expected when patients present before complications have developed [63, 95].

Treatment interventions may precipitate seizures; if the diagnosis is known, the patient should be administered benzodiazepines immediately (LoE III). Diazepam or midazolam provides a rapid onset of action. Propofol also may work through GABA agonism and may be an alternative (LoE III). The stimulation of gastric lavage also is contraindicated in a nonparalyzed patient. If the patient is asymptomatic, activated charcoal may theoretically decrease absorption if given within the first hour after ingestion. However, activated charcoal administration has not been shown to alter the outcome in strychnine poisoning. Because of the possibility of strychnine convulsions, giving anything orally after strychnine exposure should be done with great caution. When a patient is intubated, activated charcoal may be given by nasogastric tube. It is doubtful that gastric lavage would provide benefit.

The patient’s airway and ventilation must be monitored continually because respiratory compromise can occur at any time. Blood gases can reflect many abnormalities at different times in the poisoning [90]. Intubation allows aggressive pharmacologic management of the neuromuscular hyperactivity. In most cases, paralysis with a nondepolarizing neuromuscular blocker, such as rocuronium, is recommended to facilitate intubation because the stimulation of endotracheal intubation may precipitate spasms, including trismus or convulsions (LoE III) [96]. In addition to tactile stimulation, auditory and visual stimuli may precipitate seizures. Therefore, the resuscitation and intensive care unit atmosphere should be quiet, dark, and minimally invasive. Convulsions should be treated with benzodiazepines (LoE III), barbiturates (LoE III), or potentially propofol (LoE III). Continuous neuromuscular paralysis is another option if the patient cannot tolerate high doses of the aforementioned agents (LoE III).

Tetramine

No antidote exists for tetramine exposure. Activated charcoal should not be utilized in these patients given risk for aspiration from seizure. Empirically, exposed patients who are altered or seizing should be managed as one would treat a patient in status epilepticus. Universal precautions should be maintained [29].

Criteria for ICU Discharge in Rodenticide Poisoning

Agent	Criteria
Anticoagulants	Control of hemorrhage and reduction of international normalized ratio
ANTU	Improved oxygenation, off ventilator
Barium	Resolution of paralysis, weaning parameters met
Bromethalin Phosphides	Normal mental status Hemodynamic stability, coma resolution
PNU	Hemodynamic stability, acidosis controlled

(continued)

Agent	Criteria
Fluoroacetates, fluoroacetamide	Cardiac rhythm stability, no respiratory compromise
Strychnine Tetramine	Resolution of spasms and seizures with control of acidosis, off ventilator Resolution of seizures and control of acidosis off of the ventilator

Special Populations

Pediatric Patients

Children who present with bleeding complications indicating a significant exposure to anticoagulants warrant the consideration of Munchausen syndrome by proxy. Children rarely, if ever, of their own volition ingest enough brodifacoum to become critically ill with life-threatening hemorrhage [1]. In one report, children who had access to less than one box of the product could be managed without gastric decontamination [1]. In addition, children are likely to experience toxic effects from accidental pesticides exposure at lower doses as the dose per weight exposure is often more significant.

Common Misconceptions About Rodenticide Poisoning

1. Rodenticides other than long-acting anticoagulants are no longer a major risk in many countries because they are heavily regulated. Unfortunately, extremely toxic rodenticides are still readily available in some parts of the world and many products are unknown (Image 5).
2. Potassium replacement alone reverses paralysis in barium poisoning.

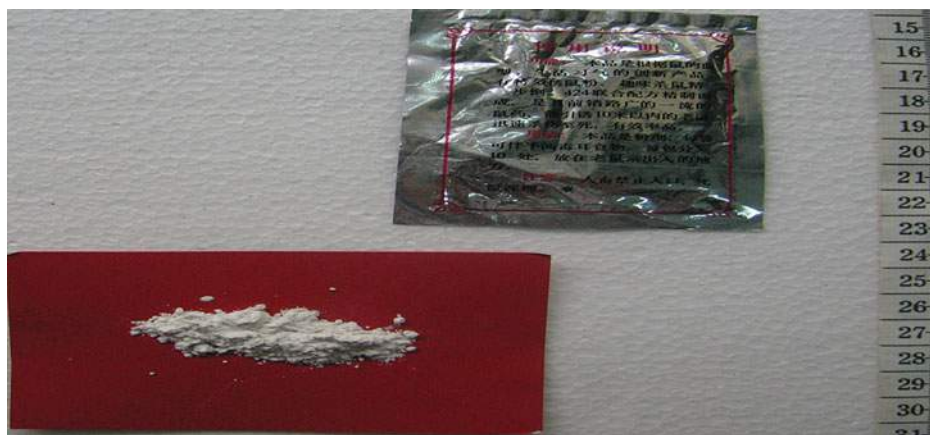


Image 5 Unknown product, many are mixed and the ingredients unknown (Courtesy of Nguyen Trung MD Poison control center, Bach Mai Hospital, Hanoi, Vietnam)

Key Points in Rodenticide Poisoning

1. In most cases, avoid decontamination procedures for strychnine and late-presenting anticoagulant poisoning.
2. The rapid onset of action of most rodenticides makes decontamination procedures of little benefit.
3. Extracorporeal removal speeds recovery from barium poisoning.
4. Respiratory compromise can be multifactorial and may develop quickly or can be insidious for rodenticides.
5. Acidosis and cardiovascular instability are common after exposure to many rodenticides.
6. Many antidotes are not readily available or may be experimental; consult a medical toxicologist when available.
7. The diagnosis of these poisonings is often difficult due to poor histories. Aggressive supportive critical care is the most important to enhance survival.

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Part XVII

Chemical Agents: Gases and Vapors

Christopher Hoyte

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This chapter reviews the clinical presentation, mechanisms of toxicity, and clinical management of carbon monoxide (CO) poisoning. Emphasis is placed on the mechanisms for toxic effects of CO because this provides a demonstration of the continuum of CO-mediated effects, highlights common pitfalls in clinical management, and underscores the challenges that exist in clinical investigations.

Clinical Importance

CO is one of many ubiquitous contaminants of the environment that requires prevention and control measures to ensure adequate protection of the public health. The incidence of CO-related mortality and morbidity is similar worldwide and may be responsible for more than half of all fatal poisonings [1–3]. When normalized to regional population densities, fatality rates are around 0.5–1 per 100,000 in Belgium, Denmark, France, South Korea, Switzerland, Taiwan, the United Kingdom, and the United States [2, 4–14].

CO poisoning has been estimated to cause 40,000 persons per year to seek medical attention at emergency departments in the United States [15, 16]. More than half of the 6000 deaths from fires in the United States each year may be due to CO poisoning [17]. Deaths from suicides by CO poisoning average about 2600 per year in the United States, whereas unintentional deaths seem to be decreasing [2]. Between 1979 and

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1988, the rate of unintentional deaths decreased from 1513 to 878 deaths per year [2], and in the 1990s, the rate of unintentional deaths decreased to 600 deaths annually [15, 16, 18]. The decline may be a result of increased public awareness with the use of CO detectors and alarms, stronger emission controls placed on vehicles, and improvements in safety of heating and cooking appliances.

Despite efforts in prevention and in public and medical education, CO poisoning remains frequent [19–21]. Often individuals with CO poisoning are unaware of their exposure because symptoms are nonspecific and mimic those of viral illnesses. This situation contributes to misdiagnosis of many cases by medical professionals [19, 22–28].

Biochemistry

The toxicity of CO is due to its propensity for forming stable complexes with transition metals. In contrast to oxygen (O₂), CO does not participate readily in reactions involving formal transfer of electrons. Its valence bond configuration is the same as that of chemically inert nitrogen, [:C≡O:] [29]. CO exhibits a small dipole moment, which is what gives CO the tendency to form highly stable linear metal-ligand complexes.

The affinity of CO for hemoglobin is more than 200-fold greater than that of O₂, and formation of carboxyhemoglobin (COHb) is a recognized effect of CO exposure [30]. Pulmonary CO uptake and the variables that influence the body store of CO and COHb level can be estimated reliably by

the Coburn-Forster-Kane equation (Fig. 1). The major issues of clinical relevance are that CO uptake depends on the partial pressure of CO and O₂ in the inspired gas, the ventilatory rate, and the duration of CO exposure [31].

In the lungs, CO binds more slowly to hemoglobin than O₂ does, but this is more than offset by the extremely slow rate of dissociation of CO from hemoglobin. The CO-hemoglobin interaction exhibits cooperativity. COHb cooperativity is driven by the association of CO with hemoglobin, whereas cooperativity for oxyhemoglobin is driven by the off-reaction of O₂ from the two α and β globin chains due to the stability of the deoxy (T state) structure. CO binds to oxyhemoglobin (R state) more rapidly than to the deoxy (T state) structure; this results in two adverse effects for O₂ delivery. First, CO displaces O₂ and is bound to hemoglobin, reducing the amount of O₂ carried to the tissues. Second, the presence of CO in the heme pocket prevents modifications of hemoglobin interchain orientation and bond formation that normally occur with O₂ dissociation, the R state-to-T state conversion. The presence of CO increases the O₂ affinity of the protein, causing a left shift of the oxyhemoglobin dissociation curve. The resulting COHb dissociation curve has virtually the same shape as the O₂ dissociation curve. Because of the increased affinity of CO compared with O₂, the fraction of total hemoglobin converted to COHb increases steeply with small increases in CO partial pressure. At a CO partial pressure of only 0.16 mmHg, 75% of the hemoglobin is combined with CO; this is why relatively small amounts (<0.1% of inspired air) of CO can inhibit the function of a large

$$\exp(-tA/V_bB) - A[\text{COHb}]_t - BV_{\text{CO}} - P_{\text{ICO}} / A[\text{COHb}]_0 - BV_{\text{CO}} - P_{\text{ICO}}$$

$$\text{where: } A = P_{\text{CO}_2}/M[\text{HbO}_2]$$

$$B = 1/DL_{\text{CO}} + P_1/V_A$$

Fig. 1 Coburn-Forster-Kane equation. *T* exposure duration, *V_b* blood volume in milliliters, *P_{CO}* average partial pressure of oxygen in lung capillaries, *M* equilibrium constant for reaction of carbon monoxide (CO) with oxyhemoglobin, [*HbO₂*] oxyhemoglobin as milliliters of oxygen per milliliters of blood, *DL_{CO}* diffusing capacity of the lungs for CO in milliliters per minute per mmHg, *P_L* barometric

pressure minus vapor pressure of water at body temperature, *V_A* alveolar ventilation rate per minute, [*COHb*]_{*t*} milliliters of CO per milliliters of blood at time *t* after exposure, *V_{CO}* rate of endogenous CO production, *P_{ICO}* partial pressure of CO in inhaled air, [*COHb*]₀ carboxyhemoglobin in milliliters of CO per milliliters of blood before exposure. Units for partial pressures of gases are mmHg

proportion of the hemoglobin in blood. When this happens, the hemoglobin concentration and O_2 partial pressure of blood may be normal, but the O_2 content of the blood is grossly reduced due to the reduced amount of oxyhemoglobin. This reduction has important clinical implications. Chromatographic measurement of oxyhemoglobin does not monitor oxygenation status adequately. Pulse oximetry commonly is used in emergency departments and intensive care units, but values do not correlate with COHb levels and overestimate arterial oxygenation [32].

The affinity of CO varies with different heme-containing proteins because amino acid residues on the protein chains modify the binding pocket at the heme porphyrin ring. In the β chain of hemoglobin A, the E7 histidine and E11 valine residues sterically interact with the heme-bound CO and push the ligand off the heme axis. This interaction has a significant effect on the heme-CO bond and on the CO combination rate. In mutant hemoglobin A chains or hemoglobin molecules from other animals that do not have these types of steric hindrances, the CO combination rates are much higher [33]. Studies with synthetic iron porphyrin proteins have shown that amino acids can impede ligand binding by presenting steric hindrances to CO [34]. Other, more subtle variations in the heme binding pocket, the so-called docking site, also influence binding kinetics. The dissociation rates for CO vary markedly among different heme proteins. These rates cannot be explained based on steric hindrance, but they appear more likely to be related to alterations in the polarity within the heme pocket [35]. The amino acid residues surrounding the heme in myoglobin modulate ligand binding affinity. The binding affinity of CO compared with O_2 is reduced approximately 50-fold compared with the affinity for the free heme moiety. The difference in myoglobin is thought to be due to the characteristic geometry within the docking site, which impedes CO more so than O_2 [36].

Although clinicians may believe the details of CO chemistry have little relevance to their practice, these may have a substantial impact on understanding of the pathophysiology of CO poisoning. Physiologic stresses of CO classically

are related to competition between CO and O_2 for hemoproteins; more recent attention has focused on interactions between CO and another small gaseous ligand, the free radical nitric oxide ($\bullet NO$) (Fig. 2). Under virtually all circumstances, the affinity of $\bullet NO$ for hemoproteins is vastly greater than that of either CO or O_2 . Despite this fact, there are situations in which CO disturbs the association between $\bullet NO$ and hemoproteins. CO increases the steady-state concentration of $\bullet NO$ in and around platelets and endothelial cells [37–39]. Electron paramagnetic resonance spectroscopy has provided direct evidence that exposure to CO increases the concentration of $\bullet NO$ in the lung and brain [40, 41]. CO does not increase activity of nitric oxide synthase (NOS) in platelets or endothelial cells, and CO does not increase NOS protein concentration in tissues of CO-exposed rats at a time when they exhibit elevated $\bullet NO$ levels [37–39, 41–43]. CO partially inhibits NOS activity in rats exposed to 3000 ppm who have COHb levels of approximately 45% [37]. It seems that CO increases the steady-state level of unbound $\bullet NO$ because it competes for intracellular sites that normally would bind $\bullet NO$. Toxic effects on cells occur because the liberated $\bullet NO$ is available to undergo reactions with superoxide anion ($O_2^{\bullet -}$), which yield the potent oxidizing and nitrating agent peroxynitrite. These events are a component to CO-mediated brain injury in some animal models [40, 44–46], and they may relate to a growing body of evidence suggesting that CO functions as a cell-signaling messenger analogous to $\bullet NO$ [47, 48]. Whenever CO is generated in vivo by heme oxygenase, if $\bullet NO$ also is produced in the vicinity, the CO may act to increase the effective steady-state concentration of $\bullet NO$.

The mechanism behind the apparent ability of CO to increase steady-state concentration of $\bullet NO$ is under investigation. The following discussion relates my current hypothesis. It is based on an assessment of potential competition between ligands using published values for the association and dissociation constants for myoglobin, which may be used as a “model” intracellular hemoprotein (Table 1) [49].

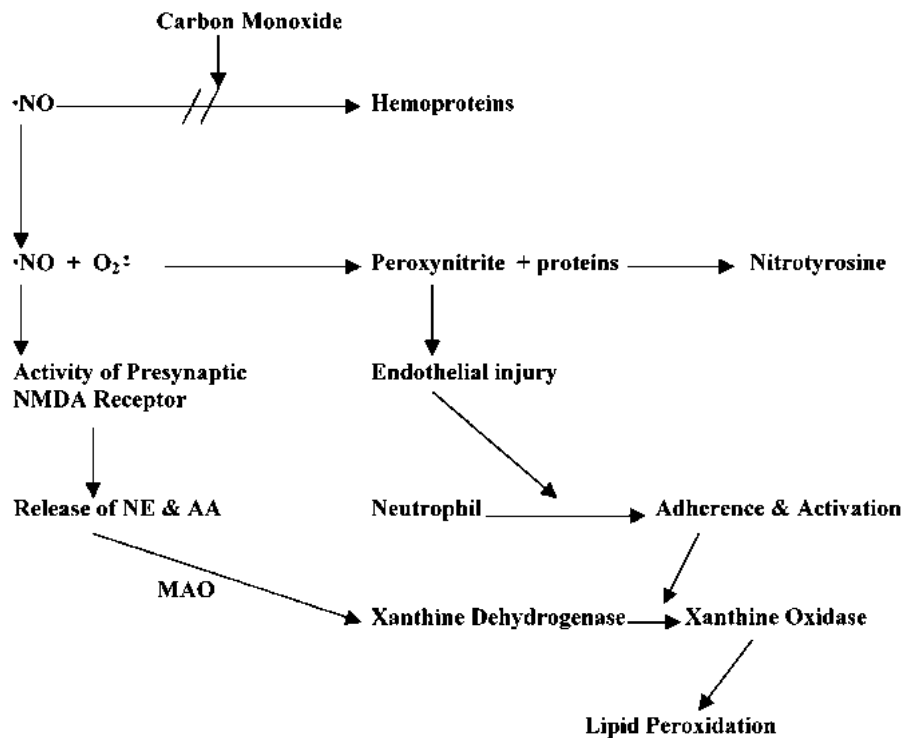


Fig. 2 Interactions between carbon monoxide and the free radical nitric oxide ($\bullet\text{NO}$). *AA* amino acid, *MAO* monoamine oxidase, *NE* norepinephrine, *NMDA* N-methyl-D-aspartate

Table 1 Rate constants for different ligands with myoglobin

Gas	Association rate constant (M ⁻¹ s ⁻¹)	Dissociation rate constant (s ⁻¹)
O ₂	14 × 10 ⁶	12
•NO	17 × 10 ⁶	1.2 × 10 ⁻⁵
CO	0.5 × 10 ⁶	1.9 × 10 ⁻²

The calculated affinity binding constant favors $\bullet\text{NO}$ over CO by a factor of 10^5 when steady-state concentrations of CO and $\bullet\text{NO}$ are equal (e.g., for $\bullet\text{NO}$, $1.7 \times 10^7 / 1.2 \times 10^{-5} = 1.4 \times 10^{12}$; for CO, $0.5 \times 10^6 / 1.9 \times 10^{-2} = 2.6 \times 10^7$). It is unlikely, however, for both ligands to have equal concentrations in vivo. Coburn [50] showed that a predictable relationship exists between the tissue concentration of CO and blood COHb to a level of 50%. At a COHb of 7%, the extravascular fluid CO concentration should be approximately 22×10^{-9} M [50, 51]. Because CO is freely soluble, a similar concentration is expected to occur inside

cells. The rate of $\bullet\text{NO}$ production by endothelial cells (which may be taken as an example because these cells are physically close to delivered CO from the blood) has been estimated to be 1.1×10^{-18} M/cell/min [52]. Even in a situation in which there is a relatively low COHb, the CO concentration may be 10^9 greater than the concentration of $\bullet\text{NO}$. Competition is feasible even when considering equilibrium kinetics.

The potential for effective competition is even more favorable for CO when considering simple competition kinetics. It is more appropriate to make an assessment of competition using the association rate constants for these ligands, rather than the affinity constants. The physiologic and clinical settings where this relationship may have bearing are early during a CO exposure from exogenous sources, whenever there is a change in CO production in vivo, or when a reduction in local $\bullet\text{NO}$ production occurs. Because the association constant for CO and $\bullet\text{NO}$ differs by a factor of only 34, even a

small increase in CO concentration relative to that of •NO would have an impact favoring CO competition with •NO for myoglobin. Adverse effects on endothelial cells in vitro that are mediated by •NO-derived oxidants can be shown with exposure to a CO concentration of only 11×10^{-9} M [43]. There also may be physiologic conditions that allow favorable competition between CO and •NO. Liver parenchyma has been estimated to generate 0.45×10^{-9} M CO/g liver/min [53].

Pathophysiology

Hypoxic effects of CO were described by Bernard [54] and Haldane [55]. An elevated COHb can precipitate tissue hypoxia which seems to be responsible for fatalities, cardiac injuries, and the acute neurologic abnormalities that develop in approximately 14% of survivors of serious CO poisoning [56–58]. Clinical and animal studies have failed to establish a consistent correlation, however, between elevated COHb levels and delayed neurologic injuries. Delayed neurologic injury is the most frequent form of CO-associated morbidity [4, 59–66]. Studies indicate that 23–47% of patients with CO poisoning develop impairments of concentration and learning, dementia, cogwheel rigidity, amnesia, or depression 6 days to 3 weeks after poisoning [65, 67–69]. These events occur despite rapid and appropriate emergency care followed by careful neuropsychologic evaluations. CO poisonings that seem to be mild also may cause subtle neurologic dysfunction, which indicates that the clinical assessment of the severity of poisoning is unreliable [65, 70–72].

Severe CO poisoning causes mitochondrial dysfunction and oxidative stress in the central nervous system. In experimental CO poisoning, mild manifestations occur when cerebral perfusion is maintained, whereas mortality and morbidity are profoundly enhanced when exposures to high CO concentrations occur in the presence of reduced cerebral perfusion [73]. The concomitant impairment of cerebral blood flow can be triggered by cardiac

dysfunction due to CO or to fixed cerebrovascular lesions [73–77].

In the presence of concomitant hypoperfusion, Coburn and associates [78] showed that 20–45% of CO present in circulating blood shifts into skeletal muscle and other tissues. CO impairs mitochondrial electron transport when cells sustain a reduction in O₂ delivery, as occurs when an elevated COHb level occurs concurrent with restricted perfusion [75, 76]. In the setting of hypoperfusion and high CO concentrations, CO binds to cytochrome *c* oxidase, which inhibits adenosine triphosphate synthesis and causes generation of hydroxyl-like radicals [76, 79]. Energy production and mitochondrial function are restored as COHb levels decrease [76]. These observations have not explained the two historical characteristics of clinical poisoning that are correlated with a high risk for delayed morbidity: (1) a prolonged exposure to CO, called a *soaking*, and (2) syncope or temporary unconsciousness [59, 80–84]. It is unclear whether the transient changes observed during CO poisoning precipitate delayed neuronal dysfunction or death [85]. In some models with neuronal injuries, it has been difficult to document evidence of impaired mitochondrial function or a cellular hypoxic stress [77].

The level of CO in tissues likely has an equal or greater impact on the clinical status of patients and development of pathology than does the blood level of CO. This phenomenon is shown most clearly with regard to CO-mediated vascular injuries. When humans or experimental animals have been exposed to relatively low CO concentrations for extended periods, capillary leakage of macromolecules from the lung and systemic vasculature has been documented [41, 42, 86–89]. In contrast, when an hypoxic stress was established in animals by exposing them for 8–45 min to extremely high CO concentrations, sufficient to cause COHb levels of 60–90%, capillary leakage was not detected [90–92]. As noted in the prior section, a proposed pathologic mechanism of CO that is independent of hypoxic stress has been shown in experimental studies to be due to elevations in the steady-state concentration of the free radical •NO (see Fig. 2) [41, 42].

CO increases the steady-state concentration of •NO in and around platelets and endothelial cells [37–39]. Electron paramagnetic resonance spectroscopy has provided direct evidence that exposure to CO increases the concentration of •NO in the lung and brain [40, 41]. Some liberated •NO undergoes reaction with superoxide anion ($O_2^{\cdot -}$) to yield the potent oxidizing and nitrating agent peroxynitrite. The major product when peroxynitrite reacts with proteins is nitrotyrosine, which can be measured in tissues. Nitrotyrosine concentration is increased in the aorta, lung, and brain when rats are exposed to CO for more than 40 min, and it is found closely associated with the vascular endothelium [40–42]. CO causes a capillary leak in skeletal muscle and in lungs that is mediated by •NO [41, 42].

These findings have provided further insight into CO-induced neuropathology because endothelial •NO-mediated changes are a prerequisite for neutrophil adherence to the cerebral microvasculature of CO-poisoned animals [40, 45, 46]. •NO-mediated vascular stress is not sufficient by itself, however, to cause neutrophil sequestration in this model of CO-mediated brain injury. During the latter portion of the exposure, when rats breathe 3000 ppm of CO and become unconscious, they invariably sustain a period of hypotension that presumably is mediated by cardiac decompensation [44, 77, 93]. Cerebral blood flow, which initially is approximately 150% greater than normal due to •NO-mediated vasodilation, decreases to about 50% below normal for 4–6 min when rats lose consciousness [77, 93]. With regard to mechanisms of brain injury, in contrast to typical hypoxic-ischemic injury, there is never a time when cerebral blood flow is nil, and the interval of hypoperfusion is less than 6 min [77, 93]. The sudden reduction in microvascular blood flow, coupled with the •NO-mediated oxidative changes to endothelium, causes neutrophils to adhere to endothelium.

Activated neutrophils attach to the vascular wall via interactions between β_2 integrin adhesion molecules and endothelial counterreceptors [94]. β_2 integrin adhesion molecules are required for neutrophil adherence and progression of the oxidative stress cascade in CO poisoning [40, 46,

95, 96]. This cascade occurs 45 min after rats are removed from CO, based on the inhibitory potential of monoclonal antibodies to β_2 integrins [47, 96]. The 45-min delay between initial adherence and β_2 integrin commitment is unusually long compared with some models of leukocyte-mediated tissue injury. The delay is due to the flux of •NO from platelets [37]. Nitric oxide inhibits β_2 integrin function [97]. Activated leukocytes liberate proteases and reactive O_2 species that cause conversion of endothelial xanthine dehydrogenase to xanthine oxidase, and xanthine oxidase activity is required for subsequent brain lipid peroxidation [40, 44–46]. These biochemical events occur within 90 min after CO poisoning. Metabolic defects in the basal ganglia and hippocampus appear at 5 days, and evidence of impaired learning plateaus 3 weeks after poisoning [98]. The cellular and biochemical events that occur during this 3-week period are under active investigation [99]. In other models of CO-mediated brain injury, hyperbaric oxygen (HBO_2) therapy has been shown to diminish cerebral edema, reduce mortality, and improve neurologic outcome [74, 100, 101].

Several investigations have suggested an association between CO-induced neurotoxicity and neurotoxicity caused by excitatory amino acids [102, 103]. Although this issue currently is under investigation, at least in some studies excitotoxicity is linked to elevations of intracellular calcium, •NO, and $O_2^{\cdot -}$ [104, 105]. Three types of receptors are activated by excitatory amino acids: *N*-methyl-D-aspartate (NMDA), D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainic acid [104]. Agents that inhibit NMDA receptor activation attenuate CO-mediated delayed neuronal degeneration of pyramidal cells in the hippocampus and cochlear ganglion cells [106, 107].

Monoamine neurotransmitters, such as norepinephrine and dopamine, are elevated after CO exposure; enzymatic breakdown and auto-oxidation generate reactive O_2 species [108, 109]. These agents seem to contribute to oxidative stress after CO poisoning because free radical production in the brain can be diminished by inhibiting monoamine oxidase B, an enzyme located in microglial cells [110–112]. Nitric

oxide augments presynaptic release of monoamine neurotransmitters by activating NMDA receptors [113, 114]. Activated microglia also can mediate neuronal injury by generating •NO-derived oxidants [115]. Microglia can attack oligodendroglia and have been associated with demyelination processes [116]. •NO-mediated oxidative stress may be a common biochemical link among different pathways of CO poisoning.

Neuropathology after CO poisoning may include neuronal death in the cortex, hippocampus, substantia nigra, and globus pallidus [117]. One of the most common abnormalities is demyelination of the cerebral cortex, which occurs in a perivascular distribution along with evidence of a breach in the blood-brain barrier [117–119]. Blood flow and perivascular abnormalities have been shown using several neuroimaging techniques [120–125]. Acute vascular and perivascular changes also have been found in brains of experimental animals [44, 60, 64]. The variability observed in lesions found in the cerebral white matter and globus pallidus of animals has been correlated with the decrease in local blood flow and metabolic acidosis [58, 126]. Clinical and experimental findings suggest that the effects of CO are global, and variations in the clinical manifestations of poisoning arise because brain regions respond differently to the stresses. Acute neurologic compromise may be due to direct hypoxic stress. The syndrome of delayed neurologic sequelae seems to be a consequence of a cascade of events involving oxidative stress and inflammatory responses.

Clinical Effects

When CO enters the body via the lungs, pulmonary cells may be injured by direct interactions, without the need for delivery of CO by blood-borne hemoglobin. Elsewhere in the body, CO is delivered by hemoglobin, and concentrations found in perivascular and extravascular sites are estimated using calculations first described by Coburn (see Fig. 1) [50]. The symptoms, signs, and prognosis of acute CO poisoning correlate poorly with the level of

COHb measured at the time of arrival at the hospital [4, 61–66, 104]. These observations have created two concerns. The first is that investigators must be careful when attempting to study patient populations because determination of the severity of poisonings and the efficacy of treatment is difficult. The second concern is that these clinical observations raise questions regarding the mechanisms of toxicity beyond the classic perspective regarding hemoglobin binding by CO.

Neurologic symptoms of CO poisoning generally are more severe with higher COHb levels, including headache, dizziness, nausea, vomiting, weakness, confusion, disorientation, visual disturbances, and unconsciousness. Cardiac rhythm disturbances include sinus tachycardia, atrial flutter and fibrillation, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation. Myocardial infarction can occur, even among patients with normal coronary vessels [127, 128]. Pulmonary edema in association with CO is relatively rare; it typically occurs as a consequence of congestive heart failure. Pulmonary edema is seen more commonly in patients with concomitant smoke inhalation, and in these patients it may be related to inhalation of the myriad toxic combustion products [129]. Skeletal muscle necrosis can occur and with it acute renal failure. Other rare complications include pancreatitis and hepatocellular injuries. Textbooks often contain tables listing symptoms associated with different COHb levels. Practicing physicians should spend little time examining these lists, however, because the relationship between clinical presentation and COHb levels is extremely poor.

Patients may sustain neurologic abnormalities that are present during the acute hospitalization and either never resolve or resolve slowly over weeks to months after poisoning. Alternatively, patients may develop a delayed neurologic syndrome in which they manifest new cognitive deficits days to weeks after apparent recovery. These manifestations include impaired judgment, poor concentration, memory loss, and a relative indifference to obvious neurologic deficits (e.g., movement disorders, incontinence, speech

disturbances, parkinsonian syndrome, and, rarely, tremors).

Diagnostic Tools

Large clinical surveys reported a correlation between neurologic morbidity and the occurrence of an interval of unconsciousness during CO exposure [59, 81, 82]. This overt insult is not always necessary, however, for neurologic injuries to occur in humans [65, 70–72]. Using traditional neuroimaging techniques, such as computed tomography and magnetic resonance imaging, brain lesions have been detected sporadically in severely poisoned CO patients [130, 131]. The primary shortcoming with these imaging techniques is their limited sensitivity; neuroimaging has not yet provided a reliable method for assessing the severity of CO poisoning. Bianco and Floris [120] and Silverman and colleagues [125] hypothesized, however, that the initial site of injury by CO may be the vasculature, based on detection of hemosiderin deposits. These deposits are thought to result from focal hemorrhages.

More sophisticated neuroimaging techniques have been used to detect abnormalities in patients who, in some cases, exhibited only subtle neurologic impairments. Abnormalities in resting cerebral blood flow [123, 124] and abnormalities in cerebral vasoactivity to CO [122] have been detected by single-photon emission computed tomography. Changes also have been detected that suggest CO causes a disturbance in coupling between neuronal O₂ demand and blood flow. DeReuck and coworkers [121] examined seven patients 5–7 days after CO poisoning using positron emission tomography with ¹⁵O₂. They found a global increase in cerebral O₂ extraction along with regional areas of diminished blood flow, especially in the frontal and temporal lobes. Although these observations underscore the vascular nature of CO-mediated neuropathology, they do not assist with clinical assessments of patients. To date, no objective parameters that prospectively assess the severity of poisoning have been identified. Some more recent findings

with state-of-the-art neuroimaging techniques have exhibited correlations with the clinical improvement in case reports, whereas others show abnormalities when no clinical changes are noted [132–134]. In experimental studies, blood levels of glutathione, oxidized proteins, and products of lipid peroxidation offer insight into CO-mediated pathology [135]. Additional work is necessary, however, to establish if these or some other survey may be useful to stage the severity of clinical poisonings.

Treatment

As in any critical care setting, initial attention must be focused on restoring or maintaining vital functions. Preservation of a patent airway, ventilation, oxygenation, and adequate perfusion is the foundation for proper actions in serious CO poisoning. Emphasis is placed on O₂ treatment because the rate of COHb dissociation is proportional to the arterial O₂ partial pressure [136].

A great deal has been written about HBO₂ therapy for CO poisoning. HBO₂ therapy is a patient treatment modality in which a person breathes 100% O₂ while exposed in a treatment chamber to increased atmospheric pressure. Treatments typically are conducted at pressures two to three times higher than normal atmospheric pressure (14.7 psi) or 2–3 atm absolute (ATA). The hyperbaric chamber per se is not the therapeutic agent. Oxygen is the therapeutic drug, and the chamber is used as a dosing device. At ambient pressures, 100% oxygen reduces the half-life of COHb from about 320 to 85 min. Furthermore, at 2.5 ATA, the half-life is reduced to 20 min [137, 138].

Indications for ICU Admission in Carbon Monoxide Poisoning

Persistent depressed level of consciousness
Cardiac ischemia
Intercurrent critical illness (e.g., aspiration, acidosis, cotoxicants)

Since 1960, HBO₂ therapy has been used with increasing frequency for severe CO poisoning because clinical recovery has seemed to be improved beyond that expected with ambient pressure O₂ therapy [63, 67, 139]. No definition has been established for staging the severity of CO poisoning, however. It is difficult to evaluate patients in a prospective manner or compare the efficacy of different treatments. For this reason, studies that have selected a discrete, presumably more homogeneous, subset of patients may provide information that is more reliable.

Support for use of HBO₂ therapy comes from animal and a basic science experience and from nonrandomized comparative studies [58, 63, 139–144]. The initial motivation for administering HBO₂ therapy was to hasten the removal of CO, based on the well-known relationship that COHb half-life is inversely related to the inspired partial pressure of O₂ [136, 145]. Also, hyperbaric oxygen increases the total amount and concentration of dissolved oxygen by approximately ten times. This is sufficient to supply the body with its metabolic needs even in the absence of hemoglobin [146]. HBO₂ therapy also hastens dissociation of CO from cytochrome oxidase [75, 76] and inhibits cerebral edema in experimental CO brain injury [74, 100]. In rats poisoned with carbon monoxide which had subsequent loss of consciousness, hyperbaric oxygen was superior to normobaric oxygen in preventing brain lipid peroxidation [46]. Vascular oxidative stress is prevented because HBO₂ therapy inhibits β_2 integrin-dependent leukocyte adhesion [96, 147]. Neutrophils from humans exposed to HBO₂ exhibit the same diminished adherence as neutrophils in animal studies [148].

In 1969, a retrospective study reported that HBO₂ reduced mortality and morbidity only if administered within 6 h after CO poisoning [140]. In a prospective trial involving patients with mild-to-moderate poisoning, 23% of patients (7 of 30) treated with ambient pressure O₂ developed neurologic sequelae, whereas no patients (0 of 30; $P < 0.05$) treated with HBO₂ (2.8 ATA) developed sequelae [65]. HBO₂ therapy also was reported to have a significant benefit in

another prospective, randomized trial [122]. Twenty-six patients were hospitalized within 2 h of discovery and equally divided between two treatment groups: ambient pressure O₂ or 2.5 ATA O₂. Three weeks later, patients treated with HBO₂ had significantly fewer abnormalities on electroencephalogram, and single-photon emission computed tomography showed that cerebral vessels had nearly normal reactivity to carbon dioxide, in contrast to diminished reactivity in patients treated with ambient pressure O₂.

Mathieu et al. [68] reported on a large trial of HBO₂ therapy for CO poisoning ($n = 575$ patients). Among noncomatose patients who had experienced transient unconsciousness, those treated with ambient pressure O₂ had a higher incidence of delayed sequelae. Most sequelae spontaneously resolved over 6 months.

Due to the concern for the development of delayed neurologic sequelae, as well as for the relatively low risk of complications in the administration of hyperbaric oxygen, greater than 1000 patients receive this therapeutic each year in the United States [149]. There is a legitimate concern over the lack of reliable methods to assess the severity of poisoning. The use of HBO₂ therapy in every CO-poisoned patient who has had loss of consciousness during CO exposure or who has a neurologic abnormality on clinical examination continues to be advocated by some. In addition to its use for patients with transient unconsciousness and neurologic signs, some clinicians treat patients with HBO₂ when they have abnormal psychometric test results and if the COHb level is greater than a certain value. Some use a COHb of 40%, whereas others use 25%, regardless of symptoms [150, 151]. Important caveats regarding HBO₂ therapy include the observation that treatment efficacy, if any, may diminish if treatment is delayed for more than 6 h after poisoning [67, 140].

A large and growing body of clinical studies is showing that the benefits of HBO₂ in the setting of carbon monoxide poisoning is not as clear as demonstrated in animal and basic science experience. Some centers have proposed using a psychometric screening test to identify patients with

subtle neurologic compromise and as a method to stratify patients for treatment. However, this approach has not been empirically validated. When examined in a prospective study, abnormalities during the initial screening did not correlate with the development of delayed sequelae [65].

The first prospective clinical trial involving HBO₂ therapy did not find it to be superior to ambient pressure treatment [69]. Additionally, Scheinkestel et al. [152] performed a prospective trial of 191 patients and reported no benefit from administration of HBO₂ and ambient pressure O₂ therapy that extended over days. Concerns with this study include the following: There was a mean delay to treatment of 7.5 h, symptoms of O₂ toxicity occurred in the experimental group, and only 46% of patients who entered the study were assessed to evaluate delayed neurologic sequelae. A reevaluation of the subset of Scheinkestel's patients presumed to have mild CO poisoning demonstrates the difficult issues with patient evaluation and selection criteria. Using the "mildly" poisoned subset of patients, Kehat and Shupak [153] examined the difference in incidence of acute or persistent neurologic sequelae between the two treatment groups. Patients treated with HBO₂ had a significantly lower incidence of sequelae than patients treated with ambient pressure O₂.

A more recent investigation of 179 patients demonstrated that there was no benefit from a single hyperbaric oxygen treatment in those with a transient loss of consciousness. The authors showed that neurologic recovery after 1 month was the same (60%) regardless of whether or not the patients had hyperbaric oxygen or normobaric oxygen [154].

The threshold for using HBO₂ therapy, if any, has not been established clearly. Despite the widespread use of HBO₂ by some centers, a recent Cochrane review was not able to demonstrate a benefit to the use of hyperbaric oxygen in the setting of carbon monoxide poisoning. While no clear benefit was established, the possibility of a benefit was also not definitely ruled out [155]. Thus, the lack of consensus in the interpretation of the existing evidence is such that that hyperbaric oxygen should not be considered the standard of care at this time.

A small amount of evidence exists that patients presenting with a history of loss of consciousness or comatose are likely to benefit most from this therapy in an attempt to prevent delayed neurologic sequelae [156]. It is likely that syncope is secondary to the hypotension needed to initiate the neurologic damage in the setting of carbon monoxide poisoning. This has been demonstrated in animal models [58, 157]. Patients who present after long exposures to carbon monoxide (6 h or no longer) are also at risk of developing delayed neurologic sequelae [80]. In addition, patients with a metabolic acidosis or those with an alteration in level of consciousness to a GCS < 9 also had a greater risk of developing delayed neurologic sequelae. Another factor considered in determination as to whether hyperbaric oxygen should be considered is the development of myocardial ischemia. Despite these assertions, controlled trials show that in patients not treated with hyperbaric oxygen, no reliable factors at the time of presentation were found for predicting patients at risk to develop delayed cognitive sequelae [156]. In this analysis, age >36 years and carbon monoxide exposure >24 h of duration were associated with a greater risk of cognitive dysfunction at 6 weeks [156]. In one prospective study investigating carbon monoxide poisoning, cerebellar dysfunction is associated with a greater risk of cognitive sequelae [156]. Signs and symptoms currently used by many clinicians to determine the need for HBO₂ include syncope, neurologic dysfunction, seizure, cerebellar ataxia, coma, as well as alteration in mental status [158–160]. This is regardless of their carboxyhemoglobin concentration. It is noteworthy that patients who suffered cardiac arrest secondary to carbon monoxide poisoning and subsequently received hyperbaric oxygen all died [161]. If the decision is made to use HBO₂, the first consideration must be the logistical requirements of transporting a patient to a hyperbaric facility. One group examined this question in their review of 297 consecutive CO-poisoned patients and concluded that transfer need not be deferred because of a concern over cardiac or respiratory arrest, myocardial infarction, or deterioration in mental status if these events had not occurred

before transfer [162]. The potential adverse effects of HBO₂ therapy per se are rare, and they usually are mild and self-limited. Relative risks always must be considered in any therapeutic setting, however. Preexisting conditions that require some forethought and possible management before initiating HBO₂ therapy include patients with claustrophobia, sinus congestion, and scarred or noncompliant structures in the middle ear (e.g., in patients with otosclerosis) [163]. Middle ear barotrauma due to eustachian tube dysfunction may occur in 2% of patients and is managed easily by oral decongestants or rarely by tympanostomy tubes [164]. Transient nearsightedness, thought to be related to lenticular changes from O₂, occurs in association with treatment courses spanning weeks in approximately 33% of patients older than age 50. This risk is not a concern when treating CO poisoning because the course of therapy typically spans only one to three treatments. The visual changes resolve 3–6 weeks after treatments cease [163]. There are no notable pulmonary oxygen toxicity risks with therapeutic protocols [165–167] because the duration of exposure usually is kept to less than 2 h. Patients may have central nervous system O₂ toxicity, which is manifested as a grand mal seizure. In the general population, central nervous system O₂ toxicity occurs with a frequency of approximately 1 in 10,000, but among CO poisoning victims, it may be more frequent, possibly due to the direct effects of CO or to concomitant respiratory acidosis. Regardless, if mechanical trauma can be avoided during the convulsion, there are no residual effects [165]. Vasoconstriction is a physiologic effect of hyperoxygenation; this causes negligible changes in blood pressure because of a small (about 10%) decrease in cardiac output, principally caused by vagal stimulation with a reduction in heart rate [168]. Previous exposure to the chemotherapeutic agent bleomycin is considered a relatively strong contraindication to HBO₂ therapy. Bleomycin exacerbates pulmonary oxygen toxicity [169, 170]. On a case-by-case basis, careful consideration of this risk must be weighed against the potential benefits of HBO₂ therapy. The only well-recognized absolute contraindication for

HBO₂ therapy is an unvented pneumothorax, based on the risk of exacerbating this condition while in the hyperbaric chamber and especially on decompression.

Special Populations

Pregnant Patients

The clinical outcomes of CO poisoning for the mother and fetus do not correlate with maternal COHb concentrations. They do not accurately estimate fetal CO-hemoglobin concentrations or fetal CO tissue burden [171]. Maternal symptoms at the time of exposure are associated with fetal morbidity and mortality [172, 173]. In some series, the fetuses of severely symptomatic pregnant patients suffered stillbirths and cerebral palsy [174]. When mother and fetus survive, many fetuses subsequently develop somatic and neurologic sequelae, including malformations of limbs, hypotonia and areflexia, persistent seizures, mental and motor disabilities, and microcephaly [175, 176].

Hypoxic stress related to impaired O₂ delivery is an obvious component to fetal distress. Normal fetal arterial PO₂ is about 20 mmHg versus 100 mmHg for maternal arterial blood. The fetal O₂ exchange typically occurs near the steep portion of the oxyhemoglobin dissociation curve. A small decline in maternal PO₂ can cause a precipitous decline in fetal PO₂. This physiologic stress occurs more quickly than that associated with CO binding to fetal proteins. The decline in fetal arterial oxygen content occurs rapidly as CO concentrations approach 3000 ppm [175]. In studies with sheep, Longo and Hill [177] showed that fetal COHb does not reach steady state until approximately 36–48 h, whereas maternal COHb reaches steady state in 7–8 h. These sheep studies derived the popular notion that fetal hemoglobin has a higher affinity for CO than maternal hemoglobin. In vitro studies, however, demonstrate that fetal hemoglobin is 0.8 times the affinity for CO than maternal hemoglobin [178].

The second insult related to fetal COHb is a disturbance in the O₂-hemoglobin dissociation

curve. Binding by CO causes a left shift of the curve, which increases the hypoxic stress to the fetus. Fetal COHb concentration rises more slowly than does maternal COHb, but when steady state is reached, the fetal level is higher; this is related to the higher affinity fetal hemoglobin has for CO compared with hemoglobin A. The human fetal-maternal COHb concentration ratio is 1.1:1.0; that is, at steady state, the fetal COHb concentration is 10–15% higher than maternal COHb. Although the slow uptake kinetics may be viewed as a protective factor for the fetus, the dynamics work in reverse for CO elimination. In studies with sheep, the half-life for fetal COHb was nearly double that for maternal COHb [177]. For this reason, clinical recommendations for treating CO poisoning in pregnant women with ambient pressure O₂ suggest that pregnant women should breathe 100% O₂ five times longer than the time it takes for their own blood to register negligible residual COHb.

The current recommendations for use of HBO₂ therapy in pregnant women are essentially the same as the recommendations to treat any other patient. First, pregnant patients should receive 100% oxygen (typically by facemask). It is important to note that elimination of CO from fetal circulation is slower (approximately 3.5 times slower) than maternal circulation. Case series show that pregnant patients presenting without loss of consciousness or alteration in mental status go on to have uncomplicated deliveries [172, 178]. Some groups also treat based solely on an elevated COHb concentration. Anecdotal clinical reports suggest that HBO₂ therapy may improve fetal outcome [173, 178–183]. The only experimental study addressing the efficacy of HBO₂ for reducing fetal risk from acute CO poisoning showed a reduction in spontaneous abortion in pregnant rats [184]. There are no significant extra risks presented to the fetus or mother due to HBO₂ therapy [185, 186]. Therefore, hyperbaric oxygen may be considered for CO-poisoned pregnant patients who present with alterations in mental status and loss of consciousness. However, given that toddlers and infants have no abnormalities in reaching their developmental

milestones in normal appearing pregnant patients exposed to CO, similar considerations for hyperbaric oxygen therapy of all patients should apply to this group.

Pediatric Patients

Clinical signs and symptoms of CO poisoning in children are the same as in adults. Children may become symptomatic during CO exposures sooner than adults, however, owing to their higher metabolic rates, respiratory exchange requirements, and smaller blood volumes [187, 188]. Studies demonstrate that pediatric patients are potentially symptomatic at lower COHb concentrations than adults [189]. Children may present with vague symptoms of nausea, vomiting, and headache, and the condition may be misdiagnosed as gastrointestinal disease [190]. Delayed neurologic sequelae have been reported in children [191, 192], and there is a case report of hydrocephalus after CO poisoning [193]. Case series demonstrate that pediatric patients appear to have a decreased incidence of delayed neurologic sequelae compared to adults [194]. Though low, there is a risk of delayed neurologic sequelae. HBO₂ therapy should be considered in pediatric CO poisoning. The threshold for treating children is the same as for adults.

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Common Errors in Cyanide Poisoning

- Failure to administer antidotal therapy rapidly when cyanide poisoning seems a likely possibility
- Failure to realize the potential for falsely elevated whole-blood cyanide concentrations when serum thiocyanate levels are above normal
- Forgetting that patients with cyanide poisoning can be cyanotic
- Failure to appreciate that cyanide poisoning can be delayed for many hours after exposure to nitriles
- Believing that all victims of cyanide poisoning must have bright red skin or blood
- Believing that hydrogen cyanide smells like bitter almonds to most persons
- Believing that cyanide impairs oxygen transport by hemoglobin or that cyanide poisoning produces a saturation gap in arterial blood

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Indications for ICU Admission in Cyanide Poisoning

Patients symptomatic from cyanide poisoning
Patients who have been exposed to potentially toxic doses of nitriles – onset of cyanide poisoning may be delayed for longer than 12–15 h

The subject of cyanide poisoning brings consternation to most physicians because they consider it a rare disorder and are generally unfamiliar with the drugs used to treat it. However, thousands of workers undergo potential cyanide exposure every day (Table 1); some victims of smoke inhalation routinely cared for by intensivists experience cyanide poisoning, and cyanide compounds are easily obtainable for use as agents of suicide, homicide, or terror.

The clinical syndrome of cyanide poisoning resembles many other illnesses, and treatment with antidotes with which most physicians are unfamiliar usually must proceed quickly without laboratory confirmation of cyanide poisoning. To provide rapid and effective therapy, the physician must become familiar with the clinical presentation of and clinical clues to the diagnosis of poisoning by cyanide.

Three main sources of cyanide exist: hydrogen cyanide (HCN), inorganic cyanide salts, and cyanogens, which are compounds that release

Table 1 Examples of occupations associated with exposure to cyanide or cyanogens

Jewelry making
Metal polishing
Metal plating
Metal stripping
Metal reclaiming
Metal hardening
Mining
Nylon production
Pesticide manufacturing
Pesticide applicator
Laboratory work
Products of combustion
Chemical manufacturing

cyanide or that undergo metabolism to cyanide after absorption. HCN and inorganic cyanide salts are discussed first and in most detail as these are of greatest clinical relevance. Nitriles, the most commonly encountered cyanogens, which can produce delayed-onset and prolonged cyanide poisoning, are discussed in a separate section at the end of this chapter.

Hydrogen Cyanide and Inorganic Cyanide Salts

Sources and Chemistry

Hydrogen Cyanide

HCN (boiling point 27.7 °C) exists as a gas or liquid at commonly encountered temperatures. An aqueous solution of HCN (prussic acid or hydrocyanic acid) also is available. Liquid HCN and solutions of prussic acid may release gaseous HCN into the surrounding air. Although a bitter almond odor is attributed to HCN, most persons describe the odor as pungent, musty, or metallic, and about 20% of the population does not easily detect the odor [1]. The senior author has administered HCN odor challenges to more than 400 firefighters; none of them thought the odor resembled almonds, and a consistent fraction of 25% were unable to detect any odor. These findings are similar to those previously reported [53]. These findings, along with rapid olfactory fatigue, make it possible for large numbers of victims to be ill from HCN without any alert from a strong, bitter almond odor.

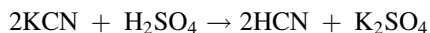
Inorganic Cyanide Salts

Numerous inorganic cyanide salts are used commercially. The most common ones are sodium, potassium, and calcium cyanide. Sodium, potassium, and calcium cyanide are crystalline, white solids that are freely soluble in water.

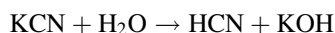
Hydrogen Cyanide Formation from Cyanide Salts

Although cylinders or containers of HCN gas or liquid can release toxic amounts of HCN, most

accidental exposures to HCN result from reactions with cyanide salts. When most inorganic cyanide salts come in contact with mineral acids, large quantities of HCN are formed and are released into the atmosphere. Using potassium cyanide (KCN) and sulfuric acid (H₂SO₄) as an example:

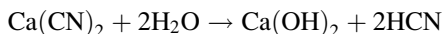


Lethal amounts of HCN can result from mixing water-soluble cyanide salts with water. As an example with KCN:



The percentage of cyanide converted to HCN (pK_a 9.3) in aqueous solutions of cyanide salts depends on the pH of the solution. The pH of a cyanide salt solution must be kept above 10.5–11 to prevent formation and release of significant quantities of HCN. Deaths from inhalation or dermal absorption of HCN have occurred when workers contaminated with powdered inorganic cyanide salts continued to wear wet clothing rather than having completely undressed in decontamination showers [2].

Solid cyanide salts also can react with water vapor in ambient air to form HCN. Fumigation powders containing sodium cyanide (NaCN) or calcium cyanide (Ca(CN)₂) are sprinkled on floors or down rodent burrows. In the presence of water or water vapor, HCN is released and reaches lethal concentrations in air. In the case of Ca(CN)₂:



Smoke, including that from cigarettes, commonly contains HCN [3–5]. Combustion of almost any organic compound containing carbon and nitrogen can generate HCN under the correct conditions [6]. Cyanide poisoning may be a contributor to death from smoke inhalation, especially in fires involving plastics.

Pharmacokinetics

Absorption. HCN is extremely well absorbed by inhalation and can produce rapid collapse and

death within minutes at high concentrations [7–9]. Because HCN is nonionized and of low molecular weight, significant absorption can occur through the skin if high enough concentrations are present [10, 11].

After ingestion, most cyanide salts are absorbed rapidly from mucous membranes, being converted to HCN upon contact with water. Depending on the dose, the onset of symptoms may occur within minutes, with death occurring within minutes to longer than an hour. At times onset has been so sudden that victims have had time only for a warning cry before unconsciousness [110]. When cyanide salts are placed in capsules and prevented from contact with oral mucosa, onset of symptoms may be delayed for several minutes or longer, depending on the dose, though collapse may still occur within 1 min after significant ingestions [111].

Exposures of large areas of skin to solid cyanide salts or aqueous solutions can result in absorption of lethal quantities of cyanide across skin. The dermal absorption rate of cyanide increases as the pH of a cyanide solution decreases because of increasing fractions of cyanide being found as HCN at lower pH values [2].

Brief contact between small areas of skin and dry, powdered cyanide salts would not be expected to produce toxicity. However, prolonged skin contact with smaller skin areas still can produce toxicity [12]. Increased absorption occurs across abraded or burned skin [13]. Onset of symptoms following large acute skin exposures has been delayed for 30 min if decontamination has not been effective, such as when a worker continues to wear wet, contaminated clothing [2].

Distribution. At physiological pH, virtually all cyanide in the body exists as HCN, and *cyanide* is used synonymously with *HCN* in this chapter when referring to cyanide in the body. Cyanide distributes widely after absorption. Measurable cyanide concentrations are found in the liver, spleen, kidney, brain, heart, spinal cord, lung, and fetus after acute poisoning. Because cyanide is concentrated within erythrocytes by binding to normally low concentrations of methemoglobin (Fig. 1), cyanide's apparent volume of distribution varies depending on circulating methemoglobin

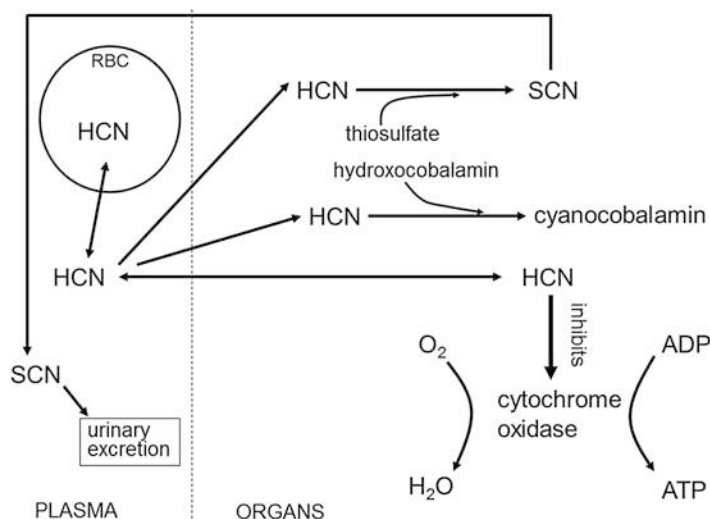


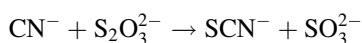
Fig. 1 Schematic diagram of cyanide's distribution and elimination. At physiologic pH, virtually all cyanide is present as hydrogen cyanide (HCN). HCN that has entered plasma after absorption is concentrated within red blood cells, at least in part by binding to the normally small amount of methemoglobin, which contains ferric (Fe^{3+}) iron. HCN also easily diffuses across cell membranes into various organs, where it binds to and inhibits many

enzymes, the most important being cytochrome oxidase. HCN binds to the binuclear center (copper and iron) of cytochrome oxidase to inhibit electron transport through this complex. This produces a decrease in oxygen consumption and, indirectly, a decrease in adenosine triphosphate formation. HCN is detoxified by transsulfuration to thiocyanate (SCN^-), which is excreted in the urine

concentrations and depending on whether such binding is saturated [14–16].

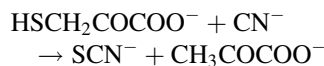
Metabolism. Humans detoxify cyanide by transferring sulfane sulfur to cyanide to form thiocyanate (SCN^-) (see Fig. 1). Thiocyanate undergoes renal clearance with an elimination half-life of about 2.7 days in persons with normal renal function [17].

The exact mechanism for cyanide's transsulfuration in vivo is controversial. Two main enzymes convert cyanide to thiocyanate. Rhodanese (thiosulfate sulfurtransferase, EC 2.8.1.1) is restricted to mitochondria and found in various tissues, especially the liver, kidney, and skeletal muscle [18, 19]. A reaction catalyzed by rhodanese in vitro involves the transfer of a sulfur atom from thiosulfate ($\text{S}_2\text{O}_3^{2-}$) to cyanide:



Another enzyme, β -mercaptopyruvate–cyanide sulfurtransferase (EC 2.8.1.2), resides in the liver, kidneys, and erythrocytes [19] and transfers

sulfur from mercaptopyruvate to cyanide to form SCN^- by the following reaction:



The aforementioned controversy surrounding in vivo cyanide transsulfuration revolves around several pieces of seemingly conflicting data. Although rhodanese was historically credited with cyanide's detoxification, thiosulfate – a substrate for rhodanese – is thought to be unable to penetrate the inner mitochondrial membrane where rhodanese is located [20, 21]. Ballantyne and others [19, 20, 22] suggested a paradigm whereby numerous sulfur sources are acted on by various sulfurtransferases, including rhodanese and mercaptopyruvate sulfurtransferase, to form sulfane sulfur, which then complexes with albumin in the blood. A nonenzymatic reaction of the sulfane–albumin complex with cyanide could account for thiocyanate formation. Other data suggest, however, that the sulfane–albumin complex seems to play a minor role in detoxification of

cyanide *in vivo*. In rats in which the blood has been replaced by a fluorocarbon emulsion, sodium thiosulfate still efficiently antagonizes cyanide [23]. In the absence of the blood or circulating albumin, cyanide's detoxification can be attributed only to sulfurtransferase reactions occurring in tissue sites other than the blood. Regardless of the exact mechanism explaining cyanide's transsulfuration, investigators agree that sulfur sources such as thiosulfate are required for and greatly accelerate conversion of cyanide to thiocyanate.

Cyanide's affinity for the cobalt ion (Co^{2+}) causes it to combine with hydroxocobalamin to form cyanocobalamin (see Fig. 1), which is excreted in the urine and bile. This route of detoxification normally plays a minor role in acute cyanide poisoning but serves as the basis of antidotal therapy with parenteral hydroxocobalamin [24].

Data on the rate at which toxic concentrations of cyanide are eliminated are limited because of inaccurate measurements of whole-blood cyanide concentrations that have been reported in poisoned patients owing to conversion of plasma thiocyanate to HCN during analysis (described later). Induction of methemoglobinemia, a treatment strategy, causes HCN to redistribute from tissues into the blood (decrease in apparent volume of distribution), producing changes in blood cyanide concentrations that do not reflect absorption or elimination. Schulz [16] wrote that because of limited availability of sulfane sulfur at endogenous concentrations, transsulfuration of cyanide is saturable, with an average elimination rate of 1 μg HCN/kg/min in an adult. Cole and Vesey, who reported decreases in elevated and accurately measured red blood cell and plasma cyanide concentrations after infusions of sodium nitroprusside were stopped, found that elimination appeared to be first order, with a half-life of about 30 min in the absence of sodium thiosulfate supplementation. When sodium thiosulfate was given, the elimination half-life decreased to about 10 min [25]. The cyanide levels were not high enough, however, to be associated with serious toxicity. The possibility of saturable elimination kinetics at higher cyanide concentrations cannot be excluded.

Pathophysiology

Cyanide inhibits more than 40 enzymes [20, 26, 27]. Cyanide's affinity for cytochrome oxidase in the mitochondrial inner membrane accounts for most toxicity. Cytochrome oxidase serves as the terminal enzyme in the electron transport chain responsible for oxidative phosphorylation and transfers electrons onto oxygen to produce water. After binding to the copper-iron binuclear center of cytochrome oxidase [28], HCN prevents electron transport, which inhibits oxidative phosphorylation and oxygen consumption [29]. Cyanide's ability to inhibit glutamate decarboxylase might produce a decrease in brain γ -aminobutyric acid concentrations and contribute to seizures [30].

A metabolic acidosis and decrease in oxygen consumption accompany serious cyanide poisoning. The metabolic acidosis is frequently incorrectly attributed to elevated circulating lactate concentrations resulting from glycolytic conversion of glucose to lactate in the presence of impaired oxidative phosphorylation. Unquestionably the glycolytic conversion of glucose to lactate is accelerated and becomes an important source of adenosine triphosphate (ATP) during cyanide poisoning, resulting in elevated lactate concentrations. However, ATP production via the conversion of glucose to lactate is not significantly acidifying [31–33]. Although the exact amounts of ATP and lactate generated in glycolysis vary with cellular pH and concentrations of available substrates [32], glycolytic production of lactic acid and ATP results in minimal production of protons regardless of pH [32, 34, 35].

An understanding of the generation of ATP in oxidative phosphorylation and of hydrolysis of ATP in metabolic processes explains metabolic acidosis in cyanide poisoning. Cells hydrolyze ATP to adenosine diphosphate and phosphate for energy, and ATP hydrolysis results in net proton production [36]. Conversely, in oxidative phosphorylation, there is a net consumption of protons during ATP synthesis. When homeostatic mechanisms are operating normally, a normal pH is maintained to a large extent because ATP is being hydrolyzed at the same rate that it is being synthesized via mitochondrial oxidative

phosphorylation; that is, proton production from ATP hydrolysis (including from ATP produced in glycolysis) is balanced by mitochondrial proton consumption during ATP synthesis in oxidative phosphorylation [34]. Oxidative phosphorylation is an important buffer of protons for this reason. When cyanide impairs the electron transport chain, and oxidative phosphorylation slows or stops, protons created by the cellular hydrolysis of preformed ATP and of ATP produced anaerobically in glycolysis are no longer buffered by aerobic ATP synthesis [32, 37]. Cyanide's binding to cytochrome oxidase impairs electron transport, resulting in a decrease in oxygen consumption and ATP production. Cells accelerate anaerobic glycolytic ATP production with the conversion of glucose to lactate. Although cellular and circulating lactate concentrations increase, the lactic acid is not responsible for acidosis. Rather, the acidosis occurs because cells hydrolyze ATP generated in glycolysis, producing protons [37], while the ability to buffer hydrogen ions via oxidative phosphorylation is impaired.

There are several reasons why cyanide poisoning is characterized mainly by dysfunction of the cardiovascular system and central nervous system. In the presence of acidosis and decreasing ATP concentrations from impaired oxidative phosphorylation, organs most sensitive to energy deprivation (brain, heart) suffer first. Cytochrome oxidase in the heart is also more sensitive to inhibition by cyanide [38]. Finally, cyanide concentrations are higher in the brain and myocardium than in other organs at the time of death [20].

The minimal concentration of HCN in air required to produce death in humans remains ill-defined because most acute fatal poisonings result from large exposures. Animal species vary in their sensitivity to cyanide, and data indicate that prolonged exposures to HCN concentrations greater than 90 ppm are incompatible with life [39]. In human cases of poisoning in which ambient HCN concentrations have been reported, headache, metallic taste, and other minor symptoms have developed after several minutes of exposure to air containing 10–30 ppm of HCN [39]. Death may occur within 1 h of continuous inhalational exposure to 100 ppm of HCN [20, 39]

and within several minutes of breathing more than 300 ppm of HCN. Humans have survived a 90-s exposure to 453–557 ppm of HCN (estimated) and a 3-min exposure to 500 ppm of HCN [8, 9]. Ballantyne [20] suggested that the inhalational 5-min median lethal concentration for HCN is 680 ppm and the 30-min median lethal concentration is 200 ppm.

A lethal oral dose of HCN (in solution) is estimated at 50 mg in an adult; the ingestion of 5 mL of 20% hydrocyanic acid has been fatal. The lethal oral doses of KCN or NaCN are estimated at 200–300 mg, but survival has followed much larger doses with intensive supportive care [40–42].

Clinical Presentation

Onset of symptoms of cyanide poisoning may occur within seconds after the inhalation of concentrated HCN gas or mucosal contact with inorganic cyanide salts. The inhalation of moderate HCN concentrations may not produce toxicity until minutes to hours into the exposure. Persons who are asymptomatic or only moderately symptomatic after the inhalation of HCN do not worsen after exposure is terminated. Delayed onset of symptoms after the inhalation of HCN does not occur. Absorption may be delayed after ingestion of cyanide sequestered in capsules, with peak symptoms not occurring for 20–40 min or so.

The main hallmarks of acute cyanide poisoning, which are nonspecific, are central nervous system and cardiovascular dysfunction and a metabolic acidosis. Central nervous system dysfunction ranges from anxiety to confusion, delirium, lethargy, coma, convulsions, and cerebral death. Large acute exposures may result in collapse into generalized seizures. Tachypnea may occur early in cyanide poisoning from initial stimulation of carotid body receptors by relatively low concentrations of cyanide. Lethal concentrations of cyanide rapidly produce apnea.

Cardiovascular toxicity early in cyanide poisoning is characterized by tachycardia and, at times, mild transient hypertension. As the illness progresses, hypotension, tachycardia,

bradycardia, heart blocks, ventricular arrhythmias, and asystole follow. Wexler and colleagues [43] described electrocardiographic changes in 16 men who received 0.2 mg cyanide/kg body weight intravenously. Sinus arrest lasting 0.88–4.2 s immediately preceded tachypnea and was thought to be vagally mediated. The periods of sinus arrest were followed by irregularities in sinus rhythms, with slowing of heart rates for periods of a few seconds to 2 min. There was gradual acceleration of heart rate to levels higher than control values. Wexler [43] also described electrocardiographic changes in four men executed by inhalation of HCN. They reported progressive shortening of the ST segment until, terminally, the T wave originated on the R wave. This “T-on-R” phenomenon has been described in other cases of cyanide poisoning [40].

Other common signs and symptoms in patients with cyanide poisoning include diaphoresis, weakness, nausea, and vomiting [44]. In serious poisoning, additional organ systems fail, leading to rhabdomyolysis, renal failure, hepatic necrosis, and adult respiratory distress syndrome [20, 41, 45].

The alkaline nature of granular cyanide salts or their aqueous solutions explains occasional corrosive injury when they come in contact with moist mucosal surfaces, especially the gastrointestinal tract [46]. Dermal injury also has followed acute skin contact with alkaline cyanide solutions [47].

Victims of cyanide poisoning may be left with permanent neurologic sequelae, including necrosis of the basal ganglia [48, 49]. Lesions in the basal ganglia are not specific for cyanide but are seen after severe hypoxemia or after poisoning by many metabolic toxins, including carbon monoxide, ethylene glycol, sodium azide, manganese, and methanol.

Diagnosis

When confronted with a case of suspected cyanide poisoning, physicians must make therapeutic decisions before results of cyanide levels are available. Certain historical points, physical findings, and general laboratory data must be used to seek evidence of cyanide poisoning.

Rapid collapse into coma or convulsions suggests the possibility of cyanide poisoning, but many patients may have gradual onset of symptoms over minutes to hours if exposures have been prolonged but not as intense, and toxicity may never become severe enough to produce coma. As noted earlier, the alleged bitter almond odor of cyanide is rarely noted, and it is possible for several persons in an exposure incident to die of cyanide poisoning without anyone complaining of or noting an abnormal odor. Even at autopsy on internal examination of the body, a bitter almond odor is not a reliable finding [46].

Many patients with serious cyanide poisoning are hypothermic. Depressed oxygen consumption from cyanide may produce an increased oxygen content of peripheral and mixed venous blood [50–52] if cardiac output is maintained. Bright red venous blood or retinal veins suggest the possibility of cyanide poisoning [53]. Most victims do not have unusually bright red skin or blood, however, and many victims exhibit cyanosis [49, 54, 55] because low cardiac output and intrapulmonary shunting in any patient with severe shock can cause arterial hypoxemia, despite low oxygen consumption. The absence of bright red skin or blood should never be used to exclude the possibility of cyanide poisoning.

An anion gap metabolic acidosis is always present in serious cyanide poisoning, unless the patient had a preexistent serious metabolic alkalosis or has received significant doses of sodium bicarbonate. Arterial lactate concentrations are elevated, but the lactate concentration does not always account for the entire increase in anion gap or base deficit because lactate is not actually responsible for acidosis (discussed earlier).

Cardiovascular and metabolic parameters obtained from invasive monitoring in patients with cyanide poisoning may reveal changes compatible with many disorders, including sepsis, toxic shock syndrome, or hepatic failure. Similar to cyanide poisoning, all of these conditions can produce metabolic acidosis, hypotension, decrease in oxygen consumption, increase in mixed venous oxygen content, decrease in the arterial-venous oxygen content difference, and

systemic vasodilation. Because baseline values (i.e., before cyanide poisoning) for oxygen consumption and mixed venous oxygen content are unknown for individual patients; because both parameters are influenced by cardiac output, which can vary from normal to increased early in cyanide poisoning to profound depression near death; and because both parameters depend on adequacy of oxygenation (e.g., adequate respiration, normal ventilation/perfusion), it is impossible to determine absolute cutoffs for oxygen consumption or mixed venous oxygen content that should strongly suggest cyanide toxicity. There are no studies examining the predictive values of these parameters for the diagnosis of cyanide poisoning. About the only statement that can be safely made is that a clearly normal or elevated oxygen consumption in a comatose patient does not suggest cyanide toxicity.

Claims [50, 56] that cyanide combines with hemoglobin to produce cyanhemoglobin and a difference between calculated arterial hemoglobin saturation and that measured by multiwavelength cooximetry (percent saturation gap) are unfounded and have never been documented. In fact, studies have shown that erythrocytes mixed with cyanide fail to show impaired oxygen carrying capacity until after a time that death would already have occurred [57], and cooximetry of whole blood containing lethal concentrations of cyanide does not show a percent saturation gap [58]. An unexplainable percent saturation gap is unexpected in patients with isolated and untreated (i.e., no methemoglobinemia) cyanide poisoning.

Cyanide Concentrations

The diagnosis of cyanide poisoning can be confirmed by measurement of circulating cyanide concentrations. Plasma cyanide is in equilibrium with tissue cyanide and correlates with tissue cyanide concentrations [15, 59]. In the blood, most cyanide is concentrated within red blood cells, making red blood cell cyanide concentrations many times higher than concentrations in plasma. The higher levels of cyanide found in red blood cells are more easily measured, and red blood cell cyanide concentrations correlate with

concentrations in plasma and tissue. Red blood cell cyanide concentrations are best used to confirm the diagnosis of cyanide poisoning.

Red blood cell cyanide concentrations of healthy adults are generally less than 29 $\mu\text{g/L}$ (1 $\mu\text{mol/L}$) [16]. In nonanemic patients with normal methemoglobin fractions, early metabolic disturbances from cyanide toxicity (e.g., metabolic acidosis) begin to appear at red blood cell cyanide concentrations of about 1 mg/L [60]. Obvious cyanide toxicity is apparent when red blood cell cyanide concentrations reach about 5 mg/L .

Plasma cyanide concentrations can be used to diagnose cyanide poisoning, but accurate measurement is difficult given the much lower levels and the high volatility of HCN, allowing HCN to escape into the atmosphere when the tube of the blood is opened for separation of plasma and cells. Wilson and Mathews [61] reported that plasma cyanide concentrations in healthy subjects averaged 4 $\mu\text{g/L}$ (0.15 $\mu\text{mol/L}$) in nonsmokers and 6 $\mu\text{g/L}$ (0.22 $\mu\text{mol/L}$) in smokers. Cottrell and colleagues [62] reported that mild metabolic acidosis developed in some patients receiving sodium nitroprusside under anesthesia when plasma cyanide concentrations reached approximately 30–35 $\mu\text{g/L}$ (approximately 1 $\mu\text{mol/L}$). Vesey and Cole [63] estimated the minimal lethal plasma cyanide concentration to be 243 $\mu\text{g/L}$ (9 $\mu\text{mol/L}$). Sheep dying from intramuscular potassium cyanide injections had plasma cyanide concentrations ranging from 900 to 2200 $\mu\text{g/L}$ (33–81 $\mu\text{mol/L}$) [20]. Because of difficulty in accurate measurement, plasma cyanide concentrations are best reserved for experimental studies in which collection, processing, and analysis are under tight quality control by personnel who regularly perform such measurements.

Measurements of *whole-blood* cyanide concentrations commonly offered by reference laboratories can fail to reflect accurate measurements of circulating cyanide. During acidification of whole blood during analysis, oxyhemoglobin released from red blood cells combines with thiocyanate in plasma to generate HCN *de novo* [14]. Falsely high whole-blood cyanide concentrations can result whenever plasma thiocyanate

concentrations are elevated significantly above normal (but not to toxic levels), even while cyanide concentrations are quite low or within the normal range. Examples of such situations in which this occurs are in patients receiving sodium nitroprusside infusions, patients with cyanide poisoning who have been treated with sodium thiosulfate for cyanide poisoning, and patients who have been exposed to cyanide and have successfully metabolized it to thiocyanate (with or without ever having experienced cyanide poisoning). Reported whole-blood cyanide concentrations may be higher than actual values and may easily mislead the physician into thinking that cyanide toxicity was present when it was not. Whole-blood cyanide concentrations generally should not be ordered unless their limitations are recognized when interpreting results. The potential for falsely elevated whole-blood cyanide levels also may contribute to the relatively wide range of upper boundaries for normal concentrations reported in the literature, ranging from about 0.05–0.5 mg/L (1.717 $\mu\text{mol/L}$).

Finally, cyanide concentrations can change during transportation and storage of tissue [1, 7, 64]. Several reports describe a decrease in cyanide concentrations in whole blood during storage, whereas others describe increases in cyanide content. The freezing and thawing of whole-blood specimens causes whole-blood cyanide concentrations to rise compared with prefrozen values [65]. The mechanism is probably mechanical hemolysis causing HCN formation from oxyhemoglobin and plasma thiocyanate during thawing. Whole-blood specimens should not be frozen during storage and transport.

Differential Diagnosis

The toxicologic differential diagnosis of cyanide poisoning is extensive and includes asphyxiation (e.g., inert gases, methane, nitrogen, carbon dioxide); poisonings by hydrogen sulfide and sulfide salts, methanol, ethylene glycol, pentaborane, azide, arsine, stibine, phosphine, phenol, cresol, methyl halides, and carbon monoxide; and, when cyanosis is present, methemoglobinemia. Any

illness characterized by sudden convulsions may be accompanied by hypotension, hypoxemia, and metabolic acidosis (e.g., poisoning by isoniazid or strychnine). Sudden unexpected collapse into unconsciousness or convulsions accompanied by metabolic acidosis and decreased oxygen consumption despite adequate oxygen delivery makes one lean toward the diagnosis of cyanide or sulfide poisoning.

Treatment

Pharmacologic Bases for Antidotal Strategies

The antidotal treatments described herein are based on practice in the United States. While the same antidotes are used widely around the world, we realize that there may be regional variation in antidotal practices and availability. In the United States, two antidotal strategies for treating cyanide poisoning are available: the combination of nitrite and thiosulfate and administration of hydroxocobalamin.

Nitrite and Thiosulfate

Parenteral delivery of sodium nitrite and sodium thiosulfate serves to induce methemoglobinemia and enhance conversion of cyanide to thiocyanate, respectively. Hydrogen cyanide binds to the binuclear iron–copper center of cytochrome oxidase to produce toxicity. Cyanide expresses low affinity for ferrous iron (Fe^{2+}) in hemoglobin. However, when iron of reduced hemoglobin is oxidized to the ferric state, methemoglobin is formed, and cyanide exhibits high affinity for Fe^{3+} in methemoglobin. Induction of methemoglobinemia with nitrite serves to create a large circulating sink of ferric iron that binds cyanide, allowing cyanide to dissociate from cytochrome oxidase in tissue and redistribute into plasma and into red blood cells, where it combines with methemoglobin to form cyanmethemoglobin (Fig. 2) [29].

Methemoglobin cannot carry oxygen and shifts the oxygen–hemoglobin dissociation curve to the left. The body has extensive mechanisms for maintaining methemoglobin fractions within

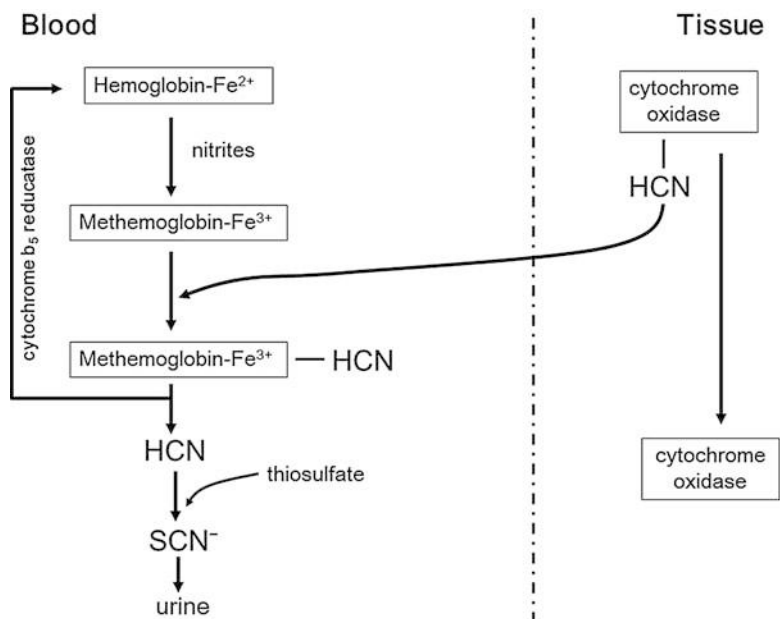


Fig. 2 Antidotal strategies in the treatment of cyanide toxicity with nitrites and thiosulfate. Hydrogen cyanide (HCN) binds to cellular cytochrome oxidase in tissues to inhibit oxidative phosphorylation. Sodium nitrite converts some ferrous hemoglobin (Fe^{2+}) to methemoglobin (Fe^{3+}), creating a large circulating sink of ferric iron. HCN quickly

dissociates from cytochrome oxidase and moves from tissue to bind to methemoglobin, forming cyanmethemoglobin and reversing inhibition of cytochrome oxidase. As cyanmethemoglobin is reduced back to Fe^{2+} , HCN is released. Sodium thiosulfate markedly enhances transsulfuration of HCN to thiocyanate (SCN^-)

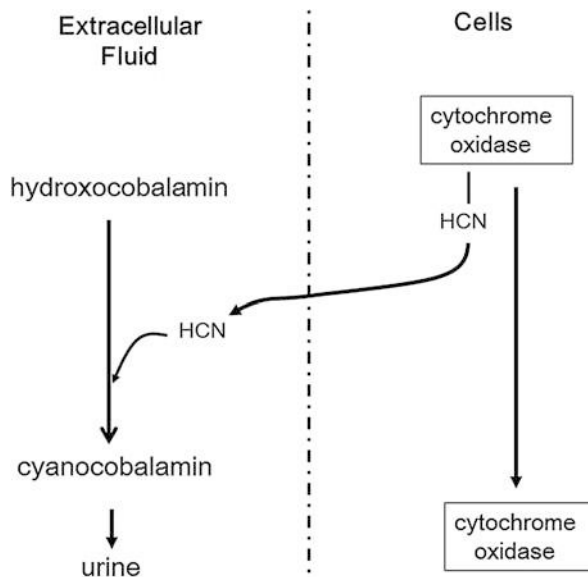
erythrocytes at less than 1–2% (i.e., 1–2% of all heme pigments are in the met form). Methemoglobin fractions of 20–30% are tolerated, however, without life-threatening symptoms in otherwise healthy persons without anemia [66].

The historically recommended initial dose of sodium nitrite for nonanemic symptomatic adults with cyanide poisoning is 10 mL of a 3% solution (300 mg) intravenously over several minutes [67]. Several authors advocate methemoglobin fractions of 25–40% (assuming no anemia) to be most effective [68–70]. Much lower methemoglobin fractions are achieved, however, with the recommended dose of 300 mg of intravenous sodium nitrite [67, 68]. Peak methemoglobin fractions of 10.1% after 400 mg of intravenous sodium nitrite and of 17.5% after 600 mg of intravenous sodium nitrite were described by Moser [71]. Kiese and Weger [68] noted that methemoglobin fractions increased to a mean of 7% in six volunteers receiving intravenous sodium nitrite, 4 mg/kg. A single

volunteer developed a methemoglobin fraction of 30% after 12 mg/kg of intravenous sodium nitrite.

Methemoglobin fractions may not peak until 30 min after 4 mg/kg of intravenous sodium nitrite or until 60 min after 12 mg/kg of intravenous sodium nitrite, though they begin to rise immediately [68]. Despite the slow peak of methemoglobinemia after 300 mg of intravenous sodium nitrite, the combination of intravenous sodium nitrite and sodium thiosulfate remains superior to more rapid methemoglobin-forming agents such as 4-dimethylaminophenol [21] possibly because of a more sustained methemoglobinemia produced by sodium nitrite. The fact that dramatic improvements in symptoms have occurred well before methemoglobin levels have peaked [51, 72] also suggests that mechanisms other than methemoglobin production may be important in nitrite's antidotal action [21, 73]. Recent animal data suggest nitric oxide can overcome cyanide inhibition of cytochrome c oxidase, offering a

Fig. 3 Antidotal strategy in the treatment of cyanide toxicity with hydroxocobalamin. Hydrogen cyanide (HCN) binds to cellular cytochrome oxidase to inhibit oxidative phosphorylation. Hydroxocobalamin combines with cyanide, mainly in extracellular fluid, to form cyanocobalamin, which is excreted in the urine



possible contributing mechanism for sodium nitrite's antidotal effects [74–76].

Sodium thiosulfate (a source of sulfane sulfur) enhances conversion of cyanide to thiocyanate. The recommended dose is 12.5 g intravenously over a few minutes. Although methemoglobinemia can rapidly reverse serious cyanide poisoning, cyanide eventually is released from cyanmethemoglobin as this pigment is reduced to hemoglobin [77]. Coadministration of sodium thiosulfate with sodium nitrite enhances transsulfuration of cyanide that is unbound or that is released from cyanmethemoglobin to thiocyanate. Thiocyanate is of low-order toxicity and undergoes renal elimination with a half-life of 2.7 days in patients with normal renal function. The combination of sodium nitrite and sodium thiosulfate increases the required lethal dose for cyanide 13 times in some animal models, whereas lethal dose increases of 3–4 times are noted when each agent is given alone [78].

Some animal data suggest that vasodilation from nitrites might be beneficial in treating cyanide poisoning. α -Adrenoceptor antagonist vasodilators (e.g., phenoxybenzamine, chlorpromazine) enhance antidotal effects of thiosulfate in animal models of cyanide poisoning but have little action by themselves [79, 80]. Similarly, injection of erythrocytes exposed to nitrite *in vitro* (to produce methemoglobin) that are then washed free of excess nitrite

provides a degree of protection equivalent to that produced by nitrite directly injected into animals poisoned with cyanide, indicating that vasodilation plays a relatively unimportant role in explaining nitrite's antidotal action compared with methemoglobin induction [77].

Hydroxocobalamin

Hydroxocobalamin, the second approved antidotal therapy in the United States and used widely in other countries, exploits cyanide's affinity for cobalt. Hydroxocobalamin (Vitamin B_{12a}) combines with cyanide to form cyanocobalamin, which is excreted in the urine [24] (Fig. 3). Hydroxocobalamin's low apparent volume of distribution (0.45 L/kg) suggests mainly an extracellular site of action, and its elimination half-life in smoke inhalation victims averaged about 26 h [81].

In a dog model of acute cyanide toxicity, treatment with hydroxocobalamin (75 mg/kg or 150 mg/kg) was associated with increased survival (79% and 100%, respectively) compared to placebo (18%) [82]. Survival benefit has also been shown for hydroxocobalamin compared to placebo (73% versus 0%) following cyanide-induced cardiac arrest in pigs [83]. In some, but not all, animal models, the addition of intravenous sodium thiosulfate to hydroxocobalamin therapy

enhances antidotal activity of hydroxocobalamin, but thiosulfate must be infused separately [84].

In comparing hydroxocobalamin with nitrite-based antidotes in cyanide-poisoned swine, Bebart and Tanen found that hydroxocobalamin (150 mg/kg) with sodium thiosulfate (413 mg/kg) was associated with a faster return to baseline mean arterial pressure than sodium nitrite (10 mg/kg) with sodium thiosulfate, but there was no difference in mortality or other clinical parameters [85].

As is the case for sodium nitrite, neither randomized controlled trials of hydroxocobalamin in humans with cyanide poisoning nor human trials comparing hydroxocobalamin and other antidotes exist. Only uncontrolled and unblinded case series have been published. For example, Borron et al. [86] reported eight of 12 patients with known or suspected cyanide salt ingestions survived after treatment with hydroxocobalamin (5–20 g). An obvious advantage of hydroxocobalamin (and cobalt-EDTA and sodium thiosulfate) is lack of methemoglobin induction, which could be advantageous in treating severely anemic patients or those patients with cyanide poisoning from smoke inhalation, who also may have concomitant carbon monoxide poisoning. Borron et al. reported uncontrolled, unblinded observations on the use of hydroxocobalamin (median dose 5 g, maximum 15 g) for suspected cyanide toxicity after smoke inhalation [87]. In patients with what were reported to be toxic ($>39 \mu\text{mol/L}$) and lethal ($>100 \mu\text{mol/L}$) *whole-blood* cyanide levels, survival was 74% and 62%, respectively. The lack of control groups makes it impossible to know whether the treatment with hydroxocobalamin was effective in this setting. A French study of prehospital use of hydroxocobalamin for presumed cyanide toxicity after smoke inhalation found an overall survival rate of 41.7%, highlighting the generally poor outcomes typical for critically ill smoke inhalation victims [88].

Hydroxocobalamin produces bright red discoloration of the skin, urine, and plasma [89]. Plasma discoloration may interfere unpredictably with various chemistry laboratory analyses, including AST, bilirubin, creatine kinase, iron, and

magnesium [90–92]. Hydroxocobalamin also impedes accurate measurements of carboxyhemoglobin, methemoglobin, and oxyhemoglobin by cooximetry, which could have significant implications on management of smoke inhalation victims [92–94]. The magnitude of the interference depends on the specific cooximeter and may vary with carboxyhemoglobin and hydroxocobalamin concentrations. Hydroxocobalamin-induced discoloration of body fluids may have consequences extending beyond laboratory misinterpretation. There exists at least one case report describing hemodialysis malfunction after administration of hydroxocobalamin due to a “blood leak” alarm triggered by discolored body fluids [95].

Hydroxocobalamin has been shown to raise blood pressure after initial administration, commonly a desired effect in cyanide toxic patients. Other reported side effects comprise rare allergic reactions including urticaria, edema, and anaphylaxis [24].

Other Antidotes

Amyl nitrite inhalation has been used in the past for treatment of cyanide poisoning but is relatively ineffective as a methemoglobin-producing agent as compared to intravenous sodium nitrite [67]. Thus, its use has been abandoned in the United States, but remains in use in the prehospital setting in other countries.

Inhalation of 100% oxygen (along with nitrite and thiosulfate or hydroxocobalamin antidote) enhances survival over breathing room air in animals, but no advantage of hyperbaric oxygen therapy over the administration of 100% oxygen at 1 atm has been shown [96].

Cobalt-EDTA (ethylenediaminetetraacetic acid), a chelator of cyanide that then undergoes renal elimination, has been used in some countries [97]. It is available in 20-mL ampules, each containing 300 mg of cobalt-EDTA. The recommended dose is one ampule (300 mg) intravenously over 1 min. Repeat doses can be given after 1 and 5 min if there is no response, and slower infusion rates should be allowed for noncritically ill patients. The main side effect seems to be an anaphylactoid reaction, which can be life-threatening.

Cobinamide, a water-soluble analog of hydroxocobalamin, is currently under investigation as an alternative antidote that would not necessarily require intravenous administration. An intramuscularly administered antidote is desirable in the prehospital setting, particularly when intravenous access is difficult. Additionally, cobinamide contains two cyanide-binding sites and neutralizes 2 mol cyanide per mole compared with 1 mol cyanide per mole for hydroxocobalamin and is, thus, more potent. A swine model demonstrated intravenous cobinamide to be as effective as hydroxocobalamin at one fifth the dose for return of spontaneous breathing after acute cyanide poisoning [98].

Precursors to beta-mercaptopyruvate, including those that can be administered orally, are effective cyanide antidotes in animals and work by accelerating conversion of cyanide to thiocyanate by beta-mercaptopyruvate sulfurtransferase [99]. None are available for use in humans at present.

Vasodilation and hypotension produced by nitrites has, in part, led investigators in the armed services and in other countries to examine other methemoglobin-forming agents for the treatment of cyanide poisoning [69, 100]. DMAP (4-dimethylaminophenol) induces methemoglobinemia more rapidly than nitrite, but toxic side effects limit its use [100, 101].

General Management

Patients who are symptomatic after the inhalation of HCN do not require decontamination. A person who has inhaled HCN without becoming seriously ill is not in danger of developing delayed onset of more serious symptoms after exposure is terminated [7]. After removal from exposure, no decontamination is required after exposures to HCN gas other than removal of outer layers of clothing if exposure has just occurred.

Patients who have undergone significant skin contamination with solid cyanide salts or solutions may serve as a threat to rescuers and treating medical personnel. *All* clothing (including shoes or boots) should be removed, and the victim should be thoroughly decontaminated with copious volumes of water before entering a hospital. Inadequate decontamination results in generation

of HCN from water and remaining cyanide salts, with potential for off-gassing of HCN or delayed absorption of HCN through the skin.

Patients who have ingested cyanide salts and who have remained asymptomatic for 1–2 h would not be expected to become ill. It seems unlikely that activated charcoal could be given quickly enough after oral ingestion of cyanide to change the clinical course of cyanide poisoning. Distending a patient's stomach with a solution of charcoal when the patient may become unconscious or begin convulsing at any moment may promote vomiting and pulmonary aspiration. Gastric emptying by lavage is not known to be effective and generally is not recommended.

Symptomatic patients who have ingested cyanide salts may regurgitate HCN gas. Mouth-to-mouth ventilation is not recommended in such instances. The odor (usually poorly described) of HCN can be noted sometimes around the mouth of comatose patients who have ingested cyanide compounds, but there has never been a death or severe illness from inhalation of HCN in a person who has cared for such a patient, although mild symptoms (nausea, light-headedness) have been claimed. A letter to the editor claimed that mouth-to-mouth resuscitation of a cyanide-poisoned dog produced coma in the rescuer [102].

Antidotal Therapy

After addressing airway, ventilation, and circulation, efforts should be directed immediately toward antidotal therapy in symptomatic patients. There are two commercially available cyanide antidotes in the United States from which to choose. First, Nithiodote[®] (Hope Pharmaceuticals, Scottsdale, AZ) contains one 10 mL vial of 3% sodium nitrite (300 mg) and one 50 mL vial of 25% sodium thiosulfate (12.5 g) for intravenous injection. Each of these agents also may be purchased individually. Second, hydroxocobalamin is commercially available as Cyanokit[®] (Meridian Medical Technologies, Columbia, MD), which contains one vial of 5 g lyophilized hydroxocobalamin [103]. Other preparations/brands of sodium nitrite/sodium thiosulfate combinations or hydroxocobalamin are available in other countries, with generally similar dosing recommendations.

Antidotal Therapy for Cyanide Poisoning

As soon as an intravenous line is established, choose therapy #1 or therapy #2:

1. Nitrite/thiosulfate therapy:
 - a. 300 mg sodium nitrite (10 mL of 3% solution) intravenously. For critically ill patients, infuse over 2–3 min. For less severely poisoned patients, infusion can be over several minutes to limit hypotension (for children, give 0.2 mL/kg of 3% sodium nitrite).
 - b. Next infuse 12.5 g of sodium thiosulfate (50 mL of a 25% solution) intravenously over 2–5 min (for children, give 1 mL/kg of 25% solution).
2. Hydroxocobalamin therapy
 - a. 5 g hydroxocobalamin over 15 min (for children, give 70 mg/kg body weight)

As soon as an intravenous line is established, one of the two antidote therapies should be given, as described in detail below:

Nitrite/Thiosulfate Therapy

Ten mL of a 3% solution of sodium nitrite (300 mg) should be given intravenously. For moribund patients, the sodium nitrite can be given over 1–2 min. For less severely ill patients, it can be given more slowly to prevent significant falls in blood pressure. The administration of an entire ampule (10 mL) of 3% sodium nitrite to a small child potentially may produce lethal methemoglobinemia [70]. The same is true for adults with severe anemia. Children without anemia can receive 0.2 mL of 3% sodium nitrite/kg body weight, up to 10 mL.

After the administration of intravenous sodium nitrite, immediately give 50 mL of 25% sodium thiosulfate intravenously to adults over several minutes. The pediatric dose is 1 mL of 25% sodium thiosulfate/kg body weight [70].

Doses of sodium nitrite and sodium thiosulfate can be repeated if signs of cyanide poisoning (e.g.,

metabolic acidosis with coma) persist for 30 min or recur. In our experience, methemoglobin fractions remain less than 20% in nonanemic adults who received two doses of 300 mg of sodium nitrite given within 10 min, and this is in keeping with data by Moser [71]. If cooximetry is readily available, however, total hemoglobin and methemoglobin concentrations should be quickly measured before repeating a dose of sodium nitrite to ensure that dangerous methemoglobinemia will not occur, especially in children.

The best available data for use of sodium nitrite and thiosulfate in the treatment of cyanide toxicity constitutes level III evidence.

Hydroxocobalamin Therapy

Five grams lyophilized hydroxocobalamin should be reconstituted in 200 mL normal saline or another crystalloid and given intravenously over 15 min. In severely ill patients or those with insufficient clinical response to the initial treatment, a second dose of 5 g may be administered over 15 min (for patients in extremis) to 2 h for a total of 10 g. Children should receive 70 mg hydroxocobalamin per kg body weight for each dose.

Some toxicologists would immediately follow hydroxocobalamin administration with 12.5 g sodium thiosulfate intravenously, but it is not known whether this adds any benefit to adequate doses of hydroxocobalamin.

The best available data for use of hydroxocobalamin in the treatment of cyanide toxicity constitutes level III evidence.

Pediatric Doses of Cyanide Antidotes

Intravenous sodium nitrite and sodium thiosulfate

- If child is ill and not known to be anemic, give 0.2 mL/kg 3% sodium nitrite intravenously up to initial dose of 10 mL.
- Give 1 mL/kg 25% sodium thiosulfate solution.

Intravenous hydroxocobalamin

- Give 70 mg/kg hydroxocobalamin.

When patients remain seriously ill after maximal doses of one of the antidotal strategies, it is reasonable to add the alternative strategy. For example, if metabolic acidosis and coma remain after two doses of nitrite/thiosulfate therapy and methemoglobin fractions are approximately 25%, then administration of 5 g hydroxocobalamin is a reasonable addition. Conversely, if 10 g hydroxocobalamin have been given and the patient remains critically ill with metabolic acidosis, then administration of the nitrite/thiosulfate antidote is acceptable.

Treatment is otherwise supportive. Severe metabolic acidosis may require treatment with sodium bicarbonate. Rhabdomyolysis is treated by ensuring a brisk urine output and keeping the urine pH above approximately 6.0.

Special Populations

Cyanide toxicity in patients receiving sodium nitroprusside is discussed in the chapter on that topic.

Smoke Inhalation and/or Severe Anemia

When treating cyanide poisoning in the presence of concomitant carbon monoxide poisoning or severe anemia, hydroxocobalamin and/or sodium thiosulfate can be given without concern for further impairing oxygen delivery by induction of low-grade methemoglobinemia. However, there are no studies showing effectiveness of such therapy or trials that compare nitrite with other antidotes in this setting. Of note, red discoloration of hydroxocobalamin has been reported to produce falsely low carboxyhemoglobin readings by multiwavelength cooximetry [94]. This complicates the diagnosis of carbon monoxide poisoning if hydroxocobalamin is given before the blood is drawn for cooximetry studies and can prevent following serial carboxyhemoglobin fractions during oxygen therapy.

Pregnant Patients

As a small lipophilic molecule, HCN distributes easily to most organs, including the fetus. In fact, newborns of smoking mothers have higher blood

cyanide concentrations than newborns of nonsmoking mothers [104]. No studies have examined the efficacy or toxicity of sodium nitrite, sodium thiosulfate, or hydroxocobalamin in pregnant women. No guidelines exist for dosing of sodium nitrite to pregnant women with cyanide poisoning, although maternally administered sodium nitrite produces methemoglobinemia in the fetus [105]. In third-trimester gravid ewes with cyanide toxicity from sodium nitroprusside infusions, the administration of sodium thiosulfate prevents increases in circulating fetal cyanide concentrations, even though thiosulfate does not appear to cross the placenta [106]. This finding is best explained by the ability of thiosulfate to keep maternal cyanide levels low, allowing for cyanide to diffuse back out of the fetus into the maternal circulation for detoxification. In 2010, the US Food and Drug Administration approved hydroxocobalamin for use in pregnant women with cyanide toxicity. Dosing in pregnancy is unchanged from adult guidelines for hydroxocobalamin [103]. Given limited available data, pregnant patients with cyanide poisoning should be treated similarly to other patients. Fetal health is best ensured by ensuring the survival of the mother.

Cyanogens

Cyanogens are natural or synthetic compounds that, after absorption, undergo metabolism to release HCN (Table 2). (The term *cyanogen* also is used as a synonym for ethanedinitrile.) Nitriles (R-C-CN) and sodium nitroprusside account for most toxic exposure to synthetic cyanogens. Cyanide glycosides (e.g., amygdalin) are found naturally in many foods and plants. Because ► [Chap. 40](#), “Sodium Nitroprusside” is discussed in its own chapter and cyanide glycosides are discussed in ► [Chap. 112](#), “Cardiotoxic Plants”, the toxicity of nitriles is emphasized in this section. Nitriles are used as solvents, as intermediates in chemical synthesis, in nylon production, and for other purposes. Acetonitrile was commonly used in artificial fingernail glue remover, with tragic results in children who accidentally ingested these products.

Table 2 Examples of Cyanogens

Acetonitrile
Acrylonitrile
Butyronitrile
Cyanogen
Cyanogen bromide
Cyanogen chloride
Lactonitrile
Methacrylonitrile
Nitroprusside
Propionitrile
Succinonitrile

Clinical Presentation

Nitriles can be absorbed by inhalation, through dermal contact, or after ingestion. Poisonings by nitriles differ, however, from poisonings by inorganic cyanide salts and HCN in three general ways. First, there may be a delay between exposure and the onset of symptoms for many hours, because hours may be required for nitrile metabolism to release enough HCN to produce symptoms. Second, because of continued metabolism of nitriles, HCN production and symptomatic cyanide poisoning may continue for hours to days, requiring prolonged antidotal therapy. Third, nitriles themselves possess toxicologic properties beyond those of HCN production, including mucosal irritation, nephrotoxicity, and peripheral neurotoxicity. Different nitriles vary as to whether most of their toxicity is explained by HCN release or by other toxic effects. These principles are best illustrated by briefly reviewing published examples of nitrile poisoning.

Muraki and colleagues [107] described a 35-year-old man who became ill 15 h after cleaning the inside of a reactor kiln with acetonitrile. Initial symptoms were nausea, vomiting, and weakness. More than 20 h after exposure, he had a convulsion and depressed level of consciousness with severe metabolic acidosis (pH 6.55; PCO_2 31 mmHg). Treatment eventually was instituted with sodium nitrite and sodium thiosulfate. The patient required mechanical ventilation and developed acute tubular necrosis from severe rhabdomyolysis (peak serum creatine kinase 325,000 IU/L) but eventually recovered completely.

Mueller and Borland [108] reported a 39-year-old woman who deliberately swallowed acetonitrile. Symptomatic cyanide poisoning developed 11 h later and was treated successfully with repeated doses of sodium nitrite and sodium thiosulfate. The half-life of acetonitrile was 40 h, and antidotal therapy was required for more than 24 h, with good outcome.

Treatment

Because patients who have ingested cyanogens such as acetonitrile may experience the onset of cyanide poisoning several hours after exposure (e.g., inhalation, ingestion), they should be observed closely for 24 h in the hospital in a monitored setting with cyanide antidotes readily available. Theoretically, activated charcoal might prevent absorption of cyanogens, and it might be reasonable to administer charcoal to such patients if they can be treated soon after ingestion. The disadvantage of distending a patient's stomach with a suspension of charcoal when the patient is at risk for rapid deterioration, convulsions, vomiting, and aspiration must be weighed against theoretical benefits that have not yet been shown in human studies.

Patients should be regularly evaluated at the bedside for evidence of cyanide poisoning. The onset of significant changes in vital signs, the onset of metabolic acidosis, or the voicing of new complaints (nausea, weakness, dyspnea) should warrant treatment of presumed cyanide poisoning with sodium nitrite and sodium thiosulfate or hydroxocobalamin, as in acute poisoning by inorganic cyanide compounds.

No studies provide guidance as how to repeat cyanide antidotes after initial dosing to symptomatic patients after nitrile exposure. After initial doses, it seems reasonable to provide a continuous infusion of sodium thiosulfate to enhance cyanide transsulfuration as it is being produced. At our center, we have infused 1.2 g/h of sodium thiosulfate for 24 h to such patients with good results and based this dose on a known safe constant infusion dose used in sodium nitroprusside therapy. More severely ill patients might require larger doses, however. If patients

experience recurrence of symptoms despite sodium thiosulfate infusion, it also seems reasonable to give repeated doses of sodium nitrite so as to maintain methemoglobin fractions between 7% and 25% or to repeat doses of hydroxocobalamin, but exact dosing schedules have not been studied or described.

With regard to acrylonitrile toxicity, studies suggest that an infusion of *N*-acetylcysteine, such as when used for acetaminophen toxicity, may be beneficial in promoting metabolism by a pathway that does not lead to cyanide release [109]. No controlled human studies have shown the benefit to such therapy, however.

Key Points in Cyanide Poisoning

1. In the body, virtually all cyanide exists as hydrogen cyanide (HCN).
2. HCN binds to cytochrome oxidase of the electron transport chain on the inner mitochondrial membrane to prevent oxygen consumption and electron transport, impairing adenosine triphosphate formation.
3. Rapid collapse with central nervous system dysfunction (coma, seizures, confusion), metabolic acidosis, and cardiovascular changes (hypotension, tachycardia) suggests the diagnosis of cyanide poisoning.
4. Other clues to diagnosis are hypothermia, occasionally bright red venous blood or retinal veins with cherry-red skin (but cyanosis also is common), elevated mixed venous oxygen content, and impaired oxygen consumption. Cyanide is not detected on routine urine or plasma drug screens.
5. HCN does not smell like bitter almonds to most persons, and it is possible for a group of victims to have cyanide poisoning without anyone noting a bitter almond odor.
6. In the United States, the traditional antidotal strategy is based on inducing methemoglobinemia with nitrites (to bind HCN) and enhancing cyanide's metabolism to

thiocyanate with sodium thiosulfate. An alternative strategy is administration of hydroxocobalamin to bind to HCN. No well-designed studies have compared these strategies in human beings.

7. If cyanide levels are measured, red blood cell cyanide levels are most helpful. Plasma cyanide concentrations are difficult to measure accurately. Whole-blood cyanide concentrations, which are offered by most laboratories, can be falsely elevated in several situations. Unless specimens are handled, stored, and transported correctly and analyzed in a timely manner, reported values for whole-blood or plasma cyanide may not reflect concentrations that were present when the specimen was obtained.
8. Nitriles such as acetonitrile or acrylonitrile are metabolized slowly to HCN after inhalation, ingestion, or skin contact. Cyanide poisoning may not appear for hours after exposure and may persist for 1–2 days.

Criteria for ICU Discharge in Cyanide Poisoning

Patients who were symptomatic from exposure to inorganic cyanide compounds or hydrogen cyanide:

- No antidotal therapy (hydroxocobalamin, nitrites, or thiosulfate) given in last 12 h
- No signs or symptoms of cyanide poisoning (e.g., no metabolic acidosis, normal vital signs)

Patients exposed to nitriles or other cyanogens:

- If never symptomatic, at least 24 h must have passed since exposure.

(continued)

- If patient developed signs and symptoms of cyanide poisoning, at least 24 h must have passed since patient has received any cyanide antidotes, and the patient must have remained asymptomatic during this time without antidotal therapy.

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Hydrocarbons are a diverse group of chemicals made up of carbons and hydrogens that are the building blocks of life. Because they are ubiquitous, they are found not only in plants and animals but also in alcohols, solvents, natural gas, petroleum derivatives, and many industrial chemicals. In 2013, the National Poison Data System, a database maintained by the American Association of Poison Control Centers, reported 33,025 hydrocarbon exposures and 18 deaths. Eighty-five percent of all exposures were classified as unintentional, and 29% occurred among children less than 6 years of age [1]. Because not all exposures are reported to poison centers, this number certainly under represents the actual incidence of hydrocarbon exposures. Also, many low dose chronic hydrocarbon exposures cause toxicities, including cancer, that are most often seen by providers other than medical toxicologists. This chapter focuses on the critical care toxicology of hydrocarbon exposures; therefore, most of the chronic toxicities will not be discussed.

Biochemistry and Clinical Pharmacology

Hydrocarbons are divided into two main categories: aliphatic (straight-chain or branched-chain) and aromatic (cyclic hydrocarbons with resonating double bonds); for example, propane is aliphatic whereas benzene is aromatic (Fig. 1). Polyaromatics are composed of at least three

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Sample Hydrocarbons:



Fig. 1 Sample hydrocarbons

benzene rings such as in benzopyrene. Alicyclic hydrocarbons consist of carbon chains in a ring structure (but do not contain resonating ring structure such as in benzene) that function similarly to aliphatics; an example is cyclohexane. Halogenated hydrocarbons contain halogen atoms (fluorine, chlorine, bromine, or iodine) in place of hydrogen atoms; an example is lindane (hexachlorocyclohexane). Saturated hydrocarbons have only single covalent bonds between their carbons, whereas unsaturated hydrocarbons contain double (alkenes) or triple (alkynes) bonds between adjacent carbons.

The physical state of hydrocarbons depends primarily on the size of the molecule. Methane, ethane, propane, and butane have chains that are 1, 2, 3, and 4 carbons long, respectively, and exist as gases at standard temperature and pressure. Hydrocarbons that contain 5–20 carbon atoms exist as liquid, and those that are more than 20 carbon atoms are semisolid or solid at standard temperature and pressure.

Physical properties of hydrocarbons play a crucial role in determining toxicity after ingestion: compounds with low surface tension and low viscosity have higher chance of spreading into the trachea during swallowing (higher risk of aspiration), and those with high volatility have greater tissue penetration and surfactant disruption (greater lung damage) [2]. Surface tension is the cohesion of molecules as generated by van der Waals forces; low surface tension allows them to spread rapidly over the contacted surface making them more easily aspirated. Viscosity is the resistance of a fluid to flow; low viscosity means the fluid flows more easily and allows for deeper penetration into the distal airways. Volatility is the tendency of a liquid

to vaporize into a gaseous state; increased volatility (smaller molecule size) enables easier generation of gas that can be inhaled deeper into the airways. This enhances tissue and cell membrane penetration and surfactant disruption.

When intentionally inhaled for recreational purposes, these hydrocarbons are considered inhalants. The US National Institute of Drug Abuse classifies inhalants into volatile solvents, aerosols, gases, and nitrites. Volatile solvents are a group of liquids with relatively high vapor pressures and include glues, fuels, paint thinners, and liquid in felt-tip markers. Vapor pressure is the force exerted by the vapor (substance in a gas phase) above a liquid surface; the higher the vapor pressure, the more likely it will overcome the atmospheric pressure and vaporize. Substances with high vapor pressure are considered volatile. Aerosols consist of sprays that contain both propellants and solvents and are often included in personal hygiene products such as hair sprays and deodorants. Propellants are pressurized gases, generally hydrocarbons, used in creating movement of a fluid, whereas solvents are substances that dissolve a solute to form a solution and are often hydrocarbons; both can be intoxicating.

Clinical Manifestations and Life-Threatening Complications

Oral Ingestion

Different routes of exposure result in distinct clinical toxicities (Fig. 5). When ingested, hydrocarbons are primarily gastric irritants that will cause

spontaneous vomiting in about 35% of patients [3]. Although rare, hemorrhagic gastritis can occur [4]. In the absence of aspiration, most exposures result only in gastrointestinal discomfort [5]. This was confirmed in an experimental canine model in which kerosene was injected directly into the stomachs of dogs who had previously undergone esophageal ligation [6]. The most concerning element of most oral hydrocarbon ingestions is the high risk of pulmonary aspiration and its associated complications.

Aspiration and pulmonary injury most often occur in children who attempt to ingest liquid hydrocarbons. However, similar injuries resulting from patients siphoning diesel [7] or “fire-eating” (an artistic performance of spraying liquid hydrocarbons by mouth over a flame) [8] have also been reported. Hydrocarbons cause pulmonary toxicity by disrupting the surfactants that line the distal bronchioles and alveoli. They do so by two mechanisms. First, they decrease the maximum surface tension of the surfactants, which limits the ability of surfactants to attract each other at higher external pressures. Second they increase the minimum required surface tension to initiate surfactant molecular aggregation. Because pulmonary surfactants line the alveoli and distal bronchioles, this surfactant disruption leads not only to alveolar instability and collapse but also to distal airway obstruction [9]. The end result is ventilation-perfusion mismatch, bronchospasm, shunt formation, and hypoxia. Aspiration of halogenated

hydrocarbons, such as trichloroethylene, causes mucosal irritation and can lead to caustic pneumonitis and acute lung injury [10].

Initial symptoms of aspiration are nonspecific and include cough, nausea/vomiting, drowsiness, fever, tachypnea, tachycardia, and occasionally altered mental status. In one series of patients with aspiration, fever was the most common sign, occurring in up to 94% of patients [11]. However, most studies indicate that fever is much less common. In another study of 274 children with hydrocarbon pneumonitis, only 64% had fever, 51% had vomiting, and 38% had cough [12]. When present, the fever resolves within 24 hours in 41% of patients, and only 6% have fever that lasts longer than 5 days [13]. Physical examinations are notoriously insensitive in identifying patients with complications from a hydrocarbon ingestion.

One specific form of pulmonary toxicity is the development of exogenous lipid pneumonia (ELP), a pulmonary disease that results from the inhalation or aspiration of animal, vegetable, or mineral oils. (Fig. 2) Most cases occur from chronic exposures to mixtures of inert, long-chain, saturated hydrocarbons derived from petroleum. According to one study of 44 cases, most chronic exposures were due to either ingestion of liquid paraffin for the treatment of constipation or inhalation of cutting mist or oily vapors by workers in metallurgic plants. Their mean exposure was for 9.5 years [14]. However, ELP has also occurred

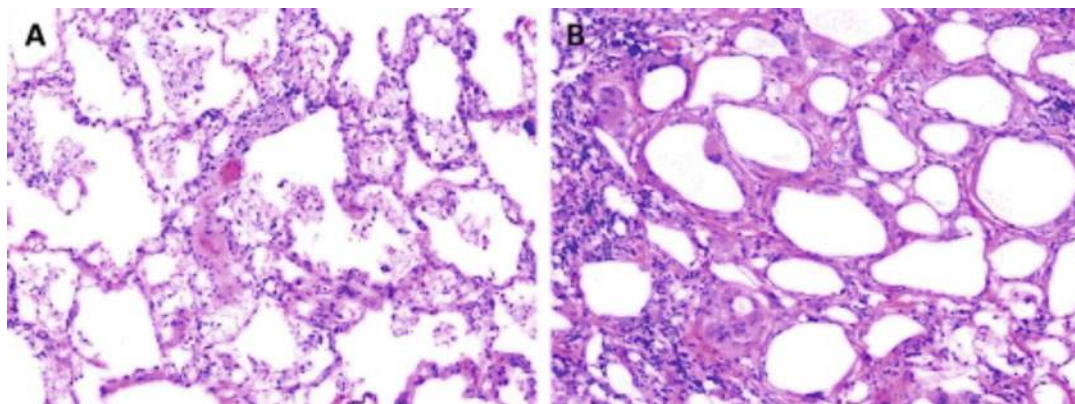


Fig. 2 Exogenous lipid pneumonia: https://openi.nlm.nih.gov/detailedresult.php?img=2668105_CPT-62-05-0387-f22&req=4

after single, large intravenous injections of peppermint oil [15], olive oil [16], and lamp oil (liquid paraffin) [17]. Usual symptoms include cough and dyspnea; however, acute respiratory distress syndrome requiring mechanical ventilation has also been reported. Medical conditions that predispose to ELP include dysphagia, hypopharyngeal diverticulum, tracheoesophageal fistula, achalasia, and gastroesophageal reflux [18].

Inhalation

Most clinically significant hydrocarbon inhalation exposures occur as a result of intentional abuse and their ability to produce euphoria similar to that of ethanol inebriation. There are three main methods of inhalant abuse: sniffing is inhaling directly from the container that holds the hydrocarbon, huffing is inhaling from a cloth that was soaked in the hydrocarbon by holding it over the nose and mouth, and bagging is the breathing of vapors directly from a bag containing a hydrocarbon in order to maximize the concentration of inhaled fumes [19]. Gaseous hydrocarbons, such as refrigerants, propane, and inhalation anesthetics, are gases at room temperature and pressure but are compressed into liquids inside containers. When the container is opened and pressure released, these liquid hydrocarbons change phase into a gas and are released. Because the phase change from a liquid to a gas requires energy, ambient heat is absorbed resulting in decreased temperature surrounding the liquid. Thus, if the phase change occurs close to the skin, it can cause freeze burns. Nitrites, or “poppers,” consist of cyclohexyl nitrite, amyl nitrite, or butyl nitrite. Instead of causing direct central nervous system (CNS) intoxication, they relax smooth muscles and heighten sexual experiences [20].

Neurophysiologic effects of inhalants are poorly understood. There is evidence that they lead to CNS depression via gamma-aminobutyric acid (GABA) agonism, *N*-methyl-D-aspartic acid (NMDA) antagonism, inhibition of normal cell-cell signaling, and enhanced serotonergic transmission [21]. They also directly activate dopamine neurons in the ventral tegmental area, thus reinforcing their abuse [22]. Chronic abusers

develop tolerance to these effects and may increase the amount inhaled to compensate. They may acquire physical dependence and thus cessation of use results in a withdrawal that includes craving, irritability, and insomnia [23].

Inhalation of hydrocarbon vapors causes altered mental status and in high concentrations act like simple asphyxiants via displacement of oxygen. Symptoms of hydrocarbon intoxication generally consist of two main stages: the first involves euphoria, excitability, disinhibition, and impulsive behavior; the second stage is characterized by CNS depression with slurred speech, confusion, hallucinations, diplopia, tremors, ataxia, and weakness [24]. High frequency users are more likely to feel euphoria and grandiosity but also experience more depressed moods and suicidal ideation [25]. Chronic exposure to inhaled toluene, as described in one case of a 22-year-old male with daily toluene sniffing for 10 years, can lead to irreversible leukoencephalopathy and presents as cerebellar ataxia, parkinsonism, encephalopathy, convulsions, and/or deficits in higher functioning [26]. Neuroimaging in these patients reveals abnormalities in the cerebral cortex, cerebellum, hippocampus, basal ganglia, and brainstem [27].

Inhalation of volatile hydrocarbons, especially halogenated derivatives, can lead to cardiac arrest referred to as “sudden sniffing death.” This phenomenon was initially described in the 1960s by Bass as cardiac arrest following inhalation of volatile hydrocarbons in the presence of hypercapnia or stress [28]. It was suspected that halogenated hydrocarbons may sensitize the myocardium to catecholamines which predisposes to dysrhythmias. However, subsequent epidemiological studies have shown that death in these patients occurred due to other causes including plastic bag asphyxia, aspiration, upper airway occlusion, excessive CNS depression, and combustion burn injuries [29].

Dermal

Prolonged dermal exposure to hydrocarbons can lead to a defatting process which can cause partial or full thickness skin necrosis. Histologically this

manifests as disorganization of cells, cytolysis, and enlarged intracellular spaces in the stratum corneum and stratum spinosum cells of the epidermis [30]. Because hydrocarbons are sensitizers, in cases of repeated low concentration dermal exposures, they can cause allergic dermatitis, a form of delayed type IV hypersensitivity [31].

Unique Toxicities

Various hydrocarbons have unique toxicities some of which will be reviewed in the following section.

Hepatotoxicity

Hepatotoxicity and liver failure can occur following hydrocarbon exposure. Halogenated hydrocarbons are particularly hepatotoxic, whereas most other hydrocarbons induce only mild hepatic injury. Carbon tetrachloride is the prototypical example and is one of the most hepatotoxic substances known; it induces centrilobular liver necrosis via cytochrome 2E1 metabolism in a manner similar to the acetaminophen (paracetamol) induced hepatocellular damage [32, 33].

Renal Toxicity

Both halogenated and nonhalogenated hydrocarbons can cause acute renal failure primarily via tubular injury [34]. Toluene inhalation is notorious for inducing renal tubular acidosis, ureteral calculi, and acute renal failure [35, 36]. Acute toluene exposure presents with a widened anion gap acidosis due to the formation of the unmeasured anions, benzoate, and hippurate [37]. Chronic toluene exposure results in distal renal tubular acidosis, normal anion gap metabolic acidosis, and electrolyte abnormalities including hypokalemia, hyperchloremia, hypomagnesemia, and hypophosphatemia. Some patients present with life-threatening hypokalemia and resultant muscle weakness or paralysis [38].

Hematologic Toxicity

One hematologic pathology is hemolysis, and even though most cases are mild and self-limiting,

some are severe enough to require transfusion or exchange transfusion [39]. For example, naphthalene is a potent hemolytic agent found in certain mothballs that can also induce methemoglobinemia [40]. Other hydrocarbons, especially ones that contain nitrogenous side groups such as nitrites or “poppers” can also induce methemoglobinemia when ingested or inhaled [41, 42].

Carbon Monoxide Toxicity

Another hydrocarbon-induced pathology is carbon monoxide toxicity via methylene chloride exposure. Inhalation of methylene chloride from commercial paint remover is one source of this typically occupational injury [43]. After absorption, methylene chloride is slowly released from body tissues and metabolized to carbon monoxide potentially leading to carbon monoxide toxicity 1–6 hours post ingestion [44, 45]. This slow release and metabolism causes the carboxyhemoglobin concentrations to remain elevated for much longer than in inhaled carbon monoxide.

Diagnosis

Radiographic findings in patients with hydrocarbon pneumonitis are variable. In one retrospective study of 150 hospitalized children with hydrocarbon ingestion, 90% of patients with pulmonary symptoms on arrival to hospital had abnormal chest radiographs. However, 50% of patients with no pulmonary symptoms at the time of hospital evaluation had abnormal chest radiographs, and of those 5% developed symptoms during the next six hours of observation [5]. In another retrospective study of 205 children admitted with kerosene poisoning, 5% with positive radiological evidence of pneumonitis had no clinical signs or symptoms [11]. Interstitial lobar infiltrates are the most common finding, occurring in 94% of patients who develop a radiographic abnormality and most often involve middle and lower lobes. Other potential pulmonary abnormalities are pleural effusions, collapse, and pneumothorax [11] (Fig. 3).

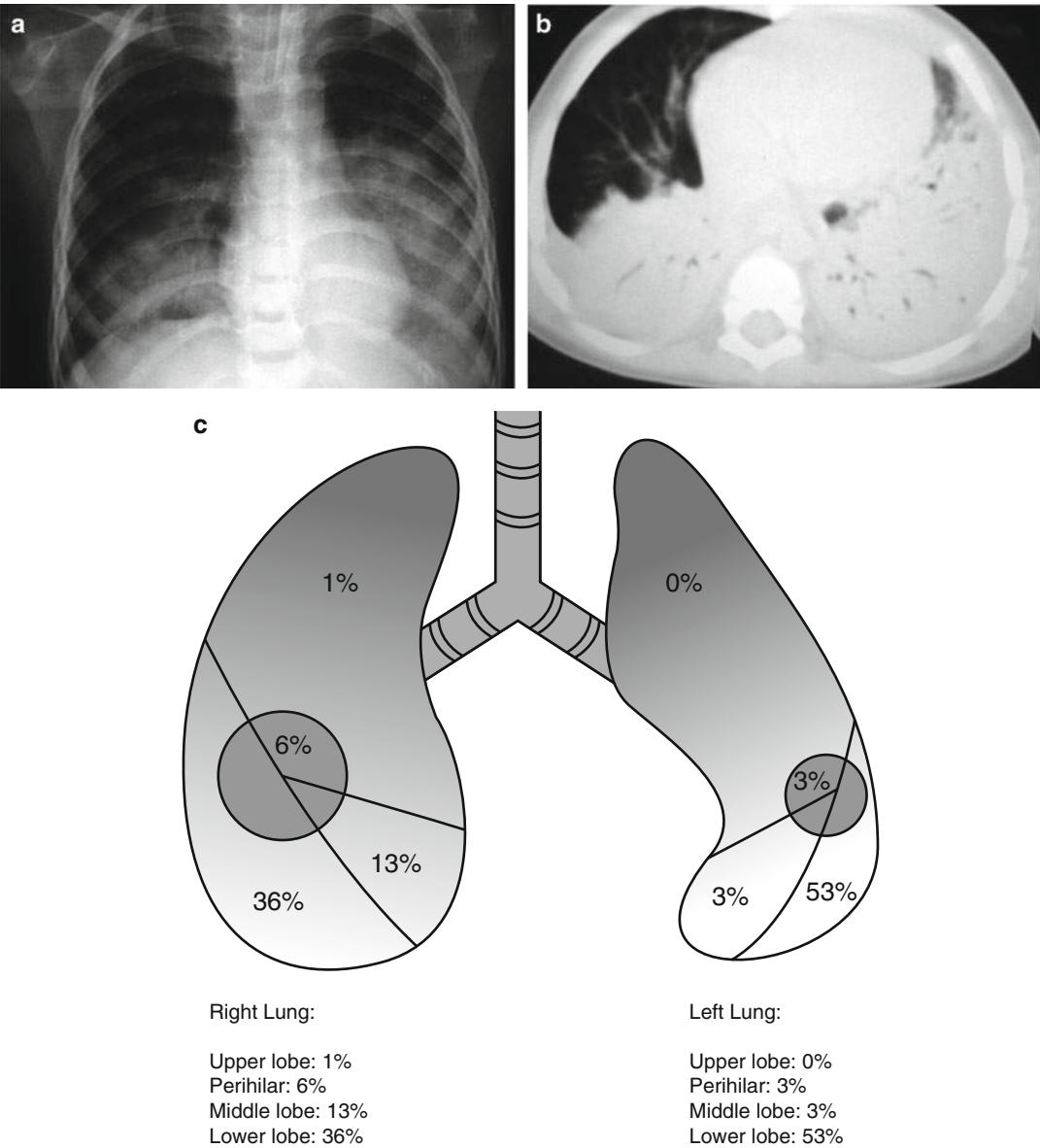


Fig. 3 Examples of chest radiographs in patients with aspiration. (a) Chest radiograph showing bilateral alveolar consolidations after aspiration [50]. (b) CT image of the

thorax after aspiration [50]. (c) Relative distribution of bronchopneumonic changes after aspiration as observed per one pediatric study [11]

Definitive diagnosis of hydrocarbon pneumonitis requires demonstration of lipid-laden macrophages in bronchoalveolar lavage fluid in the presence of history consistent with hydrocarbon aspiration. On chest computer tomography, the most common findings are consolidation with air bronchograms, ground-glass attenuation, and

areas of low attenuation within the consolidations [18].

Exogenous lipid pneumonia is diagnosed when all of the following are present: (1) presence of abnormal chest radiograph, (2) presence of intrapulmonary lipids, proven by histological examination or bronchoalveolar

lavage, (3) presence of optically empty vacuoles, sometimes confirmed by a fat stain (Fig. 2), and (4) history consistent with hydrocarbon ingestion. Computer tomography of the chest usually reveals alveolar consolidation and ground-glass opacities [14].

Renal toxicity from chronic hydrocarbon exposure can lead to a slow decline in renal function via progressive tubular injury, and albuminuria is a useful marker in gauging the severity of injury [46]. In the presence of toluene ingestion, elevated urinary hippuric acid concentration is a useful diagnostic marker.

Treatment

Pulmonary Toxicity

Treatment of hydrocarbon pneumonitis is supportive. Most patients will have mild signs and symptoms, and those with reactive airways should be given beta-adrenergic agonists for the treatment for bronchospasm [47] (Level of Evidence [LoE] III). However, severely ill patients may require mechanical ventilation for respiratory support. In one case report, high frequency percussive ventilation (HFPV) resulted in a significant clinical improvement in a patient who deteriorated while on other modes of ventilation (LeE III). The authors of that case noted how the HFPV helped with mucous plugging by mobilizing large amounts of thick oily secretions [48]. Both extra corporeal membrane oxygenation (ECMO) [49] and surfactant therapy [50] have also been described in case reports and is an option for those with refractory hypoxia (LoE III).

Corticosteroid therapy in hydrocarbon pneumonitis was believed to reduce the inflammation and subsequent fibrosis and edema. However, because clinical effects and radiographic findings are often present 30 min after aspiration, it might be too late for this treatment to exert its anti-inflammatory action. In one randomized clinical trial of 71 mild to moderately ill patients, compared to placebo, corticosteroids did not decrease the number of days with abnormal temperature, respiratory rate, pulse, or hospital length of stay

[51] (LoE I). Thus, there is no established role for corticosteroid therapy in the treatment of hydrocarbon pneumonitis.

There is no demonstrated role for antibiotics in the treatment of hydrocarbon pneumonitis. Hydrocarbon aspiration predominantly results in a sterile inflammatory chemical pneumonitis [9]. The pneumonitis is usually mild and patients are typically able to go home within a few days. However, there is a theoretical concern for the lung's subsequent susceptibility to bacterial superinfection for which antibiotics might be helpful. However, in a double-blind randomized clinical trial of 200 children with mild pneumonitis after kerosene ingestion, antibiotics did not decrease hospital length of stay, improve treatment success, or improve clinical symptoms in patients [52] (LoE I). Therefore, based on the current state of knowledge, prophylactic antibiotics have no established role in the management of hydrocarbon aspiration.

Gastrointestinal Toxicity

Gastric lavage in patients with hydrocarbon ingestion is not recommended because of concern that re-exposing the patient's glottic opening to the substance increases the risk of pulmonary aspiration. This concern is supported by studies showing higher incidence and severity of aspiration pneumonia in patients who had undergone gastric emptying [53].

Treatment with *N*-acetylcysteine is hepatoprotective in animal models and in case reports of acute human exposure to hepatotoxic hydrocarbons [54, 55] (LoE III). While data are limited regarding the effectiveness of *N*-acetylcysteine in these exposures, we recommend that it be used because of its low cost and wide safety profile. A convenient dosing regimen is that which is used for acetaminophen poisoning. The clinical pharmacology of this agent can be found in ► Chap. 154, "*N*-Acetylcysteine".

Cardiotoxicity

Toluene causes electrocardiographic QT interval prolongation which can lead to dysrhythmias [56].

These arrhythmias can persist for days and are usually treated with beta-adrenoreceptor antagonists such as esmolol [57] (LoE III). Torsade de pointes (TdP) should be treated using standard protocols. Prevention strategies and the treatment of TdP are described in detail in Chap. 22, “Toxicant-Induced Torsade de Pointes”. The Volatile organic solvents sensitize the myocardium to catecholamines, and superimposed adrenergic stimulation, such as sudden excitation or exercise, can trigger ventricular dysrhythmias [58]. Beta-adrenergic blockers can blunt myocardial sensitization [59] (LoE III). Amiodarone and lidocaine have been used successfully to terminate ventricular arrhythmias [59] (LoE III).

Nephrotoxicity

Toluene is one of the hydrocarbons that is nephrotoxic. When renal toxicity develops, treatment is focused on hydration and repletion of electrolytes, primarily potassium. Sodium bicarbonate should be used with caution to treat acidosis as it can further decrease extracellular potassium thus worsening the existing hypokalemia-induced weakness/paralysis. Hemodialysis may be required to reverse severe hypokalemia [60] (LoE III).

Neurotoxicity

Treatment of acute inhalant induced intoxication is mostly supportive. In chronic users who develop signs or symptoms after cessation, there are no consensus recommendations for the treatment of the inhalant withdrawal syndrome. Baclofen, a GABA-B receptor agonist, was described in one case series of three patients as an effective treatment for symptom relief [61] (LoE III). Lamotrigine, an anticonvulsant that decreases the release of glutamate and aspartate, decreasing NMDA stimulation; a 5-HT₃ receptor antagonist; and a dopamine uptake inhibitor showed promising results in one case report of the treatment of inhalant dependence [62] (LoE III).

Dermal Toxicity

Dermal exposure typically results in mild irritant dermatitis that can be treated by cleansing the area with soap and water to remove residual hydrocarbons, followed by emollient application. Once damage to the skin develops, it can be treated similar to burn injury. If one develops allergic dermatitis, the treatment is primarily avoidance of future exposure.

Disposition

Figure 4 provides an algorithm for the disposition of patients following hydrocarbon exposures.

Special Populations

Pregnant Patients

Very little information exists linking acute toxic hydrocarbon ingestion with adverse maternal or fetal outcome. In one case report of an acute gasoline ingestion, a 38-week pregnant female developed transient respiratory distress with fetal heart rate decelerations prompting emergent cesarean delivery. Both the mother and baby did well at discharge 15 days later [63]. The appropriate treatment approach, based on the current state of knowledge, is to treat the mother as needed in the hope that this will serve to treat the fetus.

Key Points

Hydrocarbons are ubiquitous in the outdoor and indoor environments.

Most exposures are benign; however, some may require ICU observation and treatment.

Significant exposure can affect multiple organs (i.e., central nervous system, cardiac, gastrointestinal, dermal, and respiratory).

(continued)

Disposition Algorithm:

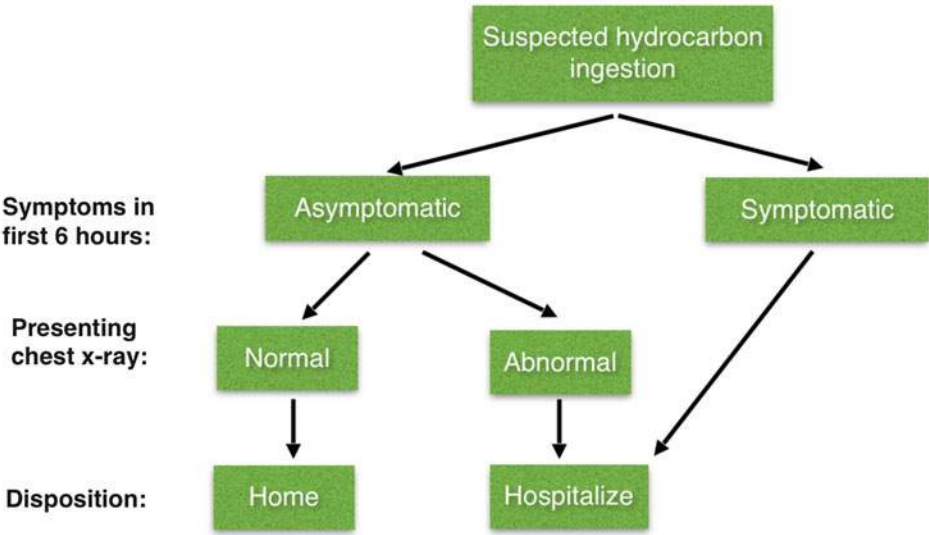


Fig. 4 Disposition algorithm

Fig. 5 Clinical effects of hydrocarbons

Pulmonary Bronchospasm Pneumomediastinum Pneumatocele Chemical pneumonitis Pneumonia Pleural effusions ARDS	Gastrointestinal Abdominal pain Nausea/Vomiting Hepatitis/Liver failure
Cardiac Arrhythmias Myocardial infarction	Renal Type I RTA Ureteral calculi Glomerulonephritis Actue tubular necrosis Acute renal failure
Neurologic CNS depression Euphoria Peripheral neuropathy Psychiatric disorders Seizures	Dermatology Allergic dermatitis Chemical burn
	Other Hemolysis Methemoglobinemia Cancers

All suspected hydrocarbon ingestions should receive a chest radiograph and be observed for at least 6 hours.

Place all symptomatic patients on cardiac monitor.

- Common Errors**
- Not recognizing hydrocarbon components of ingestion.
 - Medically clearing patients prior to completing 6 hours of observation.

(continued)

- Not recognizing subtle symptoms of toxicity during observation which should prompt automatic admission.

Criteria for ICU Admission

- Respiratory distress/failure
- Hemodynamic instability
- Altered mental status or seizures
- Presence of arrhythmias or cardiac dysfunction
- Extensive chemical burn

Criteria for ICU Discharge

- Off respiratory and hemodynamic support
- Improving mental status

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Hydrogen sulfide (H₂S), cyanide, azide, and carbon monoxide are collectively referred to as *cellular asphyxiants* or *chemical asphyxiants* because of their ability to disrupt aerobic cellular respiration. Exposure to H₂S is associated with a “knockdown” effect and may be rapidly fatal. The American Association of Poison Control Centers reported 766 H₂S exposures in 2013, with 327 treated in a healthcare facility and 10 deaths [1]. Hydrogen sulfide is the second most common cause of fatal gas inhalation in the workplace [2]. Olfactory fatigue to the smell of H₂S occurs quickly and has led to fatal poisoning of rescuers on multiple occasions [3, 4].

Hydrogen sulfide is known as “sewer gas” and is naturally produced by the putrefaction of organic substances such as sewage, manure, offal, and fish in ships’ holding tanks. Decomposition of sulfur-containing proteins by bacteria produces H₂S. Hydrogen sulfide gas can therefore be anticipated whenever organic material containing sulfur is in an anaerobic environment.

Major industrial uses for H₂S include production of elemental sulfur, inorganic sulfides, and sulfuric acid. Hydrogen sulfide is also found as an additive in high-pressure lubricants and cutting oils. Hydrogen sulfide is a commonly encountered toxin in several industries including paper making, leather tanning, and most notably, oil and natural gas production. “Sour gas” refers specifically to natural gas that contains significant quantities of hydrogen sulfide; H₂S must be removed from the gas prior to its use as fuel [5].

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Table 1 Selected natural and industrial sources of hydrogen sulfide

Natural gas wells	Sewers/waste water treatment
Oil wells	Manure pits
Sulfuric acid production	Fish in ship holds
Coke ovens	Undersea vents
Tanneries	Volcanos
Iron smelting	Tar and Asphalt manufacturing
Rayon production	Food processing plants
Kraft paper mills	Chemical refineries

Hydrogen sulfide is also naturally produced and liberated from volcanos and undersea vents. One example occurs in the Puna District on the island of Hawaii, where an active volcano emits H_2S , typically in concentrations of less than 20 parts per billion (ppb) [6]. A similar volcanic off-gassing site exists in the City of Rotorua on the north island of New Zealand [7] (Table 1).

In 2007, the first case of “detergent suicide” was reported in Japan. This method of suicide involves mixing a commercially available, sulfur-containing product with an acidic toilet bowl cleaner to produce hydrogen sulfide gas. Instructions and ingredient lists were published and rapidly popularized through internet message boards. By 2008, an epidemic of detergent suicides was underway in Japan, with nationwide deaths due to hydrogen sulfide poisoning increasing from 27 in 2007 to 1,027 in 2008 [8]. In the United States, hydrogen sulfide suicides increased from 2 in 2008, to 10 in 2009, and 18 in 2010 [9]. Detergent suicides have caused evacuation of commercial and residential buildings; fatalities among family members with secondary exposure have also been reported [8, 10].

Biochemistry and Clinical Pharmacology

Hydrogen sulfide is normally present in small amounts in the human body. As a component of intestinal gas, H_2S has been found in concentrations of 1–4 ppm with some high levels of 18 ppm [11]. Hydrogen sulfide is synthesized in small

amounts in neuronal cells and within the cardiovascular system, in addition to being released from intracellular sulfur stores. Recent studies demonstrate many physiological effects of endogenous H_2S , and it has been proposed as the third gasotransmitter, a family of small molecules that participate in cell signaling via diffusion across cell membranes [12].

Hydrogen sulfide appears to be an important vasoactive agent similar to nitric oxide. It has been reported to have an inotropic effect and alter the growth of vascular endothelial cells [13]. There is also a link between H_2S and insulin release [14]. In the CNS, there appear to be physiological roles in GABA and NMDA transmission [15]. Hydrogen sulfide can reduce reactive oxygen species both directly and via increasing glutathione production, protecting neuronal cells from death [16]. Hydrogen sulfide is currently being investigated for neuroprotective, cardioprotective, antioxidant, and anti-inflammatory effects, with several experimental H_2S -donating drugs under study [12]. At higher doses, however, predictable toxic effects of H_2S occur that are discussed in detail below.

Hydrogen sulfide is a colorless gas, slightly heavier than air, with a relative vapor density of 1.19, and is slightly less volatile than water at room temperature. It has a molecular weight of 34.08 g/mol. Hydrogen sulfide has a water solubility (3.2 g/L at 30 °C) between ammonia, which is highly soluble, and chlorine, which has low solubility. Its metabolism is rapid; no bioaccumulation occurs [11]. H_2S smells like rotten eggs. However, olfactory fatigue and the loss of the ability to smell H_2S can occur in seconds. The odor threshold is reported in the range of 1–130 ppb, with olfactory fatigue occurring around 100 ppm [17].

The principle pathway of exposure is via inhalation. It has minimal absorption through the gastrointestinal tract and intact skin. Hydrogen sulfide is highly lipid soluble and rapidly diffuses across cellular membranes. Following human exposure, distribution to tissues is rapid [18].

Hydrogen sulfide is metabolized by three major pathways. The primary metabolic

elimination pathway is via oxidation of sulfide to thiosulfate, which is converted into sulfate, ultimately being excreted in the urine [19]. Hydrogen sulfide is also metabolized by methylation and reactions with metalloproteins or disulfide-containing proteins. Though in vitro studies demonstrated H₂S-induced sulfhemoglobinemia, recent evidence suggests that clinically significant sulfhemoglobinemia does not occur in acute hydrogen sulfide poisoning [20].

Pathophysiology of Toxic Effects

Hydrogen sulfide causes cellular anoxia by the inhibition of mitochondrial cytochrome *c* oxidase. This inhibition results in disruption of the electron transport chain, impairing oxidative metabolism and the resultant production of ATP. Tissues with high metabolic demands (e.g., brain and heart) are therefore especially susceptible [11].

Hydrogen sulfide also may reduce disulfide bridges in proteins, which is thought to be the mechanism of its inhibition of succinate dehydrogenase. Because of its water solubility, H₂S has irritant effects on moist mucous membranes but also may result in distal airway injury if a high respiratory rate is maintained while exposed. Minimal H₂S is excreted via the lungs.

Hydrogen sulfide directly stimulates carotid arterial chemoreceptors, causing an increased respiratory rate. Noncardiogenic pulmonary edema may develop prior to respiratory arrest. Terminal respiratory depression likely results from H₂S being selectively taken up by respiratory center of the brainstem with an end point similar to anoxia. The underlying mechanism is thought to be inhibition of monoamine oxidase [21, 22].

Clinical Presentation and Life-Threatening Complications

Two common adverse effects occur after H₂S poisoning: mucous membrane irritation and systemic toxicity. These occur in a dose-response fashion (Table 2). Hydrogen sulfide reacts with

Table 2 Range of toxicity of hydrogen sulfide (Adapted from references [11, 23, 24])

Clinical effect	Concentration (ppm)
Eye irritation	20–100
Olfactory fatigue	100
Respiratory irritation, possible pulmonary edema	50–500
Symptomatic	50 for 0.5 h
Severely toxic	200 for 1 min
Bronchitis, noncardiogenic pulmonary edema	250 for 24–72 h
Coma and death	500–1,000
Fatal	800 – immediate; 600 – 30 min
Immediate collapse	700–1,000

water to form irritating acid sulfides. Mucous membranes are especially susceptible to the effects of H₂S because of their moisture and anatomic proximity to the environment. The irritant effects of H₂S to the face are sensed by the trigeminal nerve and the olfactory nerve detects its odor, although there may be significant overlap between these two domains.

Membrane irritation begins to occur with H₂S exposures in the range of 2–5 ppm. Mild nausea, vomiting, and lacrimation tend to occur in the range of 80–100 ppm. Higher concentrations, in the range of 500 ppm, typically are required to cause immediate respiratory symptoms. Obvious signs of systemic toxicity tend not to occur until H₂S concentrations of approximately 250 ppm have been attained. Findings at these concentrations may include cough, tachypnea, chest pain, headache, dizziness, lethargy, and confusion. At still higher concentrations, seizures and coma occur. Concentrations of 1,000 to 3,000 ppm were fatal to dogs; death occurred within 15–20 min at 1,000 ppm. At the higher concentration, respiration ceased after a few breaths [21]. The most common clinical findings after H₂S exposures are headache, nausea, vomiting, dyspnea, disequilibrium, conjunctivitis, sore throat, and unconsciousness [25]. A toxidrome for hydrogen sulfide poisoning has been proposed by Guidotti, consisting of any one or combination of the following effects:

- Odor perception (followed by olfactory paralysis)
- Conjunctivitis
- Pulmonary edema
- Acute central neurotoxicity (“knockdown”) [2].

Ocular Effects

The eyes react first to the irritant effects of H_2S . As levels increase, the conjunctivae may become inflamed and swollen. After major exposures, the cornea may develop erosions and ulcerations. Associated signs and symptoms include photophobia, lacrimation, and pain. Because both the cornea and the conjunctivae are affected, the term *keratoconjunctivitis* is used to describe the eye effects. This is known in industry as “gas eye.” Visual impairment lasting for days has been reported. The possibility of permanent blindness after hydrogen sulfide exposure remains controversial [26].

Knockdown Effects

Hydrogen sulfide is known for its rapid “knock-down” capability. At ambient concentrations of 700–1,000 ppm H_2S , exposed persons may suddenly collapse. If the exposure is terminated promptly, this situation may result in no residual effects [27]. Frequently, workers in the oil fields report this effect; after recovering, they resume their work [5]. If exposure is not terminated, respiratory arrest may occur rapidly.

Pulmonary Effects

Inhaled irritants tend to increase the respiratory rate and decrease the minute volume. Hydrogen sulfide directly produces an increase in ventilation mediated by carotid arterial chemoreceptors at doses below those sufficient to cause central apnea [28]. Significant H_2S exposure may result in redness, inflammation, sloughing, or exfoliation of the airways as H_2S reacts with the moisture of the mucosal surfaces. Hemorrhagic bronchitis

has been reported and may require ventilatory support [29].

Due to the moderate water solubility of H_2S , the gas can penetrate the deep airways of the lung and injure alveoli, causing pulmonary edema. The prevalence of pulmonary edema in H_2S -poisoned patients reaching the emergency department has been reported from 4% to 20% [2, 27]. Pulmonary edema appears to make a small contribution to mortality in H_2S poisoning, presumably because respiratory arrest occurs so rapidly in those severely poisoned. Cases of interstitial pulmonary fibrosis following hydrogen sulfide poisoning have also been reported, but appear to be exceptionally rare [30].

Cardiovascular Effects

Typical and atypical chest pain, dysrhythmias, and acute myocardial infarction with heart failure are reported after H_2S exposure [31]. Cardiovascular effects are most likely due to cellular anoxia, rather than direct toxic effects of H_2S on cardiac myocytes. In fact, recent literature describes *protective* effects of low levels of H_2S against myocardial ischemia/reperfusion injury, infarction, and cardiac dysrhythmias in animal and in vitro models [32, 33].

Neurologic Effects

Early-onset neurologic symptoms (dizziness, ataxia, headache, “knockdown”) are believed to be due to direct toxic effects of hydrogen sulfide. Coma, seizures, or signs of increased intracranial pressure from edema may occur in the setting of cerebral anoxia. Those who survive acute exposures to high levels of H_2S frequently make a complete neurologic recovery. However, some H_2S poisonings with loss of consciousness have been associated with long-term neurological dysfunction, including headaches, memory problems, motor dysfunction, and neuropsychiatric effects [24]. These are proposed to result from secondary anoxic brain injury caused by respiratory arrest, seizures, or other hypoxia resulting from H_2S

poisoning (i.e., pulmonary edema) [2]. Trauma may also accompany acute H₂S exposures due to knockdown effects, confounding the causality assessment of neurological sequelae [34, 35]. Although acute high-level exposures may result in altered neurological function, quality evidence that chronic low-level exposures cause long-term harm is lacking.

Metabolic Acidosis

Metabolic acidosis, with elevated lactate concentration, may occur in individuals with serious H₂S poisoning due to impairment of oxidative phosphorylation, ATP consumption exceeding production, and the resulting shift to anaerobic metabolism.

Death

Twenty-nine deaths from 5,563 H₂S exposures in the United States were reported to the American Association of Poison Control Centers over a 9-year period [23]. Most fatal cases involved exposures occurring in confined spaces, such as sewers, animal-handling and processing plants, waste dumps, sludge plants, tanks and cesspools, pulp mills, and other confined environments. In case reports of deaths occurring after acute H₂S exposure, individuals lost consciousness after only one or two breaths; this is known as the “slaughterhouse sledgehammer” effect [23, 36–39]. In these fatal cases, patients seemed to succumb from respiratory failure, acute pulmonary edema, or coma. Patients exposed to only H₂S gas do not have a substantial risk of secondary contamination to personnel outside the so-called hot zone. Rescuers should be trained and attired properly with positive-pressure, self-contained breathing apparatus before entering the hot zone.

Diagnosis

The exposure history and clinical presentation are the keys to making the diagnosis of acute hydrogen sulfide poisoning. A rotten egg odor on a

patient or their belongings is suggestive of H₂S, though other agents have a similar smell, including sulfur compounds such as mercaptans, carbon disulfide, and trimethylamine. Historically, dark discoloration of a patient’s coins and jewelry has been suggested as a clue to H₂S poisoning.

Important toxicologic differential diagnoses with presentation similar to H₂S poisoning include other cellular asphyxiants, such as carbon monoxide, cyanide, azide, and cyanide-related substances.

The presence of metabolic acidosis can be further evaluated by assessment of arterial blood gases with co-oximetry, electrolytes, and lactate concentrations. If the diagnosis of H₂S poisoning is not immediately obvious, cyanide, toxic alcohols (ethylene glycol, methanol), salicylate, and carboxyhemoglobin concentrations should be obtained, if indicated by the clinical history.

Sulfide ion levels can be measured on whole blood. However, lack of specificity, difficulty in performing the test accurately, and limited availability make sulfide levels useless in initial diagnosis [18]. One case series found urine thiosulfate concentrations elevated in nonfatal H₂S poisoning, despite undetectable blood sulfide levels. Urine thiosulfate may therefore be a useful means of confirming H₂S poisoning in patients who survive exposure [40]. Industrial hygienists, hazardous materials responders, and firefighters can measure H₂S concentrations in the ambient atmosphere around the site of an incident. In the case of an identified H₂S release or exposure, it is critical that H₂S concentrations are directly communicated with the individuals on site, so that appropriate precautions can be taken and secondary casualties prevented.

Treatment

Supportive care is the mainstay of therapy for exposures to H₂S. This includes removal from exposure, administration of supplemental oxygen, and decontamination of the eyes and skin. Decontamination can be accomplished by copiously irrigating exposed skin and eyes with normal saline or water. Ventilatory support, administration of

anticonvulsants if there is seizure activity, intravenous fluids, and vasopressors may be necessary. Cycloplegics and antibiotics may be needed for eye injuries. Systemic antibiotics may be indicated if there is evidence of superinfected aspirated pulmonary secretions.

Indications for ICU Admission in Hydrogen Sulfide Poisoning

Respiratory distress, respiratory failure, or signs of airway injury
Unconsciousness
Seizures or persistent neurological impairment
Electrocardiogram changes

Methemoglobin Induction

One possible antidotal therapy is induction of methemoglobinemia. Hydrogen sulfide poisoning causes lactic acidosis by the inhibition of cytochrome *c* oxidase and depletion of ATP. The formation of methemoglobinemia by nitrites creates a large pool of ferric iron, which has a greater affinity than cytochrome *c* oxidase for H₂S. Methemoglobin may therefore serve as a sink, allowing cytochrome *c* to be reactivated and reestablishing aerobic metabolism [41–43]. However, the period during which H₂S is available in blood after removal from exposure is short-lived. One animal model found no benefit to infusion of a methemoglobin solution 90 s after termination of a toxic H₂S exposure [44]. Future research is needed to determine if antidotes that propose to work by binding diffusible H₂S, including methemoglobin induction, are truly effective.

One method of inducing methemoglobinemia is by use of sodium nitrite, which may be found as a component of a cyanide antidote kit. The use of nitrites in H₂S poisoning is supported by animal studies and human case reports (Grade III evidence) [45, 46]. Intravenous (IV) access should be established as soon as possible and IV sodium nitrite administered once the decision is made to induce methemoglobinemia. The generally accepted adult dose of sodium nitrite is 10 mL of a 3% solution; the pediatric dose is 0.33 mL/kg up to 10 mL but may be adjusted based on

hemoglobin level. Because sodium nitrite is a potent vasodilator, it should not be administered rapidly, but given over 2–5 min. The thiosulfate portion of the cyanide antidote kit is not useful in H₂S poisoning. Sulfide is present in the blood only transiently, and methemoglobin therapy is *not* indicated in most patients. If a patient has persistent acidosis, shock, cardiotoxicity, or coma despite optimal supportive care, the authors recommend induction of methemoglobinemia given the above animal and case-based human evidence supporting possible benefit.

Hydroxocobalamin and Cobinamide

Hydroxocobalamin, a precursor of Vitamin B₁₂, and cobinamide, a Vitamin B₁₂ analog, both have a high affinity for sulfides and have been investigated as possible antidotes for H₂S poisoning. Animal models suggest a reduction in lethality and amelioration of cardiac depression with hydroxocobalamin treatment [47, 48]. A single fatal human case report notes a reduction in blood sulfide levels after hydroxocobalamin treatment [49]. One rabbit model shows increased survival and binding of sulfide to cobinamide [50]. However, in these animal models, sulfide is continuously infused, generating a constant supply of H₂S that may complex with an antidote before entering cells. Neither hydroxocobalamin nor cobinamide has yet proven clinically useful in human H₂S poisoning. Again, this may be due to the extreme rapidity with which free hydrogen sulfide leaves the circulation and enters tissues, once victims are removed from exposure. Any complex-forming antidote that cannot be administered almost immediately is likely to be of limited value [51–53]. Given the current absence of evidence supporting antidotal effects of hydroxocobalamin and cobinamide in humans, the authors recommend against their use in hydrogen sulfide poisoning (Grade III Evidence).

Hyperbaric Oxygen

Hyperbaric oxygen is a theoretical therapy for H₂S poisoning. A few case reports and

retrospective series have described using hyperbaric oxygen for H₂S poisoning. In these cases, positive outcomes were reported (Grade III Evidence) [54, 55]. However, these data are uncontrolled and subject to publication bias. The pillar of evidence-based treatment for human hydrogen sulfide poisoning remains supportive care, once the patient has been removed from the source of exposure. Hyperbaric oxygen therapy is rarely immediately available and logistically often interferes with the provision of supportive care. It is therefore the authors' opinion that hyperbaric oxygen should not be used in human H₂S poisoning. Current evidence that does not demonstrate a clear benefit and there is a high likelihood that hyperbaric oxygen treatment will delay other beneficial aspects of care.

Prehospital Treatment

A study of 250 cases of exposure to H₂S in the Alberta oil fields found that with increased awareness and improved prehospital treatment, the fatality rate was reduced from 6% to 2.8%, unconsciousness on hospital arrival decreased from 13% to 2%, and hospital admission rates decreased from 51% to 22%. Prehospital treatment also resulted in an overall decrease in workers' compensation claims [34].

Prevention

Safety officers, industrial hygienists, and workers in those industries should learn the hazards of H₂S and the proper response in the event of an accident. Safe evacuation and prompt medical attention are important. Real-time gas detecting devices are available and should be used to monitor levels of H₂S before entry into a potentially contaminated zone.

Common Errors in Hydrogen Sulfide Poisoning

Failure to consider hydrogen sulfide in cases of rapid knockdown, multiple victim poisonings

at a single site, or unexplained poisoning in a confined space

Failure to account for olfactory fatigue to hydrogen sulfide gas

Failure to protect emergency personnel during attempted rescue of poisoned patients

Failure to consider hydrogen sulfide in cases of seizure, coma, or metabolic acidosis

Failure to assess for trauma secondary to sudden unconsciousness

Failure to treat on the basis of clinical presentation rather than reported or suspected exposure

Failure to perform ocular decontamination

Evidence-Based Recommendations for Practice

Clinical Recommendation	Evidence rating
Supportive care should include decontamination and oxygen supplementation	III
Methemoglobin induction with sodium nitrite may be considered for severely poisoned patients that remain symptomatic in medical care	III
Patients severely poisoned by H ₂ S should be evaluated for concomitant trauma	III

Key Points in Hydrogen Sulfide Poisoning

1. Hydrogen sulfide causes a rapid knock-down effect.
2. Decontamination is essential.
3. Safe removal from exposure and supportive care is the mainstay of therapy.
4. Trauma frequently accompanies H₂S poisoning and must be evaluated and treated.
5. Induction of methemoglobinemia with IV sodium nitrite may be antidotal.
6. Vitamin B₁₂ and its analogs currently lack human evidence for effectiveness.
7. Hyperbaric oxygen therapy currently lacks human evidence for effectiveness.

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Toxic and irritating gases have been known to produce fatalities since the Athenians used a combination of pitch and sulfur to produce toxic fumes in a war against the Spartans in 428 BC. More sophisticated irritant agents were introduced during World War I, when mustard gas, chlorine, and phosgene were the primary agents of chemical warfare. These gases produced many incapacitating casualties but relatively few fatalities compared with conventional weapons. The use of mustard gas was reported in the 1988 war between Iraq and Iran, and more recently gas warfare was reported between Iraq and the Kurds.

Large amounts of irritant gases are produced; more than 0.5 million workers are exposed to anhydrous ammonia alone in the United States. In 1984, a disastrous release of large amounts of methyl isocyanate in Bhopal, India, resulted in approximately 2,500–5,000 deaths and 200,000 individuals with respiratory, eye, and other symptoms [1]. Smaller numbers are exposed to a variety of other irritant gases that are used in a multitude of industrial processes. In addition, many millions of people worldwide also are exposed to compounds related to the burning of materials that may generate toxic gases. This exposure most commonly occurs in commercial or home fires, where large amounts of hydrogen cyanide, hydrogen chloride, acrolein, sulfur dioxide, phosgene, and other irritant gases are produced (Table 1). Statistically, the major lethal gas still is the asphyxiant gas carbon monoxide.

The magnitude of the problem is significant. In 2014, over 133,000 inhalational exposures were reported to poison control centers [2]. Approximately 40% of 26,932 exposures annually involve an inhalational agent in the workplace [2]. Fumes, gases, and vapors are common causes of environmental exposures and constitute the largest mortality. Carbon monoxide, hydrogen sulfide, and hydrofluoric acid are the leading cause of death in the occupationally exposed group. The United States Department of Labor, the Bureau of Labor Statistics reports an average of greater than 11,000

Table 1 Common pyrolysis products of combustion

Substance	Toxic product
Acrylics	Acrolein
Batteries, paints	Metals (lead, zinc, manganese, cadmium, cobalt)
Coal, fuel, wood	Carbon monoxide
Fuels, fabrics, celluloid, nitrocellulose film	Oxides of nitrogen, cyanide, aldehydes
Fluorinated resins	Hydrogen fluoride
Melamine, silk, wool, polyurethane, nylon	Ammonia, hydrocyanic acid, hydrogen sulfide, isocyanates
Polyvinyl chloride	Chlorine, phosgene, hydrochloric acid
Rubber	Hydrogen sulfide, sulfur dioxide
Sulfur compounds	Sulfur dioxide
Wood, house fires, building fires	Acrolein, acetaldehyde, hydrocyanic acid, carbon monoxide, nitrogen dioxide, ammonia

nonfatal injuries and illnesses caused by inhalational exposure to harmful substances [3]. Inhalational exposure accounts for more than 58% of harmful substance-related deaths in the workplace [4]. Worldwide, the World Health Organization estimates two million premature deaths per year due to air pollution. Eighty-eight percent of those deaths occurred in low- and middle-income countries [5].

Biochemistry and Clinical Pharmacology

Exposure to toxic concentrations of inhalational agents may result in systemic injury and local injury to the respiratory system. Vapors and gases can be classified into several different types based on the physical state of the particular substance.

Dusts are a particular form of a solid organic or inorganic material that is small enough to be airborne. They usually are characterized by particles ranging from 0.1 to 25 μm in diameter.

Characteristics of Gases and Vapors

1. A gas is a state of matter in which the molecules move freely, allowing infinite expansion.
2. A vapor is a gas below its critical temperature at which it may be liquefied by an increased pressure.
3. The density of a gas is relative to air; the more dense a gas, the more likely it will seek low areas.
4. Cold gases are denser and seek low areas. Nitrogen acts as an asphyxiant in low areas when cold.

Fumes are extremely fine solid particulates that usually are formed by combustion or condensation of metals so that these metals have entered a gaseous state. Fumes usually range from 0.001 to 1.0 μm in diameter.

A *gas* is a substance that at standard conditions has a physical state in which molecules move freely, allowing infinite expansion. The vapor density of a gas by convention is expressed relative to air, which by definition has a vapor density of 1. The more dense (or the heavier) the gas, the more likely it will seek low areas in the air column. Decreased temperature increases the density of a gas. Nitrogen may act as an asphyxiant in low areas when cold. A gas is not capable of being liquefied by pressure alone and is liquefied by lowering its temperature and increasing pressure.

A *vapor* is a gas below its critical temperature at which it may be liquefied by an increased pressure alone. It may exist as either a liquid or a solid when it is in equilibrium with its vapor. So-called industrial gases – chlorine, ammonia, propane, and butane – are actually vapors.

A *fog* is a liquid aerosol formed by condensation from a gaseous to a liquid state.

Smoke is a mixture of airborne particles, vapors, and gases, resulting from the incomplete combustion of organic materials. These particles are usually less than 0.5 μm in diameter.

This chapter discusses primarily the health effects of gases, vapors, and fumes. A general

classification of toxic inhalants is presented in Table 2. Table 3 lists the common chemical exposures and their effects and the concentrations commonly associated with a significant health hazard. Although not irritants, asphyxiants are included for completeness (Table 4).

Irritant gases are gases that cause respiratory tissue injury by direct contact due to their chemical reactivity. Acid and alkaline gases, such as chlorine and ammonia, may produce extreme alterations in pH, and other gases may cause chemical reactions with membrane damage and release of free radicals. The site of the pulmonary injury is related largely to the water solubility of the various gases (Table 5). The various factors influencing the likelihood and degree of pulmonary injury are presented in Table 6.

Toxicokinetics

Inhalant gas toxicology is complex. The dose of an inhaled gas or vapor usually is expressed as the mass of the gas per unit volume, or milligrams per liter, or as the ratio of molecules of the study gas to total gas molecules; this usually is expressed as parts per million (ppm). The dose of an inhaled gas is calculated by multiplying the concentration of the gas in the breathing zone by the duration of the exposure and the minute ventilation of the individual during that exposure time:

$$\begin{aligned} &\text{Dose of an inhaled gas} \\ &= C (\text{concentration in the breathing zone}) \\ &\quad \times \text{minute ventilation} \end{aligned} \quad (1)$$

Dose-effect relationships may be expressed by Harber's rule: [6]

$$\begin{aligned} &C \times T (\text{time of exposure}) \\ &= K (\text{biologic effect}) \end{aligned} \quad (2)$$

Limitations of Harber's rule include the failure to take into account the minute ventilation or

Table 2 General classification of acute inhalational toxicants

I. Respiratory toxicants
A. Single agents
1. Asphyxiants
a. Simple
i. Carbon dioxide
ii. Methane
iii. Nitrogen
b. Chemical
i. Agents that decrease oxygen-carrying capacity
(a) Carbon monoxide
(b) Hydrogen sulfide
(c) Oxides of nitrogen
ii. Agents that inhibit tissue oxygen utilization
(a) Acrylonitrile
(b) Hydrogen cyanide
(c) Hydrogen sulfide
2. Irritants
a. High-solubility gases
i. Ammonia
ii. Methyl isocyanate
iii. Sulfur dioxide
b. Intermediate-solubility gases
i. Chlorine
c. Low-solubility gases
i. Hydrogen sulfide
ii. Oxides of nitrogen
iii. Phosgene
B. Mixtures
1. Smoke inhalation from fires
2. Smoke inhalation from smoke bombs
C. Illicit drug abuse
1. Airway burns from freebasing cocaine
2. Asphyxia from glue sniffing and organic solvent abuse
3. Drug-induced pulmonary edema
4. Pulmonary hypertension, pulmonary fibrosis, bullous emphysema secondary to intravenous drug abuse
D. War gases
1. Lethal agents (CG, DP, CL, PS, AC)
2. Riot control agents (CN, CS, CR, DM)
II. Systemic toxicants
A. Fluorinated polymers (polymer fume fever)
B. Metal oxides (metal fume fever)
C. Organic dusts (organic toxic dust syndrome)
D. Poisons (arsine, stibine, carbon tetrachloride)

Adapted from Ref. [149]

CG phosgene, DP diphosgene, CL phosgene, PS chloropicrin, AC hydrogen cyanide, CN 1-chloroacetophenone, CS *o*-chlorobenzylidene malononitrile, CR debenz (b,f)-1:4-oxazepine, DM diphenylaminearsine

tidal volume, which greatly affects the dose of inhalant reaching the alveoli. Harber's rule fails to recognize the exponential impact of increasing dose. With higher concentrations, the effect of concentration is far greater than the duration of exposure. In low concentration, the toxic effects are related primarily to duration of exposure, but only one or two breaths of a highly toxic concentrated irritant gas may be fatal. A more useful formula has been proposed by Baxter: [7]

$$\text{Toxic load} = \frac{\text{concentration to the exponent } n}{\times \text{time}} \quad (3)$$

The exponent n is any number other than 0. This reflects an exponential increase in tissue damage with increasing dose, which varies in amount with the physical properties of that gas. In some gases, the relationship is nearly linear, whereas in other exposures, such as hydrogen sulfide, the toxic effects increase in an exponential fashion so that only a few breaths in high concentration may be fatal. The primary determinant of toxicity with hydrogen sulfide is concentration rather than duration of exposure, invalidating Harber's rule [8].

In actuality, the estimate of exposure is much more complex than dose, duration of exposure, and chemical properties of a given gas. It is difficult to estimate the minute ventilation in an accidental exposure. The amount of gas going to the lower airways varies tremendously depending on whether the subject is breathing through the mouth or through the nose. Highly reactive gases, such as formaldehyde, would be taken up almost entirely in the nose if the patient were breathing through the nose, but some would get into the lower airways if the patient were breathing through the mouth. The distribution of the gas when it reaches the lower airways tends to be irregular if it is irritating to the bronchial mucosa. Studies in dogs by Winternitz [9] at the Department of Pathology at Yale during World War I showed severe congestion in some areas of the lungs with normal areas of the lung elsewhere, indicating irregular uptake of toxic war gases. It is believed that this irregular uptake

Table 3 Commonly used toxic gases and fumes and their dangerous levels of exposure

Agent	Principal occupations exposed	Time-weighted main mechanism of injury	Average ^a	IDLH level ^b
Acetic acid	Production of cellulose, dyeing, pharmaceuticals, food processing	Severe irritation of eyes, mucous membranes, skin; RADS, bronchitis, pneumonitis	10 ppm	500 ppm
Acrolein	Plastic, rubber, textile, resin making	Direct action on mucosa of the eyes and respiratory tract, irritant effects	0.1 ppm	5 ppm
Acrylonitrile	Synthetic fiber, acrylic resin, rubber making	Asphyxiant, neurotoxicity	2 ppm	4 ppm
Ammonia	Fertilizer, refrigerator, explosive production	Direct action on mucosa of the eyes and respiratory tract; tracheitis and pulmonary edema	25 ppm	500 ppm
Antimony trichloride or pentachloride	Metallurgy	Mucous membrane irritant, eye, skin, and lung; pulmonary edema	0.5 mg/m ³	—
Arsine	Smelting, refining, electronics	Systemic effects, hemolysis	0.05 ppm	6 ppm
Boron trifluoride	Fumigant, flux, catalyst	Irritant to eyes, skin, lungs; abnormal lung function	1 ppm	500 ppm
Cadmium oxide fumes	Ore smelting, alloying, welding	Tracheobronchitis, pulmonary edema, emphysema, renal effects	0.1 mg/m ³ (40 µg/m ³)	40 mg/m ³
Carbon dioxide	Foundry work, mining	Asphyxiant	10,000 ppm	50,000 ppm
Carbon disulfide	Degreasing, electroplating, sulfur processing, insecticide	Systemic effects, cardiac disease	10 ppm (1 ppm)	500 ppm
Carbon monoxide	Foundry work, petroleum refining, mining	Asphyxiant	50 ppm	1,500 ppm
Chloramine	By-product of mixture of bleach and ammonia-containing products	Common cause of pulmonary edema and pulmonary irritation in homemakers, custodians, and industrial workers	—	—
Chlorine	Bleaching, disinfectant, plastic making	Direct action on mucosa of the eyes and respiratory tract; tracheitis and pulmonary edema. Possible chronic effect and airways obstruction	0.5 ppm	100 ppm
Chloropicrin	Manufacture of pesticides	Irritation of eyes, mucous membranes, skin; pulmonary edema	0.1 ppm	100 ppm
Chromates	Electroplating	Cutaneous ulcers, dermatitis, nasal perforation, rhinitis, nose bleeds, laryngitis, tracheobronchitis, chemical pneumonitis, gingivitis, lung cancer	50 µg Cr (VI) 500 µg Cr (III)	100 mg/m ³ 100 mg/m ³
Chromyl chloride	Dye making, manufacturing chromium complexes	Severe irritant; second- and third-degree burns; eye, nose, throat, airway injury	0.025 ppm	1 ppm
Copper fumes	Welding	Systemic effects, “brass chills”	0.1 mg/m ³	—
Dimethyl sulfate	Organic chemical manufacturing	Severe eye and skin burns, laryngeal edema, late-onset pulmonary edema	0.1 ppm	100 ppm
Dioxane	Solvent	Irritant to eyes and mucous membranes. May cause pulmonary edema. Primarily systemic toxicants, hepatic necrosis, renal damage	25 ppm	1,500 ppm
Ethylene oxide	Fumigant, sterilizing agent	Irritation of eyes, skin, respiratory tract; pulmonary edema, CNS depression	1 ppm	1,000 ppm

(continued)

Table 3 (continued)

Agent	Principal occupations exposed	Time-weighted main mechanism of injury	Average ^a	IDLH level ^b
Fluorine	Rocket fuel, uranium processing, manufacturing of fluorocarbons	Severe irritation of eyes, skin, mucous membranes, respiratory tract; pulmonary edema	1 ppm	25 ppm
Formaldehyde	Disinfectant, embalming fluid use, paper and photography industry	Direct action on mucosa of the eyes and respiratory tract; dermatitis, asthma (?)	1 ppm (0.8 ppm)	100 ppm
Glyphosate herbicides	Herbicide application	Acute mucosal erosions of mouth and upper respiratory tract. Damage to alveolar membrane. Gradual development of chemical pneumonitis (roundup pneumonitis)	—	—
Halon	Fire extinguishing, refrigerant	Cardiac toxicity, asphyxiation	—	1,000 ppm
Hydrogen chloride	Refining, dye making, organic chemical synthesis, pyrolysis in fires	Direct action on mucosa of the eyes and respiratory tract, tracheobronchitis	5 ppm	100 ppm
Hydrogen cyanide	Electroplating, fumigant work, steel industry	Systemic effects, asphyxiant	10 ppm	50 ppm
Hydrogen fluoride	Etching, petroleum industry, silk working, plastics, refrigerants	Direct action on mucosa of the eyes and respiratory tract, tracheitis	3 ppm	20 ppm
Hydrogen selenide	Ceramic and glass manufacturing, photocells	Irritation of eyes, nose, throat, delayed pulmonary edema	5 ppb	—
Hydrogen sulfide	Natural gas making, paper pulp, sewage treatment, tannery work, oil well prospecting	Systemic and local effects, pulmonary edema, and asphyxia	10 ppm	300 ppm
Magnesium oxide fumes	Welding, alloy, flare, filament making	Systemic effects	15 mg/m ³	—
Manganese fumes	Foundry work, battery making, permanganate manufacture	Systemic effects, possible predisposition to pneumonia, neurotoxicity	5 mg/m ³	—
Mercury fumes	Electrolysis	Direct action on mucosa of the eyes, gastrointestinal tract, and lung; interstitial pneumonitis, systemic effects	0.1 mg/m ³ (0.05 mg/m ³)	28 mg/m ³
Methane	Mining	Simple asphyxiation	—	—
Methyl bromide	Fumigating, dye and refrigerant making	Direct action on mucosa of the eyes and respiratory tract	5 ppm	2,000 ppm
Methyl isocyanate	Pesticide manufacturing	Direct action on mucosa of the eyes and respiratory tract; tracheitis, pulmonary edema, chronic airways obstruction	0.02 ppm	20 ppm
Methylene chloride	Solvent, paint remover, aerosol propellant	Primarily a CNS depressant, mild mucous membrane irritant, asphyxiant due to metabolism of carboxyhemoglobin	50 ppm	1,000 ppm
Natural gas	Mining, petroleum refining, power	Asphyxiant	—	—

(continued)

Table 3 (continued)

Agent	Principal occupations exposed	Time-weighted main mechanism of injury	Average ^a	IDLH level ^b
Nickel carbonyl	Metallurgy, coal gasification, petroleum refining	Pulmonary edema, delayed toxic pneumonitis	0.001 ppm	30 ppm
Nitrogen dioxide	Arc welding, dye and fertilizer making, farming, silo filling	Irritant to respiratory tract; tracheitis, pulmonary edema, bronchiolitis obliterans	5 ppm (1 ppm)	50 ppm
Osmium tetroxide fumes	Alloy making, platinum hardening	Direct irritation of respiratory tract	0.002 mg/m ³	1 mg/m ³
Ozone	Arc welding; air, sewage, and water	Direct irritation of respiratory tract	0.1 ppm	10 ppm
Paraquat	Herbicide	Minor irritant of mucous membranes; epistaxis, iritis, severe fatal pulmonary fibrosis. Primary absorption through skin or GI tract	0.1 µg/m ³	1 mg/m ³
Phosgene	Chemical industry, dye and insecticide making, refrigeration, fire fighting	Direct irritation of respiratory tract; pulmonary edema	0.1 ppm	3 ppm
Phosphine	Semiconductor manufacturing, fumigant	Severe respiratory irritant, pulmonary edema, asphyxiant. Inhibits electron transport and combination of heme to iron	0.3 ppm	100 ppm
Platinum, soluble salts (mist)	Alloy, mirror making, electroplating, catalysis, ceramic work	Asthmatic reactions	0.002 mg/m ³	—
Propane	Cooking, heating	Simple asphyxiation	1,000 ppm	20,000 ppm
Sulfur dioxide	Bleaching, ore smelting, paper manufacture, refrigeration industry	Direct action on the respiratory tract; bronchitis, exceptional pulmonary edema	2 ppm (0.5 ppm)	100 ppm
Sulfur pentafluoride	Production by-product of synthesis or degradation of sulfur hexafluoride	Severe pulmonary irritant, pulmonary edema	10 ppb	1 ppm
Titanium tetrachloride	Metallurgy	Highly corrosive to skin, eyes, mucous membranes—contact with water liberates hydrogen chloride and chloride. Pulmonary edema, endobronchial polyposis	—	1,000 ppm
Toluene-2,4-diisocyanate	Production of polyurethane foams, plastics, paints, wire coatings	Severe mucous membrane irritant to eyes, skin, respiratory tract; bronchitis, asthma, pulmonary edema	5 ppb	100 ppb
Trimellitic anhydride	Epoxy resins, paints, dyes, pharmaceuticals	Cough and upper airway irritation, rhinitis and asthma, flu syndrome, pulmonary disease, anemia syndrome	5 ppb	2 mg/m ³
Vanadium pentoxide fumes	Glass, ceramic, alloy making, chemical industry (catalysis)	Direct action on respiratory tract; bronchitis, asthma	0.5 mg/m ³ (0.05 mg/m ³)	70 mg/m ³
Zinc chloride fumes	Dry cell making, soldering, textile finishing, smoke grenades	Direct action on respiratory tract, irritant; pulmonary edema	1 mg/m ³	2,000 mg/m ³

(continued)

Table 3 (continued)

Agent	Principal occupations exposed	Time-weighted main mechanism of injury	Average ^a	IDLH level ^b
Zinc oxide fumes	Welding, cutting galvanized steel	Systemic effects, metal fume fever	5 mg/m ³	–
Zirconium chloride	Metallurgy	When heated, emits chloride fumes. Can produce pulmonary edema. Damages mucous membranes	5 mg/m ³	–

Adapted from Ref. [150]

CNS central nervous system, *GI* gastrointestinal, *RADS* reactive airways dysfunction syndrome

^aFigures in parentheses are US National Institute of Occupational Safety and Health (NIOSH) recommendations

^b*IDLH* immediately dangerous to life or health

Table 4 Simple asphyxiants

Heavier than air	Lighter than air
Carbon dioxide	Methane
Ethane	Nitrogen
Natural gas	Ethylene
Butane	Neon
Propane	Acetylene
Argon	Helium
Krypton	Hydrogen
Xenon	

Table 5 Gas solubility and toxic effects

1. Solubility and chemical reactivity are the major explanations for the site of action and severity of a toxic inhalation
2. Corrosive gases, such as ammonium, sulfur hexafluoride (SF ₆), mustard gas, methyl isocyanate, and silicone tetrachloride (SiCl ₄), produce intense upper airway symptoms, such as severe coughing, conjunctivitis, burning in the nose, laryngeal edema, and facial burns
3. Exposure to a soluble irritant gas can be estimated as significant if the conjunctivae are inflamed, the face is erythematous, and the nose and throat are red and irritated; this suggests a dose high enough to produce upper and lower airway damage

may be related to the fact that irritant gases may induce bronchospasm, resulting in the maldistribution of toxic effects in the lung. This belief is supported clinically by the observation that patients may have patchy pulmonary infiltrates, sparing otherwise normal areas of the lung, and heterogeneous abnormalities diagnosed by

Table 6 Determinants of severity of lung injury

Duration of exposure
Minute ventilation
Proximity to source
Density of gas and height of victim
Temperature of gas
Toxicity of gas
Water solubility of gas
Particle size of mist, fog, or vapor
Breathing pattern: oronasal versus mouth breathing
Host factors such as preexisting asthma, coronary disease, or COPD
Orthopedic or neurological problems that affect the ability to evacuate quickly
<i>COPD</i> chronic obstructive pulmonary disease

radionuclide imaging studies [10]. The breathing pattern affects the extent of lower airway damage. If the respiratory rate is rapid and the tidal volume is small, much of the ventilation is simply moving gas in and out of the anatomical dead space. If the patient is breathing deeply and slowly, there is a greater amount of gas taken into the lower airways; clinically, this may be seen in an industrial accident in which an individual remains calm and walks slowly out of the area versus another who panics and runs. If the gas immediately causes coughing, the patient is taking large vital capacity breaths before each cough, which causes deep inhalation of the gas into the lower airways. Similarly, another individual in the same environment who does not cough or

sneeze has a lower exposure. The amount of gas inhaled into the terminal airways and alveoli can vary substantially between one individual and another. Gases that are slowly reactive or not reactive in the lung, such as carbon monoxide or arsine, simply pass through the alveolar gas-exchanging surfaces into the blood. Highly reactive gases are taken up primarily by the bronchial mucosa, and there is little of the gas accessible to the circulation.

The effective dose of a gas is a function of the vapor concentration of the gas, the amount inhaled, and the amount retained in the lung. In addition, effective doses depend on the uptake of that gas in a target cell or tissue, mainly the bronchial and nasal mucosa. The effective dose is the amount of the gas that participates in a damaging reaction. This amount differs from the amount inhaled; a certain amount is going to be exhaled as dead space gas. The calculation of the effective dose of formaldehyde necessary to produce a squamous cell carcinoma of the nasal cavity in rodents is a more reliable indicator of risk than the calculation of dose simply from vapor concentration and the amount inhaled [11].

Concentration and duration of exposure further affect the kinetics of the metabolism of a gas in various tissues. In low concentration, a gas may be taken up entirely by the mucosa in the upper airways, but at higher concentration, its uptake and metabolism may be saturated, causing the effective concentration of the gas to increase with time in the lower airways. This concentration of the lower airways increases as the absorption and metabolism of the gas reaches zero-order kinetics in the upper airway. The concentration also is affected by the inhalational rate; rapid, deep breaths, which occur with coughing or exertion, overwhelm the metabolism and uptake in the upper airways.

The biological effect of a gas depends on its water or lipid solubility. Gases that are lipid soluble, such as chloroform, ether, or other halogenated hydrocarbons, may produce central nervous system effects and little or no respiratory irritation. Methylene chloride is an exception to this rule in that it has mild irritating effects and in extremely high doses may cause pulmonary edema [12]. Water-soluble gases are taken up by

the respiratory mucosa and produce their effects in the lung and upper respiratory tract and would be expected to have no systemic effects. The irritant effect of a gas is based on its reactivity or the intensity of the chemical reaction that occurs in the respiratory tissue. The reaction rate of these chemical reactions influences the site of action of the gas. A rapid reaction may occur with gases, such as formaldehyde, in which the reaction occurs so rapidly that little of the inhaled dose gets beyond the nose. Gases with moderate levels of chemical reactivity, such as chlorine, may have a greater effect on lower airways because a greater percentage of the gas bypasses the upper airway. The predominant site of action of irritant gases is influenced by the anatomy of the pulmonary airways. Miller and Kimble [10] have shown that the concentration of ozone in the airways tends to reach a maximum concentration at the 16th through 17th generation of airways. This concentration is affected predominantly by the fact that as the number of generations of airways increases, the cross-sectional diameter of the surface area of the lung increases exponentially. There is a tremendous dilutional effect of an inhaled breath of gas by this rapid change in surface area, resulting in a maximum concentration at airway generation 16 or 17. Bates [13] suggested this idea in 1972 before the elegant studies of Miller and Kimble. Additional studies have confirmed that the smaller airways and respiratory bronchioles seem to be the major site of damage after a significant inhalational exposure to the reactive gas chlorine [14].

The potential of a gas to produce a concentration high enough to be potentially injurious can be estimated by simple calculation. If one knows the vapor pressure of the gas, one can estimate the concentration at room temperature, or 25 °C, by

$$\text{ppm} = (\text{vapor pressure @ } 25^{\circ} \times \text{mmHg}/760) \times 10^6 \quad (4)$$

A compound with a vapor pressure of less than 0.76 mm Hg at room temperature attains an air concentration of less than 1,000 ppm at the saturated vapor concentration. A vapor pressure of

0.076 mm Hg would produce a concentration of 100 ppm. Using this simple formula, one can calculate the concentration of a gas in a potential exposure situation. The value of 760 mm Hg represents sea-level atmospheric pressure. At other altitudes, the relevant atmospheric pressure should be substituted.

The vapor pressure of a gas is the partial pressure exerted by that gas and is a reflection of its volatility. Factors that affect the volatility can affect the dose of an exposure greatly. Methylene diisocyanate has a low vapor pressure, so it is not volatile at room temperature. When heated or mixed with an organic solvent that has a high vapor pressure, however, its vapor pressure increases, and it may be volatilized. In the case of mixture with an organic solvent, the latter serves as a carrier. Vapor pressure and density of gases are important in understanding the dynamics of a toxic exposure. Chlorine gas, which is more than 2.5 times the density of air, tends to flow into low-lying areas. This tendency explains why there can be large differences in levels of exposure in a group of exposed workers when there is only a few feet difference in elevation between one worker and another. Depending on the climatic conditions, this gas may stratify in a green cloud that flows across a floor into low areas. A worker who is in a low area may get an exposure of ten times greater than a worker who is in a location that is a few feet higher on a scaffold or walkway. This type of property of a gas explains why gas exposures tend to produce a heterogeneous degree of injury in a group of workers. In a group of workers involved in an accident at a paper mill where chlorine was released from a tank car, the umbilical hose that went from the tank car to the bleaching plant became detached from the bottom of the tank car. Because this occurred in the winter when the building was heated and the gas was cold, the heat of the building acted as a source of convection that drafted the dense cold chlorine to the roof, where a group of construction workers has heavily exposed. People at ground level who were working in the mill had no significant exposure despite their close proximity to the gas leak [9]. Calculating the dose,

temperature, humidity, wind direction, and other climatic conditions may influence the dose to a given individual. Because the upper airway acts as an absorber of water-soluble gases, any condition that causes mouth breathing, such as allergic rhinitis or an upper respiratory infection, might result in more significant lower airway injury because of the lack of absorption by the nose. The determinants of severity of lung injury are summarized in Table 6.

Terminology

The following terms commonly are used to quantify the health effects of toxic inhalants:

Dose: Dose is the quantity of the compound received by the subject.

IDLH: Immediate danger to life or health (IDLH) is commonly used as in Table 3 and reflects data from human experience and animal models.

LD₅₀: The lethal dose (LD)₅₀ is the dose that kills 50% of the exposed population and reflects extrapolated data from animal models and therefore is only a rough estimate of human toxicity.

ID₅₀: The incapacitating dose (ID)₅₀ is the dose that incapacitates 50% of the exposed population.

Ct: The concentration time (Ct) is a measure of exposure to a vapor or aerosol. The concentration in the air and the time of exposure govern the dose received, as do rate and depth of respiration. It is assumed that when the product of concentration and time is constant, so is the biologic effect over a limited range of concentration and time. This assumption may not be true except in a laboratory setting, but for purposes of making some type of estimate of exposure, a steady-state hypothetical value is used. Concentration is expressed as mg/m³ and time as minutes so that the Ct is expressed as mg·min/m³.

LCt₅₀: The lethal concentration time (LCt)₅₀ is the Ct that would kill 50% of the exposed population; this reflects extrapolation from animal models.

ICt_{50} : The incapacitating concentration time (ICt_{50}) is the Ct that would incapacitate 50% of the exposed population.

RD_{50} : The respiratory depression (RD_{50}) is the concentration that would cause respiratory depression by 50% in 10 min of exposure.

Pathophysiology of Toxic Effects

The early responses to the inhalation of irritant gases are primarily reduced ciliary function, increased mucus production, submucosal edema, and smooth muscle constriction. These are followed by mediator-induced airway inflammation, causing symptoms of retrosternal pain, cough, and dyspnea. Aminophylline and isoproterenol attenuate leukotriene generation by lung mast cells and prevent lysosomal degranulation of neutrophils, a key component of airway inflammation. In the lungs, swelling of type 1 pneumocytes occurs, followed later by capillary leakage due to damage of the basement membrane of epithelial cells. These changes in the cytoskeleton affect the intercellular junctions, causing them to pull apart. The role of cyclic adenosine monophosphate (cAMP) in regulating epithelial cell permeability has become an area of great interest, because it has been reported that cAMP decreases the permeability of epithelial cells by altering the structure of tight junctions [15, 16].

The health effects of irritant gas or vapor exposure depend on their physiochemical properties and specific host factors. The extent of adverse effects may vary among individuals when exposed to the same agent and concentration.

Oxidant-Related Injury

Oxidant-related injury causes increases in pulmonary vascular pressure and epithelial permeability. Studies with the oxidant tert-butyl hydroperoxide have shown that pulmonary phospholipid oxidation yields arachidonic acid via phospholipase A₂ (Fig. 1). Arachidonic acid is a substrate of the cyclooxygenase pathway, leading to the synthesis of prostaglandin F_{2α} (Fig. 2), which is a pulmonary

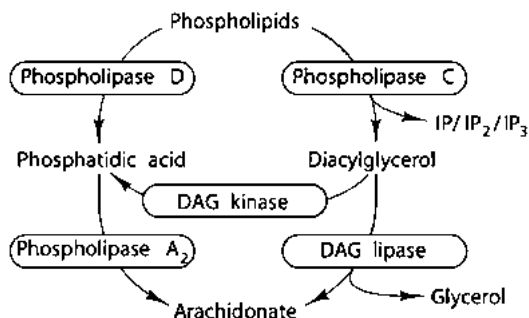


Fig. 1 Pathways of release of arachidonate from phospholipids by two-step processes. DAG diacylglycerol, IP inositol phosphate (From Ref. [148], p. 214)

vasoconstrictor. Arachidonic acid also is a substrate for the lipoxygenase pathway (Fig. 2), which increases vascular permeability [17].

A variety of prooxidants produce cell injury by causing the formation of reactive oxygen species that overwhelm the natural defense mechanisms of the cell. The reactive oxygen species include superoxides and hydrogen peroxide, which may produce highly reactive elements that damage cell membranes. Glutathione peroxidase is a key enzyme involved in the detoxification of lipid peroxides, and the maintenance of reduced glutathione is essential for glutathione peroxidase function. Several other thiol compounds have been shown to be capable of protecting animals against oxygen toxicity and against lung damage from bleomycin-induced and paraquat-induced lung injury [18–20]. The discovery that glutathione constitutes the major source of a low-molecular-weight thiol in mammalian tissue for the purposes of detoxification has resulted in great interest in the substitution of other thiol compounds, such as *N*-acetylcysteine, in the treatment of phosgene and other toxic inhalations.

Studies by Miller and coworkers [21] on the inhalation of ozone in animal models suggested that the maximum dose of ozone is found in the respiratory bronchioles. Some human data from clinical studies suggest that the respiratory bronchioles are the primary target for ozone [13]. Studies suggest that there is damage to the respiratory bronchioles in many workers exposed to a variety of soluble and moderately soluble gases. Patients may be asymptomatic, but one or more years after the exposure they may have evidence of either a

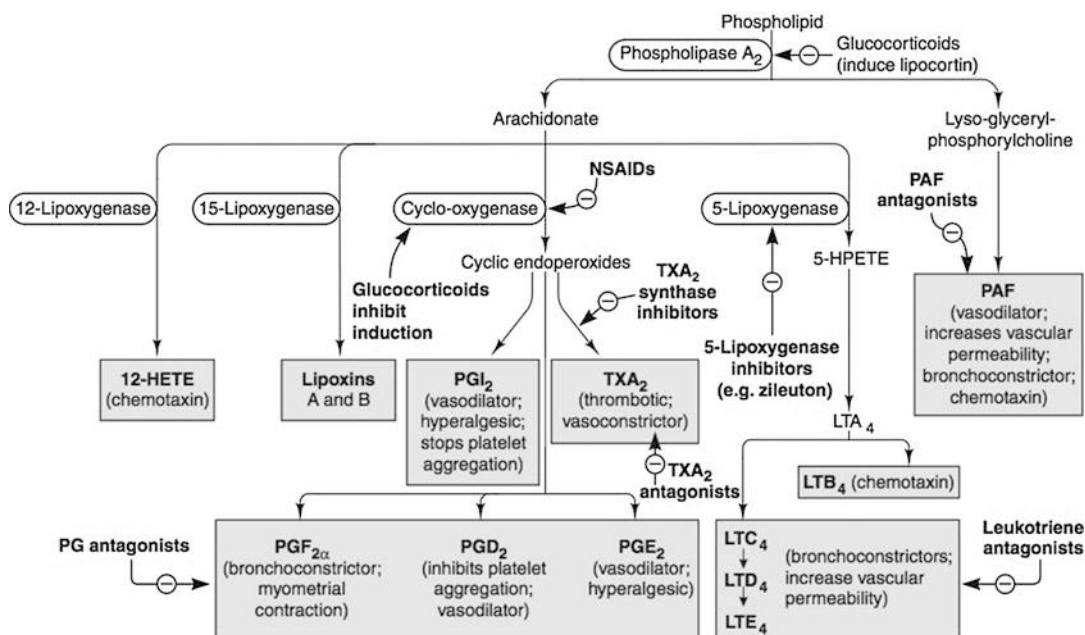


Fig. 2 The biosynthesis of prostaglandins, prostacyclin, and thromboxane from arachidonate. Compounds with biologic action are shown in *boxes*. There are two forms of cyclooxygenase (COX): One (COX-1) is constitutive and occurs in most cell types, and the other (COX-2) is induced in inflammatory cells by inflammatory stimuli. The current nonsteroidal anti-inflammatory drugs (NSAIDs) act mainly on COX-1. *HHT* 17-hydroxy-heptadecatrienoic acid, *IFN- γ* interferon- γ , *PG* prostaglandin, *TX* thromboxane. Summary diagram of mediators derived from phospholipids and their actions and the sites

of action of antiinflammatory drugs. The arachidonate metabolites are "eicosanoids." The glucocorticoids inhibit transcription of the gene for cyclooxygenase-2, which is induced in inflammatory cells by inflammatory mediators. The effects of prostaglandin E2 (PGE2) depend on which of the three receptors for this prostanoid are activated; see text. HETE hydroxyeicosatetraenoic acid, HPETE hydroperoxyeicosatetraenoic acid, LT leukotriene, NSAIDs nonsteroidal anti-inflammatory drugs, PAF platelet-activating factor, PG prostaglandin, PGI2 prostacyclin, TX thromboxane (From Ref. [148], p. 214, 215)

low residual volume or restrictive disease or reduced diffusing capacity on pulmonary function tests. Some of these patients go on to develop reactive airways dysfunction syndrome and have evidence of bronchial hyperreactivity [22].

Inhalational Fevers

Metal fumes, fluorocarbon pyrolysis fumes, or organic dusts rich in endotoxins may produce a series of febrile reactions usually characterized by chills, fever, chest tightness, myalgias, joint aches, and fatigue. This group of inhalational fevers has been called a variety of names, such as *zinc welding shivers*, *silo unloader's disease*, *humidifier fever*, *grain fever*, *mill fever*, *polymer fume fever*, *metal*

fume fever, and *organic dust toxic syndrome*. These conditions all are characterized by a subclinical alveolitis not apparent on chest x-ray or pulmonary function tests except in unusually severe cases. Inhalational fevers are associated with a neutrophilic predominance on bronchoalveolar lavage and a systemic leukocytosis. Their systemic effects are transient [23]. Inhalational fevers can be confused with toxic reactions to gases and vapors. Inhalational fevers are discussed in greater detail in the chapter on Toxin-Induced Pulmonary Syndromes.

Solubility

Water-soluble gases, such as ammonia, sulfur dioxide, formaldehyde, and methyl isocyanate,

produce irritation to mucous membranes and the cornea and usually are characterized by significant ocular symptoms, such as redness of the eyes and, with heavy exposure, delayed onset of cataracts. First-degree burns of the face may be present, and there is likely to be erythema of the nose and symptoms related to the nose and posterior pharynx because most of these gases are absorbed in the mucous membranes in the upper airway. These highly water-soluble gases also are likely to cause pharyngeal injury, reflex laryngospasm, and laryngeal obstruction because of the rapid onset of laryngeal edema [24–26].

Gases with intermediate water solubility, such as chlorine, tend to produce more upper airway irritation. Because of its intermediate solubility, chlorine may produce upper and lower airway injury. Gases with low water solubility, such as phosgene or oxides of nitrogen, produce little in the way of upper airway irritation unless they are in very high concentrations, but they produce intense damage in the lower airways and pulmonary edema. Phosgene gas was used during World War I and was responsible for approximately 80% of the deaths from gassing. Its vapor density is 3.4 times that of air. Its high density made it an ideal agent in the days of trench warfare. This gas has a relatively low odor threshold and is said to smell like freshly mown hay. The low-solubility gases are more likely to produce the delayed onset of symptoms and delayed onset of pulmonary edema. Agents associated with pulmonary edema or chemical pneumonitis are listed in Table 7.

Two properties, water solubility and chemical reactivity, are the most useful in predicting the site of damage of a substance. Most water-soluble gases dissolve in the mucous lining of the upper respiratory tract; mucus contains about 95% water and acts as a sink for water-soluble gases. After dissolving in the mucus, the gas molecules can diffuse in the underlying epithelial cells of the respiratory tract, where they can cause damage. Most of the molecules that hit mucus fail to dissolve and reenter the airspace. The remaining gas molecules may be pulled farther down the airspace, where they again are exposed to more moist mucus until they get to the lower airways. There is a concentration gradient from the upper airway to

Table 7 Agents that produce pulmonary edema/chemical pneumonitis

Acetaldehyde
Acrolein
Ammonia
Antimony trichloride or pentachloride
Beryllium
Bismuth pentachloride
Boranes
Cadmium and cadmium salts
Carbonyl fluoride
Chloramine
Chlorine
Cobalt metal
Dichlorosilane
Dimethyl sulfate
Dioxane dimethyl sulfate
Fire smoke
Glyphosate herbicides
Hydrogen bromide
Hydrogen chloride
Hydrogen fluoride
Hydrogen selenide
Hydrogen sulfide
Lithium hydride
Mercury vapor
Methyl bromide
Methyl isocyanate
Methylene chloride
Nickel carbonyl
Nitrogen dioxide
Nitrogen trifluoride
Nitrosyl chloride
Osmium tetroxide
Oxygen difluoride
Ozone
Paraquat
Perchloroethylene
Phosgene
Phosphine
Phosphorus pentafluoride
Phosphorus trifluoride
Selenium dioxide
Silanes
Silicone tetrachloride
Silicone tetrafluoride
Sulfur dioxide
Sulfur tetrafluoride
Sulfur trioxide
Titanium tetrachloride

(continued)

Table 7 (continued)

Toluene 2,4-diisocyanate in high concentrations
Trimellitic anhydride
Vanadium
War gases
Zinc oxide and chloride
Zirconium chloride

the lower airway when one takes a breath of a highly soluble gas, in that it is continually being absorbed onto the mucous blanket of the respiratory tract from the upper airway through the lower airway. The concentration may be low by the time it reaches the terminal airways. This gradient is overcome, however, when the gas is inhaled in a high concentration, and this explains why lower airway damage can occur after an exposure to a highly soluble reactive gas (see Table 5).

The opposite is true for the fate of a gas with low water solubility because there is little uptake in the upper respiratory tract, and the most important factor is the surface area of the lower airway. The greater uptake tends to occur in regions of high surface area, such as the alveoli in terminal airways, compared with regions of lower surface area, such as the trachea and major lobar bronchi. Highly reactive low water solubility vapors are absorbed primarily in the alveolar area, and this is the site of their damage. This explains why patients with phosgene exposure may present with pulmonary edema and little in the way of upper respiratory signs or symptoms, unless the gas is present in high concentrations.

Smoke Inhalation

The pathophysiology of the acute lung injury associated with smoke inhalation suggests that the influx of neutrophils is the major source of acute lung injury via the release of a variety of cytokines resulting in increased vascular permeability. Lung injury from smoke has shown that activated neutrophils seem to play an important part in the pathogenesis of the lung injury. Depletion of neutrophils with nitrogen mustard

significantly decreases smoke-induced increase in lung microvascular permeability to protein [27]. The neutrophils are recruited from the microcirculation via the upregulation of selectin-type adherence molecules on the endothelial surface. Neutrophils adhere to the endothelium, and intercellular adhesion molecule type 1 facilitates the diapedesis of the neutrophils across the endothelium into the interstitium of the lung, where they release free oxygen radicals and proteases. Sulfo Lewis C is a compound that blocks the uptake of neutrophils out of the microcirculation [14]. These studies and other studies blocking CD-18 or CD-11b in the lung injury model of acute acid instillation in rabbits suggest that compounds that prevent neutrophil migration into the lung might be useful in certain models of inhalational injury in humans [28]. Another approach that has been evaluated is the blockage of interleukin-8, which is the major chemotactic factor for neutrophils. Pretreatment with an anti-interleukin-8 antibody reduces smoke-mediated increase in the bidirectional transport of protein across the alveolar epithelium. This suggests that interleukin-8 is important in the pathogenesis of smoke inhalational injury and probably is important in other sources of inhalational injury.

A group from Taipei showed in a wood smoke model in guinea pigs that evidence of airway injury occurs within 5 min after wood smoke inhalation, followed 2 h later by parenchymal injury. The lung injury involves the release of tachykinins. Tachykinins are neuropeptides released from C-fiber nerve endings that invoke a variety of proinflammatory mediators that have the ability to increase production of oxygen radicals. The airway and late parenchymal injury is blocked by tachykinin receptor antagonists, particularly to the tachykinin NK1 receptor [29].

Clinical Presentation and Life-Threatening Complications

Davy, a British chemist, synthesized phosgene (carbonyl chloride; CAS: 75-44-5) in 1812. Phosgene is a colorless gas. The boiling point of

phosgene is 8.2 °C (47 °F); it is extremely volatile. Phosgene is hydrolyzed rapidly in the human body with the formation of hydrochloric acid and carbon dioxide ($\text{COCl}_2 \rightarrow \text{HCl} + \text{CO}_2$). Phosgene has a vapor density 3.4 times that of air, making it an ideal war gas because it accumulates in low-lying areas, such as foxholes and ditches. The first battlefield use of phosgene was at Verdun in 1917 by Germany. During and immediately after exposure, there is likely to be coughing, choking, a feeling of tightness in the chest, nausea, and occasionally vomiting, headache, and mild lacrimation. The presence or absence of these symptoms is of little value in immediate prognosis. Some patients with severe cough fail to develop serious lung injury, whereas others with little sign of early respiratory distress develop severe delayed pulmonary edema after 2–24 h. Exposure to moderate concentrations triggers lacrimation and the unique complaint that smoking tobacco produces an objectionable taste. High concentrations may trigger rapidly developing pulmonary edema with attendant severe cough, dyspnea, and frothy sputum. The onset of pulmonary edema progresses over 2–6 h and is predictive of severe injury. High concentrations may produce a severe cough with laryngospasm that results in sudden death; this possibly could be due to phosgene hydrolysis, which releases free hydrochloric acid at the level of the larynx. In the first 12 h after toxic inhalant exposure, depending on the intensity of exposure, a substernal tightness with moderate resting dyspnea and prominent exertional dyspnea becomes evident. These symptoms often are a prelude to the characteristic development of pulmonary edema. Initially small, then greater, amounts of thin airway secretions may appear. The delayed, insidious onset of severe pulmonary edema often has resulted in a patient's being medically evaluated and discharged from the medical facility, only to return some hours later with severe and occasionally lethal pulmonary edema.

Irritant gases, such as phosgene, can cause local irritation of airways, which induces bronchoconstriction, which may produce a rise in pulmonary artery pressure, increasing the pressure gradient and causing pulmonary edema

[30–33]. Airway damage can affect the surfactant system, which results in destabilization of airways with atelectasis and decrease in pulmonary compliance [34]. These substances may induce transformation of the cell surface and lead to dose-related production and liberation of cytokines, which affect capillary permeability and produce pulmonary edema. Intrapulmonary shunting from ventilation/perfusion inequalities produces hypoxia, which can enhance lung injury further. The role of various mediators in the production of epithelial injury has great implications regarding treatment. Various studies have been performed on the role of arachidonate mediators in the pathogenesis of lung injury from phosgene [17]. In many other types of oxidant lung injury, there is increased synthesis of lipoxygenase products (see Fig. 2) after phosgene exposure, which seems to contribute to the pathogenesis of pulmonary edema [15, 35]. Drugs that inhibit the lipoxygenase pathway possibly might reduce pulmonary edema in phosgene-exposed individuals [36].

Nitrogen Oxides and the Risk of Bronchiolitis Obliterans

Oxides of nitrogen, such as nitrogen dioxide, characteristically produce a triphasic illness [37]; this is called *silo filler's disease* if it is related to exposure to stored silage. Initial presentation may be cough, wheeze, dyspnea, central chest pain, fever, sweating, and weakness. Physical examination at this stage may reveal wheezes and crackles, and the patient may be hypotensive and cyanotic. The patient's x-ray can be normal or show pulmonary edema. This phase of the illness resolves, and the patient may enter the second phase of being relatively asymptomatic; 2–8 weeks later, the patient develops the third phase with symptoms of obliterative bronchiolitis – fevers, chills, wheeze, cough, dyspnea, and chest pain associated with wheezes and crackles on physical examination. The chest x-ray can be normal or show diffuse, small nodules. The late development of bronchiolitis obliterans is a serious complication that, based upon case reports and small case

Table 8 Agents that produce bronchiolitis obliterans

Ammonia
Chlorine
Cocaine freebase
Fire smoke
Hydrogen bromide
Hydrogen selenide
Hydrogen sulfide
Methyl isocyanate
Mustard gas
Oxides of nitrogen
Phosgene
Sulfur dioxide
Titanium tetrachloride

series, usually responds to steroids but can progress if not treated properly and may be fatal [38, 39]. In cases in which there is a possibility of bronchiolitis obliterans, consideration of a course of steroids for 8 weeks seems a reasonable prophylaxis for the prevention of life-threatening bronchiolitis. Table 8 lists toxic chemicals that are typically associated with bronchiolitis obliterans.

Riot Control Agents

In the past, riot control agents consisted largely of chloroacetophenone (CN) and chlorobenzylidenemalononitrile (CS) [40]. Common symptoms following exposure include rhinorrhea, lacrimation, skin irritation, chest pain, coughing, and dyspnea. Case reports have documented an association with ocular toxicity, dermal burns, laryngospasm, acute lung injury, and death following exposure to high concentrations in an enclosed space or during exertion [40, 41]. Due to toxicity, CN and CS have been largely replaced with oleoresin capsicum (OC), commonly known as *pepper spray*, which while considerably less toxic has also been associated with pneumonitis and death in case reports [42, 43]. In a case series of 22 patients, inhalation of zinc chloride, used in smoke bombs, resulted in temporary ground glass opacities on x-ray computed tomography scan and

a restrictive lung disease pattern on pulmonary function tests [44].

Patient Evaluation

When evaluating a patient with an exposure to a water-soluble gas (see Table 2), careful examination of the upper respiratory tract may provide clues estimating whether the exposure has been sufficient enough to be associated with lower airway damage. If a patient who had been exposed to the soluble gases sulfur dioxide and ammonia presents with watery, teary eyes; red face; chronic rhinitis; red, sore nose; erythema of the posterior pharynx; hoarseness; and difficulty swallowing, one can assume that this has been a heavy exposure that may produce lower airway damage [24–26]. The corollary is that if an individual is exposed to highly soluble gas, such as ammonia, and there are no upper respiratory signs or symptoms, it is unlikely that they have inhaled a dose high enough to cause lower airway disease. This caveat applies only to individuals who are exposed to high concentrations of a highly water-soluble gas of short duration. Lower levels of exposure for longer periods may produce airway damage with minimal signs of conjunctival, cutaneous, and upper airway irritation [45]. When a patient is exposed to a low-solubility gas (see Table 2), such as phosgene, there would be expected to be fewer upper respiratory tract findings, and it is important to observe the patient for 6–24 h as it may take several hours for pulmonary edema to develop. It is wise to observe such a patient in a closely monitored environment for at least 24 h if there is evidence that there has been a high exposure to one of the low-solubility gases that has occurred or if the patient is hypoxemic, tachypneic, or in any respiratory distress. Table 7 lists the common toxic gases and fumes associated with pulmonary edema and chemical pneumonitis. Referral to the list of agents that may cause pulmonary edema (see Table 7) should help the physician determine if a given exposure is likely to result in acute or delayed pulmonary edema.

These same principles are less reliable in evaluating fire-related inhalational injuries. Signs such as singed nasal hair, carbonaceous sputum, and soot in the posterior pharynx are not reliable predictors of lower airway damage [46–48]. Facial burns are seen frequently with and without fire-related inhalational injuries and lack specificity and sensitivity. More than 80% of patients with a fire-related inhalational injury do not have facial burns [47, 48].

Respiratory symptoms, such as severe coughing, respiratory distress, stridor, tachypnea, restlessness, wheezing, and chest tightness, suggest the possibility of significant airway injury and require prolonged observation and assessment with frequent arterial blood gases, oximetry, chest x-rays, pulmonary function tests, and possibly fiber-optic bronchoscopy or laryngoscopy.

Indications for ICU Admission

1. Acute respiratory failure requiring ventilatory support
2. Patients demonstrating respiratory deterioration
3. Need for nursing/respiratory care not available in lesser care areas such as floor or intermediate care unit
4. $\text{PaO}_2 < 50 \text{ mmHg}$
5. Hemodynamic instability
6. Greater than 10% body surface area burn
7. Chronic comorbid conditions predisposing the patient to respiratory compromise

Adapted from Ref. [147] [Level of Evidence III].

Central nervous system symptoms, such as dizziness, headache, confusion, disorientation, hallucinations, and seizures, may reflect signs of hypoxic brain damage due to nonirritant gases, such as carbon monoxide or cyanide, or head trauma from a fall related to being overcome by toxic fumes or other problems. Drug or alcohol abuse is common in victims of industrial accidents and house fires, and a toxicological screen may be helpful in the evaluation of the confused patient.

An elevated carboxyhemoglobin concentration may be useful in diagnosing carbon monoxide poisoning. A serum lactate greater than 10 mmol/L in a patient following smoke inhalation or greater than 8 mmol/L in those not exposed to smoke may indicate cyanide exposure and prompt administration of a cyanide antidote [49, 50] [Level of Evidence II-2]. Cardiac arrhythmias commonly accompany tissue hypoxia, and an electrocardiogram and continuous cardiac monitoring are advisable. Some patients with inhalational injuries may complain of a substernal burning chest pain that may be confused with the pain from a myocardial infarction.

Oximetry

For patients showing major signs or symptoms after gas inhalation, arterial blood gases should be obtained. Room air arterial blood gas determinations are the most useful. The PO_2 may be normal, however, in patients with toxic hemoglobinopathies, such as patients with high levels of methemoglobin or carboxyhemoglobin. Pulse oximetry does not detect these abnormal hemoglobins correctly and measures only normal saturated and desaturated oxyhemoglobin. An oximetry panel (co-oximeter), which contains measurements of carboxyhemoglobin, methemoglobin, total hemoglobin, and oxyhemoglobin, is necessary to evaluate patients' levels of carboxyhemoglobin and methemoglobin and should be performed routinely in fire exposures and inhalational injuries of unknown type. Pulse oximetry may give a false sense of security in patients exposed to carbon monoxide, oxidant gases that produce methemoglobinemia, or cyanide gas from fires.

Pulmonary Function Tests

When there is significant damage to the lower airways, spirometry may be abnormal early in the

clinical course, particularly with fire-related inhalational injury. However, normal spirometry does not exclude or predict late-onset pulmonary edema or damage to the upper airway [51]. Spirometry frequently is normal in the presence of mild restrictive disease from an inhalational injury, and measurement of lung volumes is helpful when available. Pulmonary function tests may aid in evaluating for long-term respiratory dysfunction and injury but offer little value in the acute setting. Airflow obstruction may be due to reactive airways dysfunction syndrome related to epithelial injury [22] or anatomical airway narrowing related to chronic scarring after airway inflammation. The most common late abnormality is an isolated reduction in residual volume [52]. After chlorine exposure, restrictive changes in lung function progress slowly and may not be detected for 2 or more years [53]. Isolated reduction in lung diffusion may occur but usually is accompanied by reduction in lung volumes. Methacholine challenge testing should be performed only in patients with signs and symptoms of bronchial hyperreactivity after the third month. Early transient bronchial hyperreactivity, which lasts only several days to weeks, is commonly seen after an irritant gas exposure. Detection of early bronchial hyperreactivity is not always predictive of long-term airway injury and irritability. Long-term consequences of irritant gas exposure are variable (Table 9). Most patients recover completely [54], but others may develop long-term airway irritability, restrictive lung disease, obstructive lung disease, bronchiectasis, bronchostenosis, or bronchiolitis obliterans.

Table 9 Long-term effects of acute toxic inhalation

Complete resolution of symptoms
Reactive airways dysfunction syndrome
Chronic bronchitis
Bronchiectasis (e.g., ammonia, sulfur dioxide)
Bronchiolitis obliterans (e.g., nitrogen dioxide, sulfur dioxide)
Bronchostenosis (e.g., mustard gas)
COPD or restrictive lung disease
Low residual volume

COPD chronic obstructive pulmonary disease

Key Points

1. Significant exposures to low-solubility agents (phosgene, NO) may not demonstrate respiratory deterioration until 6–24 h following exposure [II-2].
2. Treatment consists primarily of respiratory supportive care [II-1].
3. Other potential therapies include anti-inflammatory medications, nebulized sodium bicarbonate, bronchodilators, nebulized heparin, and surfactant [II-1].
4. Given the differences in pathophysiology, therapies ineffective in treatment of ARDS due to sepsis and nontoxic causes may still benefit patients with toxic inhalation-induced pulmonary injuries [III].
5. The location of a toxic inhalation victim can significantly impact the severity of exposure and extent of injury [II-2].

*Levels of evidence given in brackets

Treatment

The treatment of a toxic inhalation is primarily supportive, including oxygenation, bed rest, analgesia, and mechanical ventilation, if necessary. Contaminated clothing that might further increase the absorption of a substance through the skin should be removed, and the patient may need to be decontaminated before entering the acute care area. Consultation with a medical toxicologist or poison center (1-800-222-1222 in the USA) may aid in determining the amount of decontamination necessary. This care is outlined in Table 10. Any superficial burns should be treated conservatively. Careful attention to the eyes is important because there may be corneal burns, ulcerations, infection, anterior and posterior synechiae, corneal opacification, glaucoma, retinal atrophy, and the late development of cataracts with heavy exposures. Proper eye care, particularly copious irrigation, is essential immediately after the exposure.

Table 10 Strategies for managing inhalational injury^a

1. Decontaminate the victim (e.g., remove chemical-soaked clothing) [II-2]
2. Obtain admission arterial blood gas and cooximetry studies [III]
3. Start high-flow 100% oxygen [III]
4. Examine the patient for eye injuries, flush eyes, and treat if inflammation is noted [III]
5. Record evidence of facial burns, nasal burns, and pharyngitis [III]
6. If the victim is hoarse and has difficulty phonating, consider immediate intubation [II-3]
7. Observe the patient for delayed pulmonary edema for 24 h if the patient is hypoxemic or has been exposed to a low-solubility gas, such as phosgene [II-3]
8. Chest x-rays are not usually helpful unless the patient has significant hypoxemia, marked dyspnea, or basilar rales [II-3]
9. Avoid excessive crystalloids which may contribute to pulmonary edema [III]
10. Keep the patient on bed rest because low-level exercise can induce pulmonary edema in a vulnerable patient with subclinical pulmonary edema [II-3]

^aLevels of evidence given in brackets

The eye is often the forgotten organ in a patient with an acute irritant gas exposure [25]. Generally the eye needs to be irrigated for at least 20 min or, if this is a case of ammonia exposure, until the pH of the conjunctival sac decreases to less than 8.5. Ocular lavage needs to begin in the field at the site of injury if possible. No ointment should be applied to the eye, and contact lenses should be removed to ensure adequate irrigation [Level of Evidence III]. The patient should be referred to an ophthalmologist as soon as possible [55].

The patient who presents with tachypnea and stridor, particularly with some hoarseness, is at a high risk of developing progressive laryngeal edema and complete obstruction of the airway and should be considered for emergency expectant intubation. If signs or symptoms of upper airway damage are present, a prompt inspection of the larynx by a laryngoscope or fiber-optic bronchoscope is imperative because once sufficient edema develops, these patients are extremely difficult to intubate and may require an emergency tracheostomy [Level of Evidence II-3].

Exercise increases cardiac output and pulmonary artery pressures. This increase may unmask latent pulmonary edema, and the patient may die quickly if medical attention is not immediately available. Sedation and bed rest are recommended for the first 24–48 h [56, 57] [Level of Evidence II-3].

Corticosteroids

There has been some opinion that corticosteroids may prevent or decrease the severity of acute respiratory distress syndrome developing following a toxic inhalation [Level of Evidence III]. Based on prospective trials in the management of inhalational injuries in burn patients [58] and anecdotal reports, there is no clear benefit to administering corticosteroids for the prevention or treatment of acute respiratory distress syndrome (ARDS) secondary to toxic inhalation. Meta-analyses of multiple randomized controlled studies regarding prophylactic or early institution of high-dose systemic steroids suggested that steroids are not useful and may be harmful in ARDS and sepsis [59, 60]. A subsequent review of 33 trials randomizing a total of 3,372 patients reached similar conclusions [61]. However, a small minority of patients enrolled in these studies had ARDS induced by toxic inhalation. Differences in the pathophysiology of the most common causes of ARDS (sepsis and trauma) limit the extrapolation of these findings to inhalational injury-induced ARDS.

In patients who are likely to develop bronchiolitis obliterans or bronchiectasis at a later date, corticosteroid therapy is probably helpful [62] [Level of Evidence II-3]. Patients with silo filler’s disease or patients exposed to high doses of nitrogen dioxide particularly fall into this category. Patients with high exposure to zinc chloride may develop chronic airway disease and generally are considered candidates for systemic steroids [Level of Evidence III]. If the patient has been exposed to a gas in sufficient quantity and of the type commonly associated with bronchiolitis obliterans (see Table 8), such as nitrogen dioxide,

it is recommended that the patient be kept on moderately high doses of prednisone (20–40 mg/day) for about 8 weeks [62] [Level of Evidence II-3].

There is suggestive evidence in an animal model of chlorine inhalation of improved lung function and reduced pathologic changes in the airways with high doses of dexamethasone given after exposure [63] [Level of Evidence III]. Because of the sporadic nature of acute gas inhalational injury and the heterogeneity of the human response, however, controlled studies adequate to examine the effectiveness of corticosteroids are unlikely ever to be performed in cases of acute toxic gas inhalation. In summary, corticosteroids are recommended only in exposures which may lead to the development of bronchiolitis obliterans [Level of Evidence III].

Pentoxifylline

The role of tumor necrosis factor- α (TNF- α) has been evaluated in a smoke inhalational injury model in sheep [64]. Lymph and alveolar lavage specimens failed to show elevated levels of TNF- α . These researchers were unable to establish a role for this drug in smoke-induced pulmonary injury in sheep. Pentoxifylline, a methylxanthine normally used to treat peripheral vascular disease by decreasing red blood cell rigidity, is a potent inhibitor of TNF- α [65]. It has been shown to inhibit polymorphonuclear leukocyte phagocytosis and to decrease superoxide anion production in polymorphonuclear neutrophils and monocytes. Pretreatment of rats with pentoxifylline prior to phosgene exposure decreased the formation of inflammatory markers [66]; however, it was not found to be helpful in the treatment of acute lung injury after phosgene exposure in rats [67]. Theoretically, TNF- α blockade should be useful, but the animal data have been discouraging. Human data are mixed and often confused by the fact that pentoxifylline was not used as a single agent [68]. Combination therapy with nitric oxide looks promising in the prevention of reperfusion lung injury after lung transplantation in humans [69]. The role of this

type of combination therapy in smoke or irritant gas inhalation is unknown [Level of Evidence III].

Aminophylline and Terbutaline

Another methylxanthine, aminophylline, seems to protect against phosgene-induced acute lung injury in rabbits [70–72]. Treatment of 80–90 min after exposure reduced acute lung injury. Aminophylline may protect against acute oxidant lung injury by (1) a direct antipermeability effect, (2) inhibition of permeability-inducing sulfidopeptide leukotrienes, (3) a direct or indirect antioxidant action, (4) maintenance of cAMP concentration required to keep tight cellular junctions, and (5) possible vasodilatory mechanisms [73]. Treatment with terbutaline improved gas exchange and lung edema in swine exposed to chlorine gas [74]. The practical implication of this research is that commonly available, reasonably safe, low-cost drugs, aminophylline and terbutaline, may be effective in the acute management of an acute inhalational injury and should be given early in the clinical course in clinically significant inhalational gas exposures which may lead to acute lung injury [Level of Evidence III].

N-Acetylcysteine

Glutathione is a water-soluble antioxidant that protects against free radical injury. Free radicals are thought to be the source of cytotoxic damage in many models of irritant gas injury. Chlorine combines with tissue water to form hypochlorous and hydrochloric acid, which diffuse into cells and react with amino groups of cytoplasm, forming *N*-chloral derivatives that cause nascent oxygen to be released through a series of chemical reactions. The oxidative effects are responsible for the major toxic effects and respiratory damage. Glutathione protects cells from oxidant injury via the regulation of several biologic processes. *N*-Acetylcysteine is a compound that maintains glutathione levels in oxidant stress and has been shown to protect against endotoxin-induced and

radiation-induced damage [18, 20, 75]. It protects against bleomycin-induced damage in mice and protects alveolar type II cells from paraquat toxicity [76, 77]. In a rat model, pretreatment with intravenous *N*-acetylcysteine decreased chlorine-induced pulmonary injury [78]. *N*-Acetylcysteine also has been shown to protect against phosgene-induced lung damage by intratracheal administration in rabbits, but it was not protective when administered by the intravascular route [72, 79]. A Finnish group used *N*-acetylcysteine in the management of three patients with severe zinc chloride smoke inhalation [80]. One of the three patients survived. A randomized, double-blinded, placebo-controlled trial of 264 patients found no significant benefit of *N*-acetylcysteine for the treatment of idiopathic pulmonary fibrosis [81]. A small randomized trial of 36 patients with early ARDS and no evidence of infection found decreased pulmonary lipid peroxidation with *N*-acetylcysteine therapy (50 mg/kg in 250 mL of 5% dextrose in water) but no statistically significant clinical differences; however, extrapolation of these human studies to toxic inhalation-induced lung injury is limited [82]. The aforementioned dose could be tried by nebulizer, but this compound can be irritating and may induce bronchospasm in humans and should be given with 2.5 mg of albuterol solution every 4 h [82]. There have been no clinical trials with this drug in humans for acute inhalational injury, but a short course of the drug for 24–48 h in the appropriate clinical setting may be considered [Level of Evidence III].

Ibuprofen

Ibuprofen is a commonly used antipyretic and anti-inflammatory compound that originally was shown to modify lung injury response to aspiration in dogs in 1982 [83]. It has free radical scavenging and iron-chelating mechanisms of reducing acute oxidant lung injury [17, 84, 85]. It has been shown to be protective against acute lung injury from paraquat in rats [86], smoke inhalation in rabbits [87], and burn injury in sheep [89]. Ibuprofen also has been shown to

protect against acute lung injury from phosgene in mice, rats, and rabbits [36, 70]. Its role in the treatment of acute inhalational injury in humans is unknown. If used in humans, a dose of 25–50 mg/kg of ibuprofen (well in excess of normal therapeutic dosing) would be roughly compatible to the doses used in animal studies. Sciuto and coworkers [66] reported in a phosgene-exposed rat model that ibuprofen was effective alone and useful when combined with pentoxifylline. This study plus the study by Stewart and associates [87] in an animal smoke inhalational model suggest that further human trials are necessary before ibuprofen can be recommended [Level of Evidence III].

Antibiotics, Chest Physical Therapy, and Bronchodilators

Prophylactic antibiotics have been suggested because the sloughing of the tracheal mucosa offers a good culture medium for bacteria; however, there is no evidence that they are beneficial [58]. Antibiotics should be withheld, unless there is clinical evidence of an infection [Level of Evidence III]. Chest physical therapy and high-frequency percussive ventilation may be helpful in patients with mucus plugs and thick secretions [Level of Evidence II-3]. Bronchodilators should be administered if a patient has evidence of bronchospasm [Level of Evidence I].

Nitric Oxide

Nitric oxide attenuates acute lung injury in humans and animals [90]. Nitric oxide decreases release of key mediators of inflammation, downregulates the intrapulmonary inflammatory process, decreases pulmonary artery pressure, decreases pulmonary artery remodeling, and improves oxygenation [91–93]. Nitric oxide decreases vascular permeability [94] and theoretically should be an ideal agent for the management of irritant-induced pulmonary edema. A multicenter European trial containing 268 patients from 43 university and regional hospitals showed

the safety and effectiveness in reducing pulmonary artery pressure, improving oxygenation, and reducing the rate of severe respiratory failure in patients with ARDS but did not produce a statistically significant improvement in survival [95, 96]. Other investigators have thought that inhaled nitric oxide was useful in burn patients with respiratory failure, but this information is largely anecdotal [97]. The negative effects of nitric oxide are that in high doses (80 ppm), it paradoxically increases inflammation and activates the coagulation system in mice [98–100]. A meta-analysis of nine trials (1,142 patients) found nitric oxide does not reduce mortality in adults or children with ARDS [61]. Furthermore, a multicenter, randomized, placebo-controlled study in patients with acute lung injury not due to sepsis found no difference in duration of ventilatory support or mortality [101]. While no studies have specifically evaluated the efficacy of nitric oxide for toxic inhalation-induced injury, based upon the aforementioned studies, it is not recommended at this time [Level of Evidence III].

Perfluorocarbons

Perfluorocarbon partial liquid ventilation (PLV) is the intrapulmonary administration of perfluorocarbons. Perfluorocarbons are liquids with low surface tension and high oxygen-carrying capacity. Cell models, animal models, and human studies have demonstrated significant improvements in oxygenation and decreased pulmonary injury in nonchemically and chemically induced ARDS when compared to mechanical ventilation [102–104]. Theoretically, PLV could lavage chemicals persisting in the bronchopulmonary tree, but adequate studies are lacking. A single trial in which 312 patients with ARDS were randomized to mechanical ventilation, low-dose PLV, and high-dose PLV found a nonstatistically significant increase in mortality in the PLV groups with a statistically significant higher complication rate [105]. Further research is necessary to determine if this therapy provides any clinical benefit [Level of Evidence III].

Exogenous Surfactant

Both in vivo and in vitro studies have demonstrated the ability of toxic gases to inactivate pulmonary surfactant [106]. A single animal study in sheep found surfactant administration to significantly improve survival following hydrocarbon aspiration [107]. Multiple case reports have documented improvement with administration of surfactant in humans following hydrocarbon aspiration [108–110].

Two multicenter, randomized, double-blinded trials evaluating a total of 448 patients found surfactant did improve gas exchange during the initial 24 h following administration but had no effect on mortality or ventilator-free days [111]. Only one of the 448 patients had ARDS due to direct toxic injury to the lung. While research is limited, based upon mechanism and case reports, the administration of surfactant (dosed upon manufacturers recommended dosing for respiratory distress syndrome) following a significant toxic inhalation injury is reasonable [Level of Evidence III].

Sodium Bicarbonate and Calcium Chloride Inhalation

The concept of neutralizing halogen-induced acids has been suggested in animal studies, and sodium bicarbonate nebulization has been shown to improve arterial blood gases after chlorine exposure in an animal study [112]. Sodium bicarbonate also has been used successfully in human case reports and is recommended by some authors [113, 114]. These treatments are anecdotal, however, and there is no consensus of efficacy of this therapy. A randomized, double-blinded, placebo-controlled study comparing 44 subjects treated with nebulized salbutamol, IV prednisone, and either nebulized placebo or sodium bicarbonate found a significantly higher FEV1 240 min after treatment but no statistically significant difference in quality of life scores [115]. However, differences in the two treatment groups, the small sample size, and lack of evaluation for long-term outcomes limit the utility of the study's findings. Given the safety

profile and lack of significant adverse effects, treatment of chlorine inhalation with 4 mL of 4.2% nebulized sodium bicarbonate solution is a reasonable intervention [Level of Evidence II-2].

Exposure to hydrofluoric acid (HF) can lead to fatal dysrhythmias secondary to the fluoride ion binding serum calcium, thereby inducing a relative hypocalcemia [116]. While the majority of cases reported to poison centers are due to cutaneous exposure or ingestion, during an 11-year period, nine deaths reported to the US Occupational Safety and Health Administration involved HF. Of those nine deaths, five were administered with calcium; however, it was administered 90 min after the exposure in two victims and over 6 h after the exposure in another [117]. A case series of 13 patients exposed to HF mist at concentrations greater than 50 times the short-term inhalation limit during a single industrial accident reported all 13 surviving following the rapid administration of 4 mL of a 2.5 calcium carbonate solution mixed with normal saline and delivered with 100% oxygen as a nebulized treatment [118]. While no randomized trials are available, given the lethality of HF inhalation and the safety of nebulized calcium gluconate, rapid administration of the aforementioned dose is recommended for any inhalational HF exposure [119] [Level of Evidence III]. Significant exposures may also require intravenous calcium administration [Level of Evidence III]. Further details regarding HF injury and its treatment can be found in the chapter on Hydrofluoric Acid Toxicity.

Treatments for Smoke Inhalation

Smoke inhalational injury remains the primary determinant of burn-related mortality [119]. Smoke-related inhalational injury is complex and is due to exposure to a mixture of varying concentrations of carbon particles, liquids, heat, chemicals, and toxic gases – largely carbon monoxide, hydrogen chloride, nitrogen oxides, hydrogen cyanide, acrolein, hydrogen sulfide, hydrogen fluoride, phenol, sulfur dioxide, formaldehyde, and various other gaseous pyrolysis products. Thermal injury affects predominately the upper airway, and chemical injury from toxic gases or

chemicals attached to inhaled carbon particles, such as aldehydes and organic and inorganic acids, affects the upper and lower airways. The damage to the alveolar and capillary epithelium may occur simply from the release of cytokines from peripheral tissues after a large surface area burn, without any evidence of fire-related direct effects on the airways. This cytokine release and the effects of overhydration may produce pulmonary edema not directly related to the inhalation of smoke. Smoke itself may activate a variety of hematogenous mediators that further enhance smoke-related damage. It is important to distinguish effects relating to burns and fire-related smoke inhalational injury from inhalational irritant exposures because the usual mechanisms of lower airway injury from the latter are different from the mechanisms usually occurring from the former.

Inhalational injury associated with burns from fires comprises approximately one quarter of patients admitted to a burn unit. The subglottic or supraglottic edema following this type of inhalational injury may obstruct the airway. This type of obstruction may develop slowly over the first 12–24 h due to the initial hypovolemia and other factors. Chemicals in the smoke (see Table 1) are primarily responsible for the airway injury. Smoke particles may facilitate further airway damage via the chemicals absorbed to the surface of these particles.

Fiber-optic bronchoscopy is useful in evaluating burn patients for airway injury by showing carbonaceous material, airway edema, erythema, ulcerations, hemorrhage, blisters, or ischemia [120]. At the time of bronchoscopy, intubation, preferably over the bronchoscope, should be performed in those patients with clinically significant upper airway edema or hypoxia/hypercarbia refractory to noninvasive modalities. Because the upper airway effects from smoke inhalation may progress slowly over 18–24 h, consideration must be given to reevaluation by bronchoscopy or laryngoscopy at 24–48 h in patients who demonstrate worsening respiratory function. Tracheostomy through burn tissue generally is contraindicated because of the substantial risk of infection from the wound to the airway and the

airway to the wound [121]. Xenon-133 ventilation scanning has been used in burn patients to detect airway injury missed by fiber-optic bronchoscopy [122] [Level of Evidence III]. It has a high sensitivity, but there are false-positive results in patients with obstructive airway disease. It has been used to assess airway injury in other types of inhalational injuries [10].

The efficacy of chest x-rays has not been studied in a systematic fashion, but they are probably not necessary in every patient, particularly after a low-level exposure and normal blood gas values. The chest x-ray is useful, however, for acute inhalational injuries related to smoke inhalation and for more severe inhalational injuries accompanied by hypoxia [123] [Level of Evidence III]. The chest x-ray is sensitive to changes in lung water and is useful in following severely burned patients, in whom changes in lung water are related to sepsis, hydration, pulmonary infection, and ARDS [124].

Mortality from smoke inhalation is due mainly to the inhalation of carbon monoxide, cyanide, and other toxic gases listed in Table 3. Carbon monoxide is the most common cause of death from smoke inhalation [125]. Routine carboxyhemoglobin concentrations should be evaluated in any smoke inhalation setting. Cyanide toxicity is more difficult to diagnose but should be suspected in an obtunded victim with a blood lactate greater than 10 mmol/L. Often carbon monoxide and cyanide levels are elevated in the same victim, and dual toxicity should be considered in the obtunded smoke inhalation victim regardless of the carboxyhemoglobin level [126]. Carbon monoxide and cyanide toxicity are discussed in more detail in chapters on carbon monoxide and cyanide.

The treatment of burn-related inhalational injury is not standardized. Early investigators tried nebulized dexamethasone and aerosolized gentamicin unsuccessfully to treat patients with inhalational burn injury [58]. Drugs that reduce free radical formation and cytokine production currently are being investigated, and inhaled nitric oxide has been tried in an effort to improve ventilation/perfusion matching and decrease pulmonary artery pressure [49]. In a sheep model of

inhalational burn injury, ibuprofen reduced lung lymph flow and inhalational injury [127]. Using the same sheep model, pentoxifylline improved pulmonary function [89], and dimethyl sulfoxide with heparin reduced lung injury [128]. These treatments are still experimental. None of these therapies can be recommended at this time for the management of non-burn-related inhalational injury or burn patients [Level of Evidence III]. The strategy for management of smoke inhalation is related in part to the presence or absence of direct thermal injury to the airways.

Most smoke inhalation victims do not have direct thermal injury because of the low heat transfer capacity of heated air. The trachea is an amazingly effective heat exchanger. Moritz and colleagues [129] showed in dogs that when air at 270 °C was blown into the larynx of dogs, the temperature of the inspired air declined to 50 °C in the trachea. By contrast, steam has high heat transfer capacity (approximately 4,000 times that of air) and may cause intense upper and lower airway damage. The presence of large numbers of soot particles in the nose, pharynx, and sputum is another clue to possible thermal injury because carbon particles may be fairly efficient mechanisms for transfer of heat and irritating chemicals adsorbed on their surface, causing subsequent damage to the upper and lower airway [121]. The site of damage depends on particle size, with the larger (>10 µm) particles trapped in the nose and upper airway. Particles 3–10 µm become trapped in the tracheobronchial tree.

The site of toxic particle and gas deposition influences the type of airway injury. Airway casts and large particles may cause atelectasis. Smaller toxic particles may damage smaller airways, resulting in alveolar overdistention during mechanical ventilation and a high risk of barotrauma. The presence of irritants in the airway results in a large increase in bronchial blood flow and hyperemia of the airways. This large change in bronchial blood flow is thought to be a major factor in the development of pulmonary edema after smoke inhalation [130, 131]. Currently, there is no agreed-upon treatment for burn-related inhalational injury. Some centers in the USA use a combination of *N*-acetylcysteine

and albuterol solution every 4 h, then nebulized heparin, 5,000 U every 4 h, so that patients receive a nebulized drug every 2 h. Nebulized heparin (see later) seems to be safe and does not affect blood clotting in this dose range. Other national burn centers do not use any standard drug therapy for patients with inhalational injuries.

Nebulized Heparin Therapy in the Treatment of Respiratory Burns

Heparin is a member of a group of compounds called *glycosaminoglycans*, which are highly acidic, negatively charged polysaccharides. These are remarkable compounds with many anti-inflammatory effects, including effects on toxic oxygen metabolites, cytokines, histamine, bradykinin, TNF, prostaglandins, and many other inflammatory mediators; heparin is best known as an anticoagulant [132]. Heparin influences the remodeling of collagen at the site of wound healing, which results in earlier epithelialization of burns. Pulmonary problems are less frequent in heparin-treated burn patients [133]. In 1993, Cox and associates [134] reported that heparin improves oxygenation and minimizes barotrauma after smoke inhalation in an ovine model. Nebulized heparin has demonstrated a reduction pulmonary damage markers in rats exposed to chlorine gas and has been investigated in burn units in an effort to reduce bronchial cast formation [49]. A study in children with cutaneous and pulmonary burns associated with destruction of the ciliated epithelium and airway casts showed a response to nebulized heparin with a reduction in mortality compared with controls [135]. The usefulness in fire-related burns suggests that nebulized heparin might prove useful in chemical burns of the airway, particularly ammonia-related inhalational injury [Level of Evidence III].

Mechanical Ventilation

Mechanical ventilation with low tidal volumes and positive end-expiratory pressure is currently the

standard of care for inhalational injuries associated with severe abnormalities of gas transport [136–139] [Level of Evidence I]. Inhalational injuries from irritant gases or burns produce spotty areas of intense injury, leaving other areas in near-normal condition presumably protected by regional bronchospasm [140] this originally was reported by Winternitz [9] in studies on dogs exposed to irritant gases at the end of World War I. Mechanical ventilation with high tidal volumes and positive end-expiratory pressure may improve oxygenation but at the same time may overinflate the least affected areas of the lung, causing barotrauma and hyperinflation with increased pleural pressure causing reduced venous return, cardiac output, and oxygen delivery. Low tidal volume ventilation and positive end-expiratory pressure now are recommended for all types of lung injury and are associated with better survival from ARDS [141]. Low tidal volumes seem to reduce epithelial and endothelial injury [142]. Permissive hypercapnia is well tolerated as long as satisfactory oxygenation is maintained [143]. More recently, there has been interest in high-frequency percussive ventilation [144]. Some investigators believe that it helps mobilize secretions in burn patients with fibrin plugs. This treatment still is considered investigational.

Extracorporeal Membrane Oxygenation

In cases of life-threatening pulmonary injury refractory to mechanical ventilation and other therapies, venovenous extracorporeal membrane oxygenation (ECMO) has been reported in case reports with varying degrees of success [145, 146]. Further research is necessary to determine if a significant mortality benefit is provided by this resource intensive and costly therapy [Level of Evidence III]. The use of ECMO is discussed in more detail in the chapter on ECMO and Cardiopulmonary Bypass in the Critically Poisoned Patient.

Criteria for ICU Discharge*

1. Adequate oxygenation and ventilation without ventilatory support (significant

(continued)

exposures to low-solubility agents may not demonstrate respiratory deterioration until 6–24 h following exposure) [III].

2. When a patient's physiologic status has stabilized and the need for ICU monitoring and care is no longer necessary [III].
3. When a patient's physiological status has deteriorated and active interventions are no longer planned, discharge to a lower level of care is appropriate [III].

Adapted from Ref. [147].

*Levels of evidence given in brackets

Special Populations

Treatment guidelines are largely the same regardless of the individual exposed; however, certain populations are at higher risk of clinically significant illness following exposure. Pediatric patients' small airways, increased respiratory rate, and large lung volume to body mass ratios place them at higher risk of airway compromise and hypoxia. Furthermore, their shorter stature may result in higher exposures to higher-density gases collecting close to the ground. Decreased baseline lung functions and chronic disease predispose the elderly or those with underlying pulmonary disease to toxic inhalational exposures.

Exertion during a toxic inhalational exposure results in an increased minute ventilation rate and corresponding quantity of toxic gas [40, 41]. Furthermore, exertion following an exposure increases the development of pulmonary edema in rat models [56, 57]. This has important implications for rescue workers and individuals attempting to flee from the scene of a chemical release. Exertion should be considered in the determination of a patient's risk for significant pulmonary injury following a toxic inhalational exposure [Level of Evidence III].

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Part XVIII

Chemical Agents: Caustics and Corrosives

Diane P. Calello

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This chapter is an update of the chapter on this topic by J. G. Rella and R. S. Hoffman in the first edition of this book.

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Caustic or corrosive substances take many forms, with varied concentrations, pH, and formulations. The intent behind the exposures is likewise diverse and ranges from the suicide attempt in an adult to an exploratory taste in a young child. The heterogeneous nature of the substances, patients, circumstances, clinical presentations, and spectrum of injury makes diagnosis and treatment a daunting task for the clinician.

Definition

A caustic, or corrosive, is any substance that can destroy tissue chemically and is classically thought of as acids or alkalis. In addition, there are caustic agents that do not fit this simple classification, such as Clinitest tablets, creosote, ingredients in electric-dishwasher detergent and laundry detergent, phenol, zinc chloride, and surfactant [1–3]. The terms *caustic* and *corrosive* are also sometimes used to describe oxidizing agents (potassium permanganate), desiccants, vesicants (mustard gas), and protoplasmic poisons (hydrofluoric acid) [4]. Most recently, concentrated packets of laundry detergent, often referred to as “pods,” have arisen as a cause of aerodigestive tract burns in children who ingest them [5].

Epidemiology

The epidemiology of caustic exposures has changed over the years. The introduction of new cleaning products to the public, notably liquid lye in 1967, increased the incidence of caustic ingestions. At that time, the prototype of new liquid drain cleaners contained 30% sodium hydroxide. Because of the sudden increase in severe morbidity that followed the introduction of this product in the USA, the US Poison Prevention Packing Act of 1970 and the US Federal Hazardous Substance Act of 1973 were passed, mandating the use of child-resistant caps for products containing 2% or more of an alkaline caustic and the reduction of concentration of cleaning substances. Designed to protect young children from dangerous substances found around the house, these Acts are responsible in part for a decline in serious pediatric caustic injuries.

The exact incidence of caustic ingestions is unclear due to the manner in which these data are reported. Poison center data are gathered passively and are subject to underreporting. Moreover, caustic and corrosive substances are classified as cleaning substances and are therefore difficult to distinguish from other household cleaners. Nonetheless, caustics continue to be one of the most frequently reported substances involved in human exposures [6]. In the 2014 Annual Report of the American Association of Poison Control Centers National Poison Data System, caustics accounted for more than 30,000 exposures [6].

Children younger than 6 years old account for the greatest number of exposures to caustic substances, with most exposures being unintentional. Hawkins and colleagues [7] reported in 1980 that children younger than 5 years old accounted for nearly half of the caustic exposures in their series. These data closely resemble data reported from poison centers in 1998, in which 129,000 children younger than 6 years old represented nearly twice the number of all persons older than age 19 exposed to cleaning substances [6].

Suicidal patients are the next greatest number of patients with caustic ingestions. Although the number of intentional ingestions is a fraction of the number of unintentional exposures, they

account for nearly 80% of all serious injury requiring a major intervention.

Pathophysiology

Many factors contribute to the ability of a caustic substance to cause damage. Concentration, quantity, viscosity, contact time with tissue, pH, and titratable reserve all may be important in making caustics dangerous [8–13]. One *ex vivo* study examined esophageal damage when exposed for 10 s to 4%, 10%, and 22% sodium hydroxide. Histologic damage progressed from the mucosa to serosa as concentration increased [14]. People with suicidal intent more commonly ingest large amounts of caustic agents. The lesions found in these cases often are more extensive, and injury also involves the stomach and duodenum [8]. Burns are more common in areas of the esophagus where passage of the caustic agent may be delayed, such as at the crossing of the aorta and the left main bronchus [8, 15]. A pH of 12.5 has been cited as crucial for production of esophageal ulcerations from sodium hydroxide [13]. The contribution pH makes to the nature of a caustic injury is not straightforward, however [16]. Phenol and zinc chloride, two well-known caustic agents, have nearly neutral pHs.

Titratable reserve is defined as the volume of neutralizing substance required to bring the pH of a caustic to approximately that of a normal esophagus. In one study, titratable reserve correlated better than pH in predicting the production of esophageal injury [17]. Although titratable reserve helps explain causticity, it was not standardized for acids and bases and liquids and solids, and it does not correlate with resulting tissue strength after an exposure [18]. The best that can be said of pH and titratable reserve is that they help define the dangerous properties of a caustic agent but are only a few of the important characteristics to consider.

A caustic agent potentially can damage any tissue to which it is exposed. This may include the eyes, skin, larynx, lungs, gastrointestinal tract, and other intrathoracic and abdominal organs. Some caustics may also exhibit systemic toxicity,

such as hydrofluoric acid-induced hypocalcemia and metabolic acidemia from acid absorption.

It was historically suggested that acids caused maximum damage to the stomach and minimal injury to the esophagus, whereas alkalis caused injury in the reverse pattern. Before 1965, lye was available to the public only in solid form [19]. Although there are reports of suicidal patients mixing these crystals in water before drinking, many times ingested crystals would adhere to mucosal surfaces on initial contact, injuring the pharynx and upper esophagus, whereas a less viscous acid agent would pass rapidly through the oropharynx to collect in the stomach. These types of injuries are likely at the root of this concept. In 1967, liquid lye became available to the public in the USA, and more extensive injuries were diagnosed. One study specifically addressed this question and found no difference in distribution of injury between acids and alkalis [20]. Alkalis remain available, however, as solids, as viscous liquids, and in a formula that is designed to generate a column of foam using hydrogen peroxide. Almost all acids are available exclusively as low-viscosity liquids.

Ingested liquid forms of caustics expose all mucosal surfaces to the caustic material. This tissue injury has been studied extensively over the years. Experimentally, tissue injury occurs within seconds of contact for acids and alkalis [9, 14, 21]. After experimental exposure to alkaline substances, esophageal mucosa grossly becomes gray and gelatinous. Fats and proteins become saponified as the tissue neutralizes the caustic in a reaction that releases heat and gas [22]. Microscopic evaluation of alkaline caustic injury to esophageal tissue revealed liquefactive necrosis of the mucosa with edema and inflammation [10, 21]. Ulceration of the mucosa follows, and there is widespread thrombosis of arterioles and venules [8–10, 21, 23]. Acid-induced injury is described as a coagulation necrosis with formation of a thick eschar that theoretically may limit tissue penetration and tissue damage. Despite this difference from alkaline-induced necrosis, strong acids, like strong alkalis, perforate the gastrointestinal tract and cause injury to other intra-abdominal organs and death. Acid exposures to the esophagus also are characterized

by edema and an acute inflammatory reaction [24, 25]. At the edge of the injury, polymorphonuclear leukocytes infiltrate, and granulation tissue begins to develop [8, 10, 26]. Depending on the severity of the injury, inflammation may extend through the muscle layer, and perforations may occur. In these cases, periesophageal and intra-abdominal tissues become affected as well.

After several days, the necrotic tissue is sloughed, edema decreases, and fibroblasts begin to proliferate. Ulcerations may persist for months, and the esophagus shortens [10]. This period also includes neovascularization and the deposition of collagen [10]. Adhesions form between pockets of granulation tissue in bands, which is where stricture formation begins [8]. With the progressive remodeling that takes place over the weeks to months following a significant injury, the lumen of the esophagus begins to narrow. When enough scar tissue collects in a small area, it forms a stricture [10].

The risk of stricture formation is related to depth and circumference of the injury [27]. The depth of injury can be established only by endoscopy and direct visualization of the mucosa itself. A grading system describes the various degrees of injury, which may be associated with a risk for stricture (Table 1) [7, 28]. Grade 1 injuries are characterized by superficial mucosal hyperemia and do not progress to form strictures [19, 20, 29–31]. Grade 2 injuries include submucosal and transmucosal

Table 1 Endoscopic grades of esophageal injury

Grade	Description	Risk of stricture formation
1	Superficial mucosal hyperemia	None
2A	Noncircumferential submucosal or transmucosal ulcerations with blistering and exudate	Rare
2B	Circumferential or near-circumferential submucosal or transmucosal ulcerations with blistering and exudate	75%
3	Severe, widespread tissue destruction with deep ulcerations and extensive necrosis	100%

ulcerations with blistering and exudate [7, 19, 29, 32]. These injuries are divided into subtype A, which are noncircumferential and rarely develop strictures, and subtype B, which are near circumferential or circumferential and progress to strictures in 75% of cases [32]. Grade 3 injuries are described as severe with widespread tissue destruction, deep ulcerations, and extensive necrosis [19, 29, 32]. These injuries progress to form strictures despite any mode of therapy provided and have a high incidence of perforation [30, 33].

Significant complications may accompany the various stages of injury and recovery. Immediately, life-threatening complications include airway compromise and perforation into a great vessel [15]. Complications such as perforation may lead to periesophagitis, mediastinitis, peritonitis, infection from normal flora [8], shock, and sepsis [10]. Other complications include esophageal dysmotility [34], erosion into a bronchial artery, and formation of aorto-esophageal and tracheo-esophageal fistulae [23, 35]. Survivors of lye ingestions who develop a stricture have a 1000-fold increased risk of squamous cell carcinoma of the esophagus with a latency of approximately 40 years [36, 37], although this risk assessment was not controlled for regarding alcohol abuse and smoking [15]. Additionally, acid ingestions can cause an acidemia that results from absorption of the acid itself. Ingestion of hydrochloric acid may result in a non-anion gap acidemia because hydrogen and chloride are absorbed and accounted for in measuring the anion gap, whereas ingestion of sulfuric acid might result in an anion gap acidosis because sulfate is not measured directly in the anion gap calculation. Hydrofluoric acid confers a unique toxicity by complexing with extracellular calcium to induce severe hypocalcemia, which may be fatal (see ► Chap. 102, “Hydrofluoric Acid”). Conversely, ingestion of an alkaline substance typically does not result in alkalemia or direct metabolic derangement.

Clinical Signs and Symptoms

When a caustic agent comes in contact with tissue, severe pain often ensues throughout the mouth, lips, tongue, and oropharynx [10, 20, 38, 39].

Aspiration or direct airway injury may lead to voice change and stridor [38]. As deeper tissues become involved, dysphagia, odynophagia, chest and back pain, and vomiting may occur [10, 20, 40]. Abdominal pain with fever and tachycardia may suggest a potentially severe injury.

Many patients who have ingested a caustic agent do not present with a classic constellation of clinical signs and symptoms, however, that allow for early recognition of injury [41]. There are many cases in which a patient is reported to appear clinically well with normal vital signs and a soft, nontender abdomen yet dies within several hours or is found to have severe injury to the gastrointestinal tract [42, 43]. Many studies have found that less than half of patients with esophageal or gastric injuries diagnosed by endoscopy experience abdominal pain or have tenderness [12, 20, 28, 40]. In addition, the nature of the substance ingested may modify the initial presentation. Acids (not alkalis) are sometimes considered to be anesthetic, perhaps due to eschar formation. An ingestion of phenol, which is used commonly as a topical anesthetic agent, may not feature pain as a clinical symptom. Coingestants such as ethanol used by suicidal patients that may alter their mental status or their ability to express themselves clearly may mask any evidence of pain.

The concept that the absence of clinical signs and symptoms does not add to history has been suggested repeatedly [11, 12, 20, 40, 44]. When considering pediatric cases, the absence of clinical findings is even less reassuring [12]. It is crucial for the examining physician to be suspicious of an injury when presented with a well-appearing patient whose history includes caustic ingestion.

Predictors of Injury

Several studies have attempted to identify signs or symptoms that could be used to identify patients with a mucosal injury requiring treatment. Examination of the face, lips, and oropharynx, while advisable, is of limited predictive value for esophageal injury [8, 19, 25, 45]. One study found that 37% of patients who did not have burns to their cheeks, lips, or oropharynx had esophageal burns

in one or more places as diagnosed by endoscopy, whereas only 50% of patients with burns to their cheeks, lips, or oropharynx were found to have visceral burns [44]. As mentioned earlier, the presence or absence of abdominal pain or tenderness is also a poor predictor of gastrointestinal injury. Often less than half of patients with esophageal burns complain of abdominal pain [29].

Several investigators have evaluated whether combinations of signs and symptoms can be used to predict injury. One study that evaluated 79 pediatric patients found that the presence of two or more of the signs vomiting, drooling, or stridor correlated to a grade 2 injury or worse by endoscopy [46]. Perhaps just as important was that no patient who had only one of these three signs had a positive finding by endoscopy. No patients in this study had only stridor as a sign. Another investigator found that all patients with an alkaline-induced injury showed some symptom of injury but that no single sign accurately predicted injury. When data from 63 patients of all ages who received esophagoscopy were examined for signs of oral burns, drooling, vomiting, abdominal pain, and dysphagia, no group of signs or symptoms could identify all patients with serious esophageal injury. The study's author found that a combination of signs had a positive predictive value of only 46%. These data may be limited in that they were gathered via poison center phone calls and because suicidal patients represented 25% of the patients who had esophagoscopy, 50% of whom had positive findings [29]. Still another author was unable to correlate injury to any signs or symptoms in a pediatric population. This study population may have been difficult to assess for dysphagia and abdominal pain or refusal to drink, however, given that 79% were 12–35 months old [41].

Patients who have obvious signs of intra-abdominal injury, have an airway emergency, or have an acidosis that may indicate necrotic tissue must be presumed to have a serious injury until proved otherwise [29, 47]. One study found that adults accounted for less than half of all hospital admissions for caustic ingestions but developed 81% of all esophageal injuries requiring treatment [7]. Because many of these injuries result from

suicide attempts, all patients who attempted suicide must be presumed to have serious damage until disproved by endoscopy. Asymptomatic adult patients with unintentional ingestions in most cases do not require endoscopy [29].

Studying patients with caustic ingestions is difficult. These patients do not present frequently, requiring many years to gather substantial numbers of patients. Often children and suicidal patients comprise the greater proportion of these patients and may be difficult to assess as a whole. The ideal prospective study would include communicative patients with unintentional ingestions, to reduce confounders such as coingestants and false histories, and would have a wide range of endoscopic findings.

Treatment

As with other injuries, the initial management strategy for patients with caustic ingestions is to secure the airway, breathing, and hemodynamic stability. All patients require vital sign assessment and a rapid evaluation of the airway, including visualization of burns to the oropharynx, cheeks, and lips and so-called dribble marks. Although the absence of these signs does not exclude injuries elsewhere, their presence more strongly indicates exposure to a caustic agent.

Stridor and respiratory distress are true emergencies, given the nature of the injury. A caustic substance that contacts the respiratory mucosa causes tissue softening, edema, and, in the worst-case scenario, perforation. Direct visualization of the vocal cords may be accomplished by fiberoptic nasopharyngoscopy and can provide crucial information regarding the nature of the airway injury. As with thermal burns to the airway, edema may increase rapidly, making delayed attempts to control the airway progressively more difficult. Any signs of airway compromise or respiratory distress should prompt action to secure the airway.

For patients who require intubation, the author recommends that the intervening physicians be the most skilled available for the best possible management of complications. Intubation using

a fiberoptic instrument or with a laryngoscope in which the vocal cords are visualized directly may be attempted. When possible, paralytic agents should be avoided prior to intubation because edema, softened or partially dissolved tissue, and bleeding may complicate attempts to intubate and ventilate with bag-valve-mask apparatus. A surgical airway may be required depending on injury severity and the physician's ability to secure the airway by other means. A surgical airway should be considered a second choice for airway management, however, because the presence of a tracheostomy may interfere with reconstruction of the esophagus at a later stage [47].

Along with airway management, large-bore intravenous access should be obtained. Blood analysis sufficient for the patient to go to the operating room should be sent, including hematocrit, electrolytes, coagulation studies, and a blood type and crossmatch. Hypotension may be corrected by infusion of crystalloid or blood as needed. In general, it may be useful to consider these patients similar to patients with thermal burns regarding the potential for significant shifts of fluid and changes in hemodynamic status.

Decontamination

Topical exposure to the skin or eyes by a strong caustic agent has the advantage of being relatively easy to detect and treat. Lavage with copious amounts of water or saline is a safe and effective means of diluting the caustic and removing it from the exposed tissue (grade 3 evidence). Topical polyethylene glycol for phenol exposures may reduce tissue injury as demonstrated in animal studies [48]. A paste containing calcium salts (calcium chloride or calcium gluconate) has been reported to ameliorate pulmonary injury after hydrofluoric acid inhalation [49]. Ocular exposures require rigorous, thorough lavage with water or saline to reduce the risk of injury (Grade III recommendation).

Gastrointestinal decontamination in this setting is seldom appropriate. Use of an orogastric tube or nasogastric tube to remove any caustic material that has pooled in the stomach carries

the risk of perforation through the softened mucosa. Activated charcoal does not adsorb caustics and obscures mucosal evaluation by endoscopy. Both methods can induce emesis, which increases the risk of aspiration, reexposes tissue to the caustic, and increases intra-abdominal pressure and the risk of perforation. The risks of conventional means of decontamination far outweigh the potential benefits (Grade III recommendation).

Dilution and Neutralization

Dilution and neutralization of caustics have been proposed to limit caustic tissue damage, but clinical and research experience do not consistently support this practice. Dilution is the process by which by the addition of a neutral pH solution such as water or milk, the concentration of a caustic can be decreased and theoretically lessen damage. Neutralization involves the administration of a solution with the opposite pH, such as lemon juice in the case of an alkaline caustic, to bring the ingested substance to a more physiologic pH. Unfortunately, the risks include emesis, further tissue damage, and in the case of neutralization the generation of an exothermic reaction with heat, gas, and increased intraluminal pressure.

Studies of both dilution and neutralization have been conducted *ex vivo* and *in vitro* with inconsistent results. An *in vitro* dilution study experiment added various household items, such as lemon juice or milk, to beakers containing Clinitest tablets or crystalline sodium hydroxide and showed significantly increased temperatures [50]. Other investigations have diluted acids and alkalis with water, milk, and saline in *ex vivo* esophagi and shown decreased histologic damage to mucosal cells [51–53]. Yet other studies failed to show an appreciable change in pH when acid or base was diluted with water *in vitro* [54]. Early studies showed severe injury when *ex vivo* esophagi were exposed briefly to acids or alkalis and then washed copiously with either water or a dilute neutralizing agent [9, 21].

Neutralization studies have shown similar limited results. One *in vitro* study showed mucosal protection from acid when treated with sucralfate

partly due to acid neutralization [55]. Another study found minimal temperature increases when *in vivo* esophagi were exposed to alkali and neutralized with orange juice [39]. Still another study demonstrated decreased histologic damage in *ex vivo* esophagi when alkaline injuries were neutralized with orange juice [56].

Considering the limited demonstrated efficacy of these therapies, combined with the sizeable risk, neither dilution nor neutralization is indicated (Grade III recommendation).

Endoscopy

Endoscopy has been called the *sine qua non* for evaluating patients with caustic ingestions [57]. Endoscopic evaluation has many advantages [22, 32, 57]. Before the 1950s, the rigid esophoscope was not widely available, and the presence of severe burns could be diagnosed only after dysphagia from stricture occurred [58]. As the use of endoscopy came into the mainstream, it became widely recognized as an important tool for evaluating these patients [4, 8, 25, 31, 33, 57, 59–61]. Generally accepted guidelines for endoscopy included not passing the instrument deeper than the first serious injury (Grade III recommendation). This restriction attempted to limit the number of perforations from the procedure, but it also limited the evaluation and increased the risk of underestimating the total injury. The flexible fiberoptic endoscope has a smaller outside diameter and largely has replaced the older, rigid instrument for these evaluations. Careful, slow advancement under visual control with minimal insufflation reduces the risk of complications. The endoscope may be guided gently through areas of severe injury (Fig. 1), unless frank necrosis or obliteration of the lumen precludes its advancement [32]. Use of the flexible endoscope is described repeatedly as safe and necessary, and many studies report having no complications from the procedure [32, 40, 62].

Controversy still exists regarding when endoscopy should proceed for a patient with a history of caustic ingestion. Although most authors are in favor of early endoscopy, the times that are



Fig. 1 Endoscopy after a caustic ingestion, which shows severe necrosis in the midesophagus

recommended range from less than 6 h to 48 h. Older studies tend to refer to later times, which may reflect its limited availability and the relatively greater risk found with rigid esophagoscopy. Bikhazi and colleagues [33, 63] referred to endoscopy as elective, whereas Middelkamp and associates [31, 61] changed their recommendation from 24 to 48 h in 1961 to 12 to 24 h in 1969. Only Friedman [28] specifically recommended not performing endoscopy before 12 h because “adequate time may not have passed for the injury to manifest, and therefore the examination may underestimate the damage.” Friedman [28] recommended waiting until 24–48 h pass for best results. Since the early 1980s, there has been a growing body of experts who recommend that endoscopy be performed as soon as the patient is stable in order for the procedure to recognize a full-thickness injury as early as possible [4, 15, 35, 62–65]. *In vitro* studies showed the immediate injury these agents can cause. There is no utility in waiting to make a definitive diagnosis for these patients because to do so invites disaster in a subgroup whose injuries and outcomes are notoriously unpredictable.

Advantages of Endoscopy in Caustic Ingestion

Allows for a definitive diagnosis providing a basis for treatment

Helps limit hospital stay and unnecessary treatment for patients with minimal or no injuries

Defines the degree and character of the injury and directs management

Helps to predict complications

Allows for confirmation of adequate healing

Radiologic Investigations

Chest and abdominal radiographs may provide useful information rapidly in the early stages of management. The presence of a widened periesophageal stripe, pneumothorax, pneumomediastinum, pneumoperitoneum, or pleural effusion indicates a perforation in the gastrointestinal tract and may obviate the need for further studies. Although many authors advocate the use of these tests [11, 12, 15, 24, 38, 43, 47], the sensitivity of radiographs seems to be low. Despite one study that showed lateral chest x-rays to be 98% sensitive compared with 80% for posteroanterior chest x-rays for finding intraperitoneal air [66], several authors reported no visible free air despite clear perforations found at laparotomy [43, 47].

At one time, contrast swallow studies were used as a standard diagnostic tool for these patients. The generated images could find areas of esophageal dysmotility, whereas extravasation of dye could be used to indicate perforation. Swallow studies have low sensitivities as well and are accompanied by risks for aspiration and inflammation. Water-soluble solutions are even less sensitive and must be anionic to avoid the risk of pulmonary complications if such solutions are aspirated [11, 12, 15]. In addition, no information is gained regarding the depth of mucosal injury, limiting its utility further.

Computed tomography (CT) may have a role in enhancing diagnosis of caustic injuries. While Cattani and colleagues [64] opined that CT has little utility, more recent studies demonstrate

some value in diagnosing the extent of injury [67–69]. Moreover, CT may reveal pulmonary infiltrates which would otherwise be missed and may be appropriate if CT is unsafe or the expertise to perform endoscopy is truly unavailable [69].

Management Plan Based on Endoscopic Findings

The character and the extent of the injury indicate the management plan and disposition of patients with caustic injuries. Because endoscopy is the best tool to establish the diagnosis, management is delineated in terms of endoscopic grade of injury. Grade 1 injuries do not develop complications of stricture or tumor. When patients tolerate oral feeding, they potentially may be discharged [32]. If endoscopy shows a grade 2A injury, patchy or linear but noncircumferential submucosal damage without stomach injury, oral feeding may be resumed cautiously as tolerated. There are no studies guiding the decision of when to resume oral feeding, so this is usually done on clinical grounds. Alternatively, a feeding tube may be passed with fiberoptic guidance to resume nutritional support. As with patients with thermal burns, patients with caustic injuries enter into a hypercatabolic state and require substantial nutritional support [10, 21]. A negative nitrogen balance resulting from injury and poor nutrition inhibits healing and increases the risk of infection [12]. Patients with these injuries rarely develop stricture or other complications. Follow-up endoscopic examinations can document appropriate healing and add to disposition planning.

Patients with grade 2B or worse injuries have similar complication rates and require a longer time to heal [32, 63, 66]. Zargar and colleagues [32] divide grade 3 injuries into subtypes A and B. Grade 3A denotes small scattered areas of frank necrosis, and grade 3B denotes extensive necrosis [32]. For patients with grade 2B or worse injuries, oral or tube feeding may be contraindicated. Total parenteral nutrition, gastrostomy, and jejunostomy are options that may be used for these patients because nutrition continues to be a crucial factor in their healing. The risk of

stricture formation for patients with grade 2B injuries is high, and the use of steroids and antibiotics may be beneficial (see the following discussion on steroids and antibiotics). In general, grade 3 injuries progress to strictures regardless of therapy, and grade 3B injuries have a high risk of infection and perforation as well. These patients require surgical consultation for early resection and should be monitored closely. Various case series in which endoscopy revealed injuries grade 2 or worse reported a mortality rate of 10–15% [7, 35, 70], and in cases in which endoscopy discovered a grade 3B injury, a mortality rate of 66% was reported [32].

Use of Steroids

The utility of steroids in the treatment of caustic injuries has long been a controversial topic. Corticosteroids inhibit the inflammatory response and theoretically prevent stricture formation. Early animal models demonstrated a decrease in stricture formation but not surprisingly an increase in steroid-induced complications. Steroids may mask infection in the patient, including a brain abscess in one report [71], and may weaken already injured tissue, increasing the risk of perforation.

Many authors report using steroids as a routine part of their treatment regimen [4, 8, 10, 12, 19, 28, 31, 42, 57, 58, 61, 72–75]. Most of these reports do not differentiate, however, between grades of injury with regard to outcome. Other case series concluded that there is no risk of stricture formation from grade 1 injuries and that grade 3 injuries progress to strictures regardless of therapy. Several reports support the use of steroids, but only for cases with grade 2 injuries that may form a stricture but for which this outcome is not considered inevitable [4, 12, 19, 28, 32, 42, 74]. One well-known but often misquoted study prospectively investigated the effect of steroids on stricture formation. Sixty children were randomized over 18 years and were evaluated by rigid esophagoscopy only as far as the first serious burn. The conclusion of the study, which differs from what is stated in the abstract, is that the study lacked the statistical power to show a benefit using steroids – a type II error [71]. One meta-analysis

of 13 studies, however, found a 20% reduction in the incidence of strictures among patients with grade 2 and grade 3 injuries who received steroids and antibiotics [30]. Most recently, a randomized control trial of children with only grade 2 injuries demonstrated a significant benefit from corticosteroids (1 g/1.73 m² per day for 3 days), reducing stricture formation by 20–30% and decreasing length of parenteral nutrition therapy [76].

Corticosteroids are therefore advised in patients with grade 2 injuries to prevent stricture formation (Grade I recommendation). An appropriate dose is 1–2 mg/kg/day of prednisolone for 2–3 weeks or 1 g/1.73 m² of methylprednisolone followed by a taper of similar duration [19]. Steroid therapy is used in conjunction with antibiotics because of the increased risk of infection [71].

Use of Antibiotics

Tissue disruption from caustic injury increases infection risk which may extend to the mediastinum and peritoneum. This risk is increased further with corticosteroid use because corticosteroids inhibit the immune response and may mask the clinical appearance of an infected patient. Although there are no outcome studies showing a benefit for their use, antibiotics are used routinely with corticosteroid use to decrease the risk of infection. In the absence of steroids, there are no data to support prophylactic antibiotic use. However, many patients will mount a febrile response to caustic injury which is indistinguishable from an early infectious process, and in reality most patients receive empiric parenteral antibiotics early in the course of illness.

Use of Antihistamines and Proton-Pump Inhibitors

Antihistamines and proton-pump inhibitors have been advocated for therapeutic use in the context of caustic injury. One study evaluating intravenous omeprazole therapy reported improved endoscopic healing [77]. Histamine antagonists have not been subject to controlled studies but may be of benefit

[78]. Experimentally, serine and glycine have exhibited cytoprotective activity against chemically induced gastric lesions in rats [79, 80]

Surgical Intervention

A review of the literature presents a fascinating look at the change in the philosophy of treatment for patients with caustic injuries. In the 1960s, physicians had to wait until an injury declared itself in the form of stricture before beginning treatment. With the increased use of endoscopy, treatment with steroids and antibiotics could begin earlier, but patients with severe injuries still were treated conservatively with a watch-and-wait attitude. Various therapeutic techniques evolved only to prevent stricture formation, whereas the prevention of death was given little consideration. A certain fatalistic attitude pervades the early literature.

The conservative approach to patients with caustic injuries, including observation, hydration, nutrition, and possibly antibiotics and steroids, is appropriate for patients with minor injuries. Likewise, the decision for surgery is clear when the patient shows evidence of a perforation by endoscopy or radiography or has abdominal rigidity or hypotension.

There are many patients, however, who have serious injuries without early signs or symptoms, thereby delaying surgical intervention. Several authors have reported patients who had serious injuries to the stomach, esophagus, and other intra-abdominal organs and died without manifesting signs of the impending catastrophe until late in their clinical course [42, 43]. These patients *might* have benefited from early surgical intervention.

Since the late 1980s, more authors have advocated an aggressive surgical approach to patients with caustic injuries to decrease morbidity and mortality. Indications for surgery vary by author. One group adopted an approach that included early endoscopy, immediate laparotomy for patients with grade 2 or worse injuries, and

immediate esophagogastrrectomy for patients with full-thickness necrosis [42]. When using this aggressive approach, this group showed a decrease in the incidence of stricture formation in patients with grade 2 injuries and a much improved survival rate among patients with grade 3 injuries compared with their own hospital's records when a conservative approach was used. They concluded that the risk of missing a full-thickness injury was greater than that of the procedure and that the watch-and-wait attitude was too dangerous.

Other authors have advocated surgery for massive necrosis or an arterial pH less than 7.0 [35, 43]. Wu and Lai [47] recommended surgery for generalized abdominal pain and tenderness, continuous bleeding in the gastrointestinal tract, pleural effusion, and ascites. Although there is some debate as to whether laparoscopy provides an adequate examination of potentially injured tissues [64], many surgeons agree that the most important factor contributing to mortality is delay to diagnosis, necessitating an aggressive surgical approach if a transmural necrosis is suspected [15, 43, 65]. When managing patients with extensive necrosis or patients who may have a full-thickness injury, urgent surgical intervention including laparotomy and resection can be lifesaving (Grade III recommendation).

Lathyrogens

Lathyrogens are compounds that inhibit the activity of lysyl oxidase, the enzyme responsible for cross-linking collagen and providing tensile strength [75]. The formation of a more pliant scar can enhance dilation of the stenosis. Experimentally, many studies have attempted to attenuate stricture formation or enhance the manipulation of strictures. β -Aminopropionitrile, a potent lathyrogen, has been studied in dogs and was found to be useful in limiting stricture formation [81, 82]. Similarly, penicillamine, which chelates lysine-derived aldehyde groups to prevent collagen cross-linking, was found to limit stricture formation in rats and rabbits

[83, 84]. Colchicine stimulates collagenase activity but was not found to alter wound fibrous response in rats and delayed healing in rabbits [84, 85]. Heparin was found to decrease the incidence of stricture formation in rats, possibly through prevention of submucosal vascular thrombosis [86]. Treatment of rats with interferon gamma and epidermal growth factor also has been shown to decrease the incidence of stricture formation. *N*-Acetylcysteine also was shown in rats to be beneficial in restricting stricture formation [87]. All of these treatments are considered experimental, and their use currently is not supported for human exposures.

Management of Strictures

The development of a cicatricial contracture is the most important consequence for patients who survive the initial crisis of a caustic ingestion with significant injury. These debilitating complications may begin weeks to months after the initial injury and may be classified according to severity to assist in management (Table 2) [88]. Grade 1 strictures are incomplete and noncircumferential. Grade 2 strictures are stringlike, annular, or elastic. Grade 3 strictures are dense, short strictures. Grade 4 strictures are longer than 1 cm and are divided into subtype A, which is superficial and nonprogressive, and subtype B, which is deep, tubular, and progressive.

Various procedures are used for the prevention and treatment of strictures. Estrera and colleagues advocated the use of early intraluminal stenting for immediate and continued prophylactic bougienage of the esophagus. They compared two groups, the

first of which underwent supportive care and dilation as needed, while the second group of patients had early intervention with an intraluminal esophageal stent and radial resection. The second group of patients had esophageal mucosa which appeared more normal when the stent was removed as compared to the first group [42]. Most other authors recommend dilation therapy to normalize the size of the esophageal lumen. Three to 6 weeks after the initial injury, progressively larger bougies are passed over endoscopically placed guidewires for dilation. Fluoroscopy can provide an additional level of safety when strictures are tortuous. The risk of dilation therapy, while small at approximately 1.5% for esophageal strictures in general, is increased when a corrosive ingestion is the cause [89]. Perforation, aspiration, and dysphagia may lead to a host of complications ranging from a general decrease in the quality of life to death.

The severity and extent of the stricture, the age of the patient, and the consideration for long-term risk of esophageal carcinoma contribute to the choice of dilation versus esophageal resection or bypass. Esophageal strictures that are resistant to dilation therapy may indicate surgery. Esophageal bypass leaves the injured esophagus in place and may reroute the gastrointestinal tract using the stomach, jejunum, or colon. Advantages to this technique include a potentially less invasive procedure and avoidance of postvagotomy sequelae. Complications, although rare, can include formation of a mucocele or esophageal abscess that may rupture into the mediastinum [90]. Resection of the esophagus has the same indications as bypass and may be accomplished by thoracotomy or by blunt dissection. Esophagoplasty is a local, in situ operation on the esophagus designed to widen the esophageal lumen. Different authors advocate these various therapies, and no comparison study has been performed to determine which procedure has a superior outcome.

Gastric stenosis may occur at any site in the stomach but is most common in the antrum. Gastrectomy and partial gastrectomies have been advocated in the past. Successful balloon dilation of gastric stenoses also is reported.

Table 2 Stricture description by grade

Grade	Description
1	Incomplete, noncircumferential
2	Stringlike, annular, elastic
3	Dense, short
4A	>1 cm, superficial, nonprogressive
4B	>1 cm, deep, tubular, progressive

Summary

Exposure to caustic substances continues to be a leading source of toxic injury for adults and children worldwide. Although most childhood exposures are unintentional, often resulting in only minor injury, and adult cases are fewer, many deaths occur each year in adults and children owing to the widespread availability of these substances and their inherent dangerous nature. Many patients die either in the acute phase from massive perforation and hemodynamic collapse or in the following few days from a wide variety of complications or multisystem organ failure. These deaths and varied forms of morbidity show the complicated nature of the injury and the comprehensive intensive care these patients require.

It is not sufficient to think only in terms of limiting potentially dangerous sequelae of these ingestions. Rather, we must seek to limit the damage and complications that may result in the death of the patient, before subsequent complications arise. Despite a lack of controlled data supporting a single management plan, many authors advocate a rapid and complete evaluation of the patient with endoscopy as the most important element. Endoscopy is such a useful tool; it should be thought of in terms of which patients *should not* receive endoscopy instead of patients who should. Pediatric patients who are asymptomatic and patients who are so obviously ill that they should be in the operating room are among patients who perhaps should not undergo endoscopy. Aggressive surgical management may be considered for patients with grade 2 or worse injuries because mortality may be decreased, and endoscopic evaluation cannot evaluate the depth of mucosal injuries completely. Steroids and antibiotics may be helpful in reducing the incidence of stricture formation in patients with grade 2B injuries but probably are not likely to help other patients. The most skilled staff available must provide all of this treatment because infection, hemodynamic instability, organ failure, fistulae, and late perforations all contribute to patient morbidity and mortality. Caustic injuries can be deadly to patients and a

formidable challenge for physicians. The astute and aggressive physician can provide the best chances for the injured patient.

Criteria for ICU Admission

1. Evidence of airway injury: stridor, voice changes, drooling
2. Features of sepsis: fever, elevated WBC, vital sign abnormalities
3. Evidence of mediastinitis: septic features with abnormal chest radiograph
4. Metabolic acidosis due to tissue damage or absorption of ingested acid
5. Peritonitis

Criteria for ICU Discharge

1. No evidence of airway compromise
2. No evidence for mediastinitis, peritonitis, or septic complications
3. Patient beginning to tolerate enteral feeds

Key Points

1. A caustic may be an acid, alkali, or other concentrated substance capable of causing injury on contact. These may include a variety of household cleaners, Clinitest tablets, laundry detergent pods, and phenol derivatives.
2. Any location in the aerodigestive tract may be injured after ingestion.
3. Endoscopy is essential to grade the extent of injury and should be performed as soon as possible. Adjunctive diagnostic modalities include radiographs, CT, and contrast esophagoscopy.
4. Corticosteroids may prevent stricture formation in patients with grade 2 esophageal injuries.
5. If viscus perforation is suspected, early surgical consultation is imperative. Surgical treatment may prevent further morbidity and mortality, and options vary depending on the location of injured tissue.

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Hydrofluoric acid (HFA) is an inorganic acid used in a variety of industrial and household processes. It commonly is known for its ability to etch glass and silicone leading to widespread use in the semiconductor industry. HFA may be used as a cleaning agent in low-concentration products such as household rust removers and tile grout cleaners. While this chapter primarily discusses hydrofluoric acid, any compound that can release a fluoride ion may cause fluoride toxicity. Other fluoride containing compounds include ammonium bifluoride, which has been used as a wheel-cleaning agent, and sodium fluoride, which has been used as a rodenticide and in dental products.

Biochemistry and Clinical Pharmacology

HFA is a relatively weak acid with a pK_a of 3.8. Although concentrations greater than 50% have corrosive properties, the main toxicity of HFA is related to the fluoride ion. As a weak acid, the unionized HFA molecule can penetrate lipid tissue more easily than stronger acids [1]; once the tissue is penetrated, HFA disassociates releasing a fluoride ion. Fluoride is the most electronegative of all ions and binds strongly to cations such as magnesium and calcium.

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Pharmacokinetics of Hydrofluoric Acid [2]*Volume of distribution:* 0.5–0.7 L/kg*Protein binding:* none*Mechanism of clearance:* renal*Active metabolites:* none*Methods to enhance clearance:* alkalization of urine [3] or hemodialysis [4]

calcium, phosphate, and hydroxyapatite. It is proposed that this is similar to what occurs in vivo because hydroxyapatite is present in bone and certain connective tissues. In an animal model, serum calcium was shown to decrease in a 5:1 ratio with the amount of fluoride administered. This ratio is consistent with the formation of fluoroapatite rather than the 2:1 ratio that would be expected if CaF_2 is formed. Regardless of the mechanism, severe hypocalcemia should be anticipated after significant HFA exposure.

Pathophysiology of Toxic Effects**Burns**

HFA burns are classified based on the concentration of the acid [5]. Concentrations greater than 50% cause immediate pain and tissue destruction; concentrations between 20% and 50% may cause burns that are evident within several hours. Burns caused by concentrations less than 20% may not be evident for 24 h. Patients may complain of pain in the absence of visible effects. High-concentration (75%) burns start as classic corrosive injuries. Because HFA is less ionized than stronger acids, it has the capacity to penetrate deeply into tissue. Damage is not limited to superficial levels by tissue coagulation, as is seen with injury from other acids. In further contrast to other acids, the damage to deep tissue is a liquefactive necrosis, and affected bone may develop decalcification [6].

Hypocalcemia

Severe HFA poisoning may cause profound hypocalcemia. Hypocalcemia has been demonstrated consistently in animal models of fluoride toxicity and in reports of human poisoning [7, 8]. The classically accepted mechanism for HFA-induced hypocalcemia is the formation of insoluble calcium fluoride (CaF_2) salts. Other investigators have proposed that the hypocalcemia observed in overdose is from the formation of fluoroapatite, $3(\text{Ca}_3(\text{PO}_4)_2)\text{Ca}(\text{F})_2$ [9]. Fluoroapatite is formed in vitro when fluoride is added to a solution of

Enzyme Inhibition

Fluoride is a potent inhibitor of several enzyme systems, including enzymes involved in oxidative metabolism. Adenylate cyclase is activated by fluorides [10]. Aluminum fluoride has been identified as a molecule that complexes with the enzymes responsible for deactivation of G proteins [10]. Because trace amounts of aluminum are universally present in living systems, it is likely that aluminum fluoride forms when fluoride poisoning occurs. The relative contribution of enzyme toxicity to human fluoride poisoning is unknown.

Other

Other clinical manifestations of fluoride poisoning include hyperkalemia and metabolic acidosis [11].

Clinical Presentation and Life-Threatening Complications**Dermal Injury**

Dermal injury ranging from full-thickness burns to pain without visible injury can occur with HFA exposure [12]. Burns from high-concentration exposures (>50%) are due to the caustic effects and initially are similar to other acid burns. Because HFA tissue penetration is not limited by coagulative necrosis, there may be ongoing

deeper tissue injury even after initial decontamination. Burns caused by low-concentration HFA (20–50%) may not have signs or symptoms for several hours but can progress to full-thickness burns. In a study of 237 patients exposed to HFA concentrations ranging from 6% to 11%, the time to onset of symptoms ranged from less than 30 min in 23% to more than 24 h in 5% of patients. Slightly more than 50% of the patients had redness and swelling, 5% developed blisters, and 23% had only pain [12].

Pulmonary Injury

Hemorrhagic pneumonitis, respiratory failure, and adult respiratory distress syndrome have been reported after inhalation of HFA. These effects are likely due to caustic pulmonary injury [14–16]. Systemic poisoning is a concern after inhalation of hydrogen fluoride. One reported death was associated with high blood fluoride levels [13]. Inhalation also was implicated after an exposure to aluminum bifluoride in a patient who developed systemic toxicity. However, the authors were not able to exclude ingestion of the product [14].

Gastrointestinal Injury

Although HFA is a relatively weak acid, ingestion may cause caustic gastrointestinal injury. Clinical reports suggest, however, that significant caustic gastrointestinal injury is not universal. Accidental ingestion of small amounts of low-concentration products caused gastrointestinal symptoms of abdominal pain, vomiting, and gagging in only 20% of patients [15]. A series of dental fluoride product ingestions also reported a benign course consisting of primarily gastrointestinal upset [16]. Life-threatening fluoride intoxication and death have been reported after HFA ingestion without significant gastrointestinal caustic injury [17, 18]. Although caustic injury can occur, it is not universal, and most importantly the absence of symptoms of caustic injury cannot be used to exclude life-threatening ingestion. Severe rectal

injury and perforation has been reported after rectal administration of HFA [19].

Ocular Injury

Ocular HFA exposure results in a more severe burn than hydrochloric acid at a similar pH [20]. A thorough examination of the eyes must be done in facial splash injuries. Corneal erosions, opacification, and anterior chamber reaction commonly are seen; however, most patients reported have recovered [21, 22]. One case of delayed injury that developed 4 days after exposure has been reported. This patient also recovered [23].

Cardiovascular Toxicity

The most severe effects of acute fluoride toxicity are on the cardiovascular system. The major manifestations of fluoride toxicity on the cardiovascular system are QT prolongation, ventricular dysrhythmias, hypotension, and ventricular fibrillation [11]. The mechanism of this toxicity is likely multifactorial, involving hypocalcemia, hypomagnesemia, enzyme inhibition, acidosis, and hyperkalemia. Most authors consider hypocalcemia the major precipitant of cardiovascular toxicity.

Although most authors consider hypocalcemia the underlying cause of cardiovascular toxicity after fluoride poisoning, one animal model showed that an increase in serum potassium occurs after serum calcium decreases and that cardiac arrest was related temporally to the increase in serum potassium and was not associated with the decrease in serum calcium [7]. As fluoride inhibits the sodium-potassium exchange pump [24], the authors suggested that this poisoning leads to increased functioning of the sodium-calcium exchange pump and resultant intracellular hypercalcemia [7]. Ventricular irritability and dysrhythmias result. This intriguing work suggests that the exact mechanism of fluoride cardiovascular toxicity still is unknown.

Diagnosis

Dermal HFA exposure should be considered in patients who present with severe pain and minimal or no dermal findings after exposure to products known to contain HFA. Patients with dermal exposures that involve more than 5% body surface area at any concentration, or more than 1% body surface area exposure to 50% HFA products, are at risk for hypocalcemia and should be placed on cardiac monitors and have serum calcium and magnesium measurements obtained on arrival at the hospital. The QT interval should be monitored. QT prolongation should be presumed to be due to hypocalcemia.

Patients with symptoms of airway irritation or obstruction
Patients with a significant proportion of body surface area affected
Patients who have ingested concentrated (>50%) hydrofluoric acid

Criteria for ICU Discharge in Hydrofluoric Acid Poisoning

Resolution of pain for >12 h after intra-arterial infusion
Stable serum calcium concentrations in the normal range for 12 h
No need for ongoing monitoring of airway

Treatment

There are no high-quality human studies evaluating treatment for fluoride poisoning. Therefore the treatment recommendations are based on theory, in vitro experiments, animal studies, and observational human data. Given the mechanism of fluoride toxicity, it is reasonable that animal studies may approximate human effects.

Specific Airway and Ventilatory Considerations

Patients with symptoms suggesting upper airway obstruction after inhalation or ingestion of HFA should be intubated. Patients with caustic injury to the oral pharynx or upper airway may require fiber-optic assistance or surgical airway management. Respiratory failure may occur in cases with systemic fluoride poisoning from ingestion, inhalation, and dermal exposure. Respiratory status should be monitored closely in all patients with significant exposure.

Indications for ICU Admission in Hydrofluoric Acid Poisoning

Patients with dermal burns who require intra-arterial infusion of calcium
Patients who develop hypocalcemia after ingestion, inhalation, or dermal exposure

Decontamination

Dermal

In a study of 494 cases of HFA exposures, treatment with only cold water irrigation for 20 min resulted in no patients' developing deep tissue necrosis. Many of these burns were caused by HFA concentrations greater than 40% [25]. When these results are coupled with the ease and safety of irrigation, it is clear that immediate irrigation should be considered standard therapy for HFA exposures (Level of Evidence [LoE]III).

Hexafluorine, which has an affinity for fluoride more than 100 times greater than calcium gluconate, has been advocated for decontamination of HFA exposures. All of 11 patients in a case series treated with hexafluorine following exposure to high-concentration HFA solutions did well. Although these results are promising, the lack of adequate controls in this study prevents definitive conclusions regarding the superiority of hexafluorine over standard decontamination [26].

Enteral

No prospective human trials of therapy for ingestion of fluoride poisoning have been reported. Because of the potentially caustic nature of HFA injury, gastric aspiration or lavage is not

recommended except in cases of massive ingestion where there is a possibility for aspiration of a large amount of HFA from the stomach (LoE III). Charcoal is not recommended. Although human experimental studies are not available, calcium or magnesium solutions (e.g., milk or antacids) administered early may convert fluoride to insoluble salts and prevent systemic absorption [27]. These may be of benefit if administered to patients who can tolerate oral administration (LoE III).

Inhalation

Patients who are exposed to HFA vapors should be removed from the exposure, transported to fresh air, and administered oxygen.

Ocular

Patients with ocular exposure to HFA should have immediate irrigation with water or saline (LoE III). Irrigation with other fluids is of no proven benefit, and animal studies suggest (LoE III) that irrigation with calcium salts may increase injury [20].

Extracorporeal Removal Techniques

Hemodialysis was used to treat one patient who developed hypocalcemia, mild hypotension, and prolongation of the QT interval. The authors reported an excellent response and fluoride clearance of 100 mL/min at a blood flow of 105 mL/min and a clearance of 188 mL/min at a blood flow of 200 mL/min. Nonfluoridated water was used in the dialysate [4]. Although dialysis increases the clearance of fluoride, it is unlikely that severely poisoned patients would tolerate dialysis.

Antidotes

Dermal

Classic therapies for HFA burns include magnesium oxide, ice water irrigation, and ammonium salts. Animal studies have shown, however, that calcium provides superior neutralization of fluoride ions [28]. Human case series also suggest that calcium provides outcomes superior to those of other therapies (LoE III) [12]. I recommend a

stepwise approach using progressively more invasive therapies to treat dermal injuries caused by low-concentration ($\leq 50\%$) HFA exposures. After irrigation, patients should be treated with topical 2.3–2.5% calcium gluconate gel [12]. The gel is formulated by the addition of 10 mL of 10% calcium gluconate solution to methylcellulose (preferred) or 30 mL of water-soluble lubricant, applied liberally to the affected areas and allowed to remain in place for 15 min after resolution of the pain and for a minimum of 30 min [29]. The gel is reapplied immediately if symptoms recur. The treatment is continued every 4–6 h for the next several days. Burns involving the hands may be treated by placing the gel in tight-fitting latex gloves. This approach has been associated with resolution of symptoms in at least two large series [12, 30]. Topical therapy usually is sufficient for exposure to HFA concentrations of less than 20% (LoE III). The role of topical treatment for more severe exposures is not as well defined, but it was used in a patient who was completely immersed in HFA and survived [31]. Given the low toxicity of topical calcium gel, I recommend its use as an adjunct therapy to systemic calcium administration for higher concentration exposures.

Injection of HFA skin burns with calcium to bind the fluoride ion has been recommended for more than 60 years [32]. Current recommendation is injection of 0.3–0.5 mL/cm² of 10% calcium gluconate with a 27G to 30G needle (LoE III) [33]. Local calcium injection is most useful in cases in which topical therapy is not effective in providing symptomatic relief and regional perfusion therapy is not possible (i.e., head, face, trunk, perineum) [33]. Because the volume that can be injected into the digits is limited to 0.3–0.5 mL/cm², this therapy is considered by many to be of limited utility if the digits are involved. If the fingers or toes are involved and do not improve with topical therapy, it is reasonable to move directly to regional perfusion techniques. Calcium chloride should not be used because it may cause local tissue necrosis [33].

Regional intravenous perfusion using Bier's technique has been advocated as an alternative to intra-arterial therapy for burns to the extremities (LoE III). This treatment is well described for the

upper extremity and has been used for the lower extremity [34]. The technique involves placement of a small-gauge intravenous catheter in the affected extremity. The extremity is exsanguinated using elevation and a tourniquet is inflated to 100 mmHg above the systolic blood pressure. After inflation, calcium gluconate diluted in normal saline is infused over a few minutes. While a range of doses have been reported, the largest published case series used 10 mL of a 10% solution diluted with 30–40 mL of normal saline [35]. No patient noted symptoms suggesting hypercalcemia [34]. The tourniquet is deflated gradually over 5 min after 15–25 min. Relief is usually prompt, and failure to alleviate symptoms with one treatment may be an indication for intra-arterial therapy [34], although other investigators advocate repeating the Bier technique [35]. Patients often require parenteral analgesia to tolerate the tourniquet. Addition but is not recommended. Although it provides immediate relief of symptoms, the loss of pain sensation removes the best marker of tissue toxicity.

Patients with persistent pain in an extremity after regional intravenous infusion may be treated with intra-arterial calcium infusion (LoE III). Patients usually report prompt relief of pain, and tissue loss usually is avoided [36]. For burns involving the foot or leg, the femoral artery is cannulated with a 5 F arterial catheter. The brachial artery is cannulated for hand burns involving more than the thumb and index finger, whereas burns involving only these fingers may be treated by infusion through a 20G radial artery catheter. To assist the infusion, the catheter is directed distally rather than proximally. Although some authors advocate an arteriogram to verify that the vessel is patent and supplies the affected area, confirmation that the catheter is generating an appropriate waveform every hour seems to be sufficient. Several infusion protocols have been reported. The largest series used 10 mL of 10% calcium gluconate diluted with 40 mL of normal saline and infused over 4 h [36]. The addition of 500 U of heparin to the infusion mixture may decrease the incidence of clotting. After the infusion, the line is flushed with an

additional 10 mL of saline over 15 min, then flushed hourly with heparinized saline. If tenderness or pain is present after 4 h of observation, the infusion is repeated. Using this protocol, the average number of infusions was 4.1, and no patient had significant tissue loss. Several patients required systemic magnesium replacement, and the authors recommended checking serum magnesium levels 1 h after the completion of the infusion [37].

Adjunctive therapies for HFA burns involving the hands or feet have included fasciotomy to facilitate the injection of larger volumes of calcium gluconate into the digits (LoE III) and removal of the nails when there is substantial subungual involvement (LoE III) [38]. Use of the stepwise approach should allow treatment of digital injuries without resorting to either of these steps.

Pulmonary

Currently, no therapies other than standard supportive care can be recommended for pulmonary irritant exposure. Although some authors have advocated early steroid administration, this is not supported by any controlled data, and there is a theoretical potential to increase the risk of infection. Thirteen patients with mild to moderate pulmonary irritation following HF inhalation were treated with 4 mL of nebulized 2.5% calcium gluconate [39]. No patient developed significant pulmonary toxicity or seemed to have any adverse effects. Although these results are uncontrolled and the symptoms were not severe, nebulized calcium gluconate is a reasonable intervention for symptomatic patients with mild to moderate pulmonary irritation after HF inhalation.

Systemic

Few experimental data are available regarding the specific treatment of systemic toxicity from HFA. Most studies instead have looked at sodium fluoride. Animal studies have resulted in variable results regarding the administration of calcium for the treatment of acute fluoride toxicity. Strubelt and colleagues [40] reported that calcium

increases the lethal fluoride dose by 17% in a rat model. Although the results were not statistically significant, the sample size was small and did not exclude a clinically significant effect. Simultaneous administration systemic administration of calcium chloride and sodium fluoride in a 1:1 molar ratio improved survival in a mouse model of fluoride toxicity. There was no change in survival when animals were treated with magnesium sulfate [41].

As noted earlier in the section on clinical presentation, cardiac arrest in fluoride-poisoned dogs was related temporally more closely to an increase in serum potassium than to a decrease in serum calcium. Calcium chloride, epinephrine, glucose/insulin, and lidocaine did not improve survival, whereas simultaneous administration of quinidine with calcium did. The authors hypothesized that quinidine prevents potassium efflux from fluoride-poisoned cells via calcium-mediated potassium channels and prevents fluoride toxicity. They also suggested that administration of calcium as treatment of hyperkalemia may elevate intracellular calcium levels and increase fluoride toxicity [7]. The clinical utility of quinidine in the treatment of human poisoning has not been evaluated. Because of the possibility of further prolongation of the already lengthened QT interval by quinidine, its use cannot be recommended routinely.

Infusion of isotonic sodium bicarbonate in doses to maintain arterial pH in the 7.45–7.50 range has been shown to improve survival in a rat model of systemic fluoride poisoning [40]. Acetazolamide administration further increased survival time and total fluoride dose. The terminal ratio of fluoride in cardiac tissue to serum was lower in treated animals. The authors hypothesized that alkalosis changes the distribution of fluoride and increases renal fluoride clearance. Serum alkalinization is a reasonable adjunct to calcium for treatment of severe systemic fluoride poisoning (LoE III).

Human cases documenting survival of cardiac arrest after severe fluoride toxicity are rare. The administration of large doses of calcium has been associated with survival in several cases,

however [8, 14]. In one report, a patient presented twice after ingesting an HFA-containing rust removal agent [42]. After the initial presentation, she developed hypocalcemia and subsequently had a cardiac arrest. She was treated with a total of 111.6 mEq of calcium and 16 mEq of magnesium during her resuscitation and recovered. After discharge from a psychiatric facility, the patient presented again after ingesting what was reported to be the same amount of the same rust removal agent. This time she was treated with prophylactic calcium and magnesium (a total of 65.1 mEq calcium and 32 mEq of magnesium) and recovered uneventfully. Although only suggestive, this case suggests that early administration of calcium may prevent or attenuate the severe cardiac effects that occur after large HFA exposures and is a reasonable intervention (LoE III).

Excision has been advocated after survival of one patient who went into cardiac arrest five times while receiving vigorous calcium replacement, then stabilized after excision of the burn site [43]. Although this case is interesting, it is not clear that the tissue excision contributed to the patient's survival. Because of the potential to cause serious injury during the excision, this treatment should be considered only for the most critically ill patients who are not responding to aggressive calcium repletion.

No treatment for systemic fluoride poisoning has been shown to improve survival in systematic human studies. In my opinion, aggressive decontamination and care of dermal exposures, supportive care with an emphasis on airway management, and early administration of large doses of intravenous calcium should be considered standard of care. McIvor and colleagues [7] suggested that late administration of calcium may be deleterious but still recommended early administration of calcium. Administration of an isotonic sodium bicarbonate infusion to maintain a mild systemic alkalosis (pH 7.45–7.50) may decrease cardiac fluoride concentrations, may increase fluoride clearance, and is of low toxicity. Moderate or severe systemic alkalosis (pH >7.50) may cause ionized calcium concentrations to fall, however, worsening systemic hypocalcemia.

Special Populations

Pediatric Patients

Pediatric patients are presumed to be at increased risk of toxicity from dermal exposure because they have high surface area-to-volume ratios such that a given percent body surface area exposure results in higher total body exposure.

Pregnant and Elderly Patients

There are no available data on the treatment of pregnant or elderly patients exposed to HFA. Standard therapy is recommended.

Common Errors in Hydrofluoric Acid Poisoning

Failure to appreciate that systemic toxicity can occur after dermal exposure

Failure to appreciate that systemic toxicity can occur after ingestion even in the absence of oral or gastrointestinal symptoms

Key Points in Hydrofluoric Acid Poisoning

1. Irrigate affected area immediately with water.
2. Dermal exposures should be treated initially with topical calcium; patients who have persistent pain should receive local injection or regional perfusion with calcium.
3. Systemic poisoning may occur after ingestion, inhalation, or dermal exposure and may result in rapid cardiovascular collapse.
4. Systemic poisoning should be treated with large doses of intravenous calcium.

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Part XIX

Natural Toxins: Marine

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Ciguatera poisoning is a multisystem illness caused by the ingestion of fish containing neurotoxins, commonly known as ciguatoxins, though this includes ciguatoxins, maitotoxin, and gambierol, all from the same dinoflagellate source. Ciguatera was known in antiquity, although the term “ciguatera” dates from the seventeenth century Spanish colonization of Cuba [1]. James Cook described an illness producing gastrointestinal (GI) and neurological symptoms typical of ciguatera poisoning while captaining HMS Resolution in 1774 near the Pacific Island of Vanuatu [2]. Although mortality related to ciguatera poisoning is low, symptoms can be disabling and, in a minority of cases, persistent.

Ciguatoxins are produced by microalgae living on the sea floor, which grow through photosynthesis. The epiphytic dinoflagellate, *Gambierdiscus toxicus* produces gambiertoxins, which undergo biotransformation into ciguatoxins as they move through the food chain [3–5]. Herbivorous fish and to a lesser extent mollusks and crustacea ingest microalgae and are in turn eaten by carnivorous fish [6]. Biotransformation through the food chain preserves lipophilic properties but transforms ciguatoxins into more oxidized, polar, and toxic molecules, although overall lipophilic properties are maintained [5]. Carnivorous fish are the main source of ciguatoxin exposure for humans; however, herbaceous fish can also serve as human vectors [7]. Maitotoxin, being a more hydrophilic polyether,

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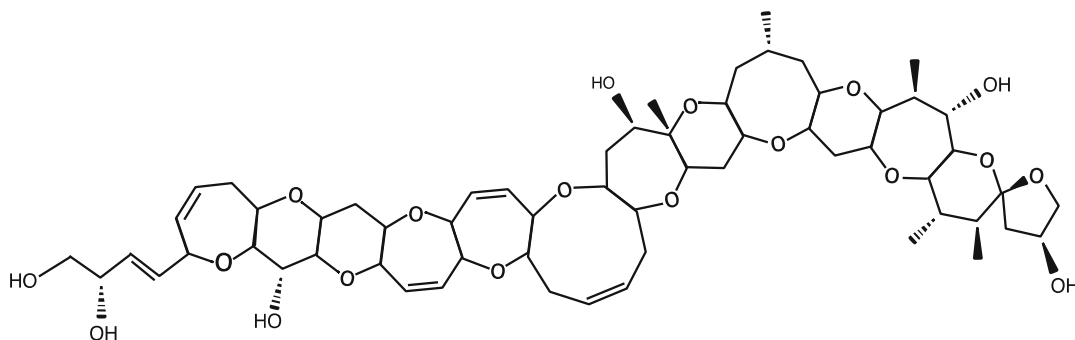


Fig. 1 Polycyclic structure of Pacific ciguatoxin-1

is not concentrated up the food chain and is restricted to herbivorous fish.

Ciguatera poisoning, the term covering poisoning by this group of toxins (ciguatoxins, maitotoxin, and gambierol) is the most common marine poisoning and is endemic in tropical and subtropical areas between the latitudes of 10° north and 10° south, particularly in the Caribbean and Indo-Pacific regions [8, 9]. This is consistent with the distribution of warm-water bottom-dwelling reef fish associated with ciguatera poisoning. Over 500 species of fish have been associated with ciguatera poisoning in humans; however, the most common are Spanish mackerel, cod, moray eels, barracuda, red bass, snapper, sea bass, groupers, coral trout, and tuna [9]. Increasingly mobile human populations, transportation of fish to global markets, and climate change mean ciguatera poisoning is increasingly encountered in non-endemic regions [8, 10–12]. Fish containing ciguatoxins do not appear, smell, or taste unusual. Ciguatera is not heat-labile, and poisoning can occur even after frying, baking, boiling, or stewing fish [7].

Ciguatera accounts for over half of all fish-borne cases of poisoning reported in the United States. The most commonly affected areas include Florida and Hawaii, with a peak incidence between May and August [13, 14]. Reported incidences vary from less than 0.1% of populations in Florida and Queensland, Australia, to greater than 50% of populations in South Pacific and Caribbean Islands [15]. Ciguatera poisoning produces a

significant socioeconomic burden in many South Pacific islands, where seafood is a major dietary component [16]. Global estimates range widely from 20,000 to 500,000 cases annually [15–17]. Difficulty in diagnosis, reluctance to report cases due to the belief that there is no effective treatment for symptoms, and lack of physician familiarity with the disease in non-endemic regions lead to a likely gross underreporting of the true incidence of the disease [9, 16–18].

Biochemistry and Clinical Pharmacology

Ciguatoxins are a group of moderately large (~1100 Da), lipophilic, colorless, odorless, highly oxygenated cyclic polyethers [19, 20]. Ciguatoxins are stable in mildly acidic and basic environments. The compounds are heat-stable, so cooking or freezing does not destroy them [5]. More than 40 ciguatoxins have been identified; their relative abundance varies with geographical location and may account for regional variation in the spectrum of clinical effects related to ciguatera poisoning [21]. Pacific ciguatoxin-1 (Fig. 1) measured in an intraperitoneal mouse assay is ten times more potent than Caribbean ciguatoxin-1; neurological features predominate in cases of ciguatera poisoning in the Pacific, while gastrointestinal symptoms are more prominent in Caribbean cases

[17]. Multiple different ciguatoxins may exist in the flesh of the same fish, with the content dependent on geographical location, species, and degree of exposure to toxic microalgae [4]. Ciguatoxins are secreted in breast milk and cross the placenta; however, little else is known about the pharmacokinetics of ciguatoxin [22–24]. Gambierol is also a lipophilic polyether, stable, concentrated up the food chain. Maitotoxin is a larger molecule, a hydrophilic polyether, less stable. Gambierol and maitotoxin have different target sites to the ciguatoxins.

Pathophysiology of Toxic Effects

Ciguatoxins are among the most potent sodium channel activators known; ingestion of 0.1 µg of Pacific ciguatoxin-1 can produce significant clinical toxicity [25, 26]. Ciguatoxins bind to site “5” on the alpha subunit of neuronal voltage-gated sodium channels, opening the channels at picomolar and nanomolar concentrations [27, 28]. Cell membrane depolarization leads to tetrodotoxin-sensitive sodium channels firing spontaneously. Increased neuronal sodium permeability increases intracellular calcium influx and axonal swelling, subsequently slowing both sensory and motor nerve conduction velocities [29–33]. Sural nerve biopsies in patients with significant neurological symptoms have shown edema of Schwann cells and myelin fibers. Nerve conduction studies have demonstrated evidence of a polyneuropathy with reduction of sensory and motor conduction velocities and an increase in absolute and relative refractory periods, particularly in sensory small fiber neurons [34, 35]. Increases in intracellular calcium concentration disrupt intestinal cell ion-exchange mechanisms, producing fluid secretion and diarrhea [35].

A large number of in vitro animal and human studies suggest ciguatoxins possess other cellular effects, which may contribute to the spectrum of observed clinical effects. These include stimulation of neurotransmitter release from motor nerve terminals, induction of membrane

potential oscillations in dorsal root ganglion cells, antagonism of voltage-gated potassium channels, alteration in function of C-polymodal nociceptors, and nitric oxide-mediated release of inflammatory cytokines capable of stimulating N-methyl-D-aspartate (NMDA) receptors [36–39]. Gene expression studies and measurement of inflammatory markers post-ciguatera exposure in patients with persisting symptoms suggest disruption of innate and adaptive immune responses and the development of a chronic neuro-protective anti-inflammatory response [40–42].

Maitotoxin targets several different ion channels, but especially calcium channels, causing increased calcium influx into cells, though also affecting some sodium channels. This results in neurotransmitter secretion and contraction of excitable tissues, among other effects, though the clinical correlation remains uncertain. Less is known about gambierol, though it appears to target voltage-gated potassium channels, blocking potassium efflux [43].

Clinical Presentation and Life-Threatening Complications

The time of onset of clinical effects following ingestion of fish containing ciguatoxins varies, with documented cases reporting symptom onset between 1 and 48 h, although in one large series, symptoms occurred within 12 h in 75% and 24 h in 96% of cases [7, 44–46]. Characteristically, an acute gastrointestinal illness is followed by a variable array of neurological symptoms [7, 45–52]. Less commonly cardiovascular, neuropsychiatric, and other generalized symptoms occur. Clinical manifestations of ciguatera poisoning are summarized in Table 1.

Gastrointestinal symptoms usually occur within 12 h of ingestion and may be severe, resulting in fluid depletion requiring intravenous replacement. They may be accompanied by diaphoresis and headache. Diarrhea appears to be the most commonly reported gastrointestinal symptom with one large case series of over

Table 1 Clinical manifestations of ciguatera poisoning (life-threatening complications in bold)

Gastrointestinal	Neurological	Cardiovascular	Other
Abdominal pain Nausea and vomiting Watery diarrhea Dehydration	Seizures Coma Paraesthesias Cold allodynia Peripheral dysesthesias Headache Sensation of loose or painful teeth Numbness of tongue, lips, perioral area Weakness Ataxia Vertigo Visual disturbance (scotoma, transient blindness, blurred vision)	Bradycardia Hypotension (may just be orthostatic hypotension in many cases)	Respiratory failure Diaphoresis Hyperthermia Hypothermia Metallic taste Singultus Myalgias Arthralgias Pruritus Rash on palms and soles Depression Fatigue Dysuria Proctalgia Testicular pain Dyspareunia (male and female)

3,000 patients reporting a 70% incidence [7]. Abdominal pain, nausea, vomiting, and diarrhea typically resolve within 24 h but may last up to 4 days.

A plethora of neurological symptoms have been reported in association with ciguatera poisoning, typically appearing within 24 h of exposure but sometimes delayed up to 72 h [7, 45–52]. Common symptoms include distal limb and perioral paraesthesias and cold allodynia; these have been reported present in 90% of patients in one series [7]. Cold allodynia is often described as temperature reversal; however, it is more accurately described as dysesthesia (an unpleasant sensation) resulting from exposure to cold [49, 53]. If present in the context of fish ingestion and gastrointestinal symptoms, cold allodynia is highly specific for ciguatera poisoning. Cold allodynia can be significantly disabling, preventing patients from washing with cold water or even walking across tiled floors [53]. In one prospective study, 80% of patients had abnormal temperature sensation and 50% abnormal pain and vibration perception [54]. The dysesthesias have frequently been described as tingling or “electric shock” type sensations. Light touch sensation may

also be reduced [54]. Tendon areflexia, dysphagia, and cerebellar dysfunction can occur but are rare [54]. Coma has also been reported [7, 55].

Cardiovascular dysfunction has been reported early in the course of severe cases, manifesting most commonly as bradycardia and hypotension, most likely orthostatic in nature in most patients [56–58]. Nonspecific ECG abnormalities have also been reported, but the incidence of cardiovascular features of poisoning is relatively rare [45–52].

Myalgia and arthralgia occur in up to 80% of cases [7]. Dental pain, a sensation of loose teeth, a metallic taste, rash (typically on the palms and soles), pruritus, fatigue, and depression are less common [7, 60, 61]. Fever or mild hypothermia can occur [44, 62]. Proctalgia, dysuria, testicular pain, pain with penile erection and ejaculation, and dyspareunia have been reported [2, 63–66]. There are reports of male to female and female to male sexual transmission of ciguatera-related symptoms [67].

The pattern and severity of symptoms can vary between individuals who have eaten the same fish, which may reflect the presence of a multitude of different ciguatoxins present within one fish [8]. Severity of symptoms appears to be related to the

size of the fish and the parts eaten; more severe toxicity occurs following ingestion of the head or organs [47]. However, some case series suggest that there is no clear dose-response relationship, with variability between amount of fish reportedly ingested and subsequent severity and duration of symptoms between individuals [46, 62, 68]. Although the most common symptoms are paresthesias, cold allodynia, myalgias/arthralgias, and diarrhea, their pattern is often complex and highly variable with some patients not experiencing a number of these common symptoms, just a few, or multiple different ones [69].

Although GI symptoms normally resolve over a few days, neurological symptoms, cardiovascular symptoms, pruritus, myalgias, arthralgias, singultus, headache, depression, and fatigue have been reported to last months to several years in a up to 5% of cases [9, 44, 47, 69, 70].

Predicting the course of the disease based on the severity of the initial presentation is unreliable; some patients with relatively minor symptoms go on to develop troubling chronic symptoms, while others with severe poisoning requiring critical care interventions are asymptomatic within weeks [68]. There are also regional variations in clinical patterns of toxicity. Gastrointestinal symptoms predominate acutely in the Caribbean, while neurological symptoms are more commonly seen early in the course of poisoning in the Indo-Pacific regions [5].

Sensitization to ciguatoxins has been reported. Apparent recurrence of symptoms years after the initial exposure has been documented following ingestion of fish (including fish not normally associated with ciguatoxins), alcohol, and other foods including nuts, chocolate, mushrooms, and seeds [6, 9, 67]. Postulated mechanisms of sensitization include long-term storage of ciguatoxins in adipose tissue or an underlying immunological mechanism [9, 70]. There have also been reports of ethanol and caffeine exacerbating symptoms during the initial few days of the disease [26, 72, 73]. Evidence from the South Pacific region where seafood is a major dietary component suggests that repeat ciguatoxin exposure may lead to more severe symptoms

compared to the initial episode of poisoning [7, 65].

Life-threatening clinical toxicity is rare but may occur in cases of significant dehydration, cardiovascular dysfunction, and respiratory failure or when seizures occur and adequate supportive care is not able to be provided. There are rare reports of patients with rapid progression of respiratory distress and development of coma. Deaths have been reported outside of the United States, but the overall mortality rate is much less than 0.5% [58, 64].

Diagnosis

Ciguatera poisoning is a clinical diagnosis, based on the history of ingestion of reef fish, the occurrence of typical symptoms including gastrointestinal and neurological features, and the exclusion of other diagnoses. There is no clinically useful qualitative or quantitative investigation available in human biological fluid. Cases occurring distant to tropical and subtropical areas may be undiagnosed because of the rarity of cases and lack of local physician knowledge or awareness of ciguatera poisoning. Ciguatera poisoning shares a number of clinical features with scombroid poisoning, neurotoxic shellfish poisoning, bacterial sepsis, and polyneuropathies such as multiple sclerosis. A diagnosis of ciguatera poisoning is more likely to be made if multiple patients present with typical symptoms following ingestion of fish.

Ciguatoxin can be detected within fish flesh using high-pressure liquid chromatography–tandem mass spectrometry [74] or a number of in vivo and in vitro animal tissue assays [15]. A history of ingestion of fish possibly containing ciguatoxin, the development of typical clinical features of poisoning, and detection of ciguatoxin in fish remnants is currently the diagnostic gold standard. However, these assays are rarely available for physicians and are not completed in a time frame likely to influence clinical management. Additionally, analytical assays suffer in terms of sensitivity because of

the heterogeneous nature of ciguatoxins found in any one fish. Traditional methods of testing fish for the presence of ciguatera in tropical areas include smearing the fluid from fish organs across one's gums and waiting for paresthesia to develop [75].

Treatment

Airway and Ventilation

In rare cases where coma occurs, endotracheal intubation and ventilation may be indicated for airway protection. Artificial ventilation may be required in rare cases of respiratory failure.

Circulation

Bradycardia usually responds to atropine (level of evidence [LOE II]) [56–58]. Hypotension should initially be treated with intravenous fluid and correction of bradycardia (LOE III) [58, 76]. In rare cases, inotropic support may be required [58].

Decontamination

The potential benefit of oral-activated charcoal administration has not been studied in ciguatera poisoning. Theoretically, activated charcoal may reduce the severity of poisoning if administered to a conscious patient with a protected airway within an hour of ingestion; however, early onset of gastrointestinal symptoms of toxicity may limit charcoal administration (LOE III). Activated charcoal has not been shown to alter the outcome in ciguatera poisoned patients.

Extracorporeal Techniques

Ciguatoxins are large, extremely lipophilic, and have a wide volume of distribution. Extracorporeal elimination techniques are not useful in treating ciguatera poisoning (LOE III).

Specific Treatments

Non-antidotal

Management of ciguatera poisoning is primarily supportive. Dehydration secondary to vomiting and diarrhea should be corrected with administration of intravenous crystalloids. Electrolyte disturbances should be treated in a standard manner. Patients may benefit from administration of an antiemetic to treat nausea and vomiting or an antihistamine to treat pruritus. Neuropathic pain associated with ciguatera poisoning can be difficult to treat. Case reports and small case series suggest possible benefit from a number of drugs including amitriptyline for pruritus, headaches, and paresthesias [77, 78], nifedipine for headaches [78], and fluoxetine for chronic fatigue (LOE III) [79]. Gabapentin and pregabalin have been reported as effective treatments for ciguatera-related dysesthesias (LOE III) [80, 81]. Patients should be warned to avoid consumption of alcohol, caffeine, or fish if these exacerbate their symptoms. Traditional herbal medications and remedies are commonly used in the South Pacific region to treat ciguatera poisoning, with over ninety different plant species listed as potentially useful in New Caledonia alone [82, 83]. However, there are no studies demonstrating their effectiveness or safety [76].

Antidotal

Mannitol is the most widely studied specific treatment for ciguatera poisoning. Mannitol reverses in vitro effects of ciguatoxin, including neuronal cell edema [84]. Mannitol was originally used to treat two patients in the South Pacific with cerebral edema associated with ciguatera poisoning. The neurological effects resolved completely in both patients. A further 22 patients were treated with complete resolution of neurological effects in 17 [85]. Mannitol was subsequently used widely, and case reports and case series reported beneficial effects in treatment of neuropathic pain and other symptoms when administered up to several weeks postexposure [70, 86–88]. Gastrointestinal symptoms do not appear to resolve with mannitol administration. A randomised non-blinded trial of 65 patients in French Polynesia demonstrated a statistically significant reduction in symptoms in the group ($n = 34$) receiving a mannitol infusion

compared to the supportive care ($n = 29$) group [89]. A blinded, randomized controlled trial of 50 patients receiving either mannitol ($n = 25$) or a normal saline infusion ($n = 25$) showed an improvement in clinical features of poisoning in both groups [54]. Mannitol was not superior to normal saline in this study; however, 25% of the patients in the mannitol group were treated greater than 69 h postexposure, while other reports had suggested mannitol was most beneficial if administered within 48–72 [70, 85–88]. A subgroup analysis of patients treated within 24 h of ingestion did not demonstrate a beneficial effect of mannitol over normal saline but suffered from small patient numbers. True blinding in this study has also been questioned with 84% of patients receiving mannitol reporting pain at the infusion site, compared to 36% in the normal saline group [54, 68]. Mannitol may reduce edema within neurons via an osmotic effect, inhibit the ciguatoxin-induced opening of neuronal sodium channels, and increase the dissociation of ciguatoxin from its binding site [30, 90]. It may cause fluid shifts and hypotension and so must be used with caution in significantly dehydrated or hypotensive patients. Mannitol may ameliorate the non-gastrointestinal clinical effects of ciguatera poisoning and is more likely to be beneficial if administered within 48–72 h of exposure (LOE II-3). Based on the available evidence, mannitol should be considered as an intervention in any patient presenting with significant non-gastrointestinal effects, within 48 h of ciguatera exposure. Mannitol must not be administered to shocked or volume-depleted patients.

Other antidotes have been developed but require further study before potential human use can be attempted or recommended. Brevenal is a naturally occurring cyclic polyether molecule that has been artificially synthesized and acts as an antagonist of brevetoxins [91]. Brevetoxins share properties with ciguatoxins and act at the same voltage-gated sodium channel. In vitro studies have demonstrated the ability of brevenal to antagonize the effects of brevetoxin. However, further study is required to evaluate the possible utility of this molecule in treating ciguatera poisoning [92, 93]. Monoclonal antibodies

synthesized to neutralize ciguatoxin CTX3C have been shown to neutralize CTX3C in vitro and in vivo in a mouse model [94], though the large number of identified ciguatoxins present in any one fish may limit the utility of this approach.

Indications for ICU Admission in Ciguatera

Poisoning

- Persistent hypotension not responsive to fluid
- Persistent bradycardia not responsive to atropine
- Respiratory failure requiring support
- Coma requiring intubation for airway protection
- Seizure activity requiring supportive care
- Severe electrolyte disturbance

Criteria for ICU Discharge in Ciguatera

Poisoning

- Normal vital signs
- Not requiring inotropic support
- Normalizing electrolytes

Special Populations

Infants and Elderly Patients

Because of the possibility of dehydration, care should be taken to ensure adequate fluid balance and electrolyte correction in infants and elderly patients before treatment with mannitol.

Pregnant Patients

Pregnant patients should be warned that there are some reports of transient neurologic abnormalities in infants born to mothers who have had ciguatera fish poisoning [95]. There are other reports of spontaneous abortion and premature labor [50]. Nursing mothers with ciguatera poisoning should be advised against breast-feeding because there are some reports of diarrheal illness in infants breast-fed by ciguatoxic mothers [50].

Other Patients

Patients who have been affected previously by ciguatera fish poisoning may have more severe symptoms on reexposure [7].

Key Points in Ciguatera Poisoning

1. Ciguatera fish poisoning is a worldwide phenomenon.
2. Poisoning occurs after the ingestion of fish containing ciguatoxin, which is derived from dinoflagellates.
3. Initial symptoms are gastrointestinal, with neurologic symptoms following.
4. Neurologic symptoms may be delayed in onset and prolonged.
5. Life-threatening features are rare but may include coma, respiratory insufficiency, seizure, bradycardia, and hypotension.
6. Management is essentially supportive, although mannitol may benefit some patients.

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Jellyfish

Jellyfish belong to the phylum Cnidaria (Greek derived from ‘nettle’) and are mostly free-swimming marine animals that may have an umbrella-shaped bell with varying length tentacles. The pulsations of the bell are relied on as their mode of locomotion, while the tentacles are typically used for capturing prey. Jellyfish have a worldwide distribution, occupying every ocean and some freshwater lakes. The phylum is comprised of several distinct life forms and four important classes of jellyfish: Cubozoa, Hydrozoa, Anthozoa, and Scyphozoa. The defining feature of Cnidaria is the cnidocyte, and the tentacles of most jellyfish are lined with thousands of them (Figs. 1 and 2). Each cnidocyte contains a harpoon-like organelle known as a cnida or cnidocyst. On the external surface of the cnidocyte is a cnidocil which, when activated by pressure, osmotic, or chemical changes, acts like a trigger, releasing the previously coiled harpoon. Once forcefully expelled, a process that takes microseconds, the harpoon is capable of penetrating human tissue. Venom is forced out of the cnidocyte under pressure through the epidermis and upper dermis and, particularly if dermal capillaries are inoculated directly, can enter the systemic circulation. It is sometimes stated that these may be inadvertently accelerated by the rubbing or shaking of a startled human victim, but there is no reliable evidence that this actually occurs.

The Cubozoa, or box jellyfish, are not considered true jellyfish, but represent the phylum’s most dangerous species (*Chironex fleckeri*, *Malo kingi*, and *Carukia barnesi*). This class contains cube-shaped, four-cornered jellyfish that are ordained with up to 15 tentacles per corner. *Chironex fleckeri* (roughly translated from Greek as the “assassin’s hand”) is commonly referred to as the big box jellyfish. This species of jellyfish is endemic to Australia, particularly off the Northern Coast [1]. As an adult the *C. fleckeri* has a bell the measures up to 38 cm with tentacles that may reach 3 m in length. The much smaller *Carukia barnesi* (family *Carybdeid*), aka “Irukandji jellyfish,” which as an adult, has a bell that measures a

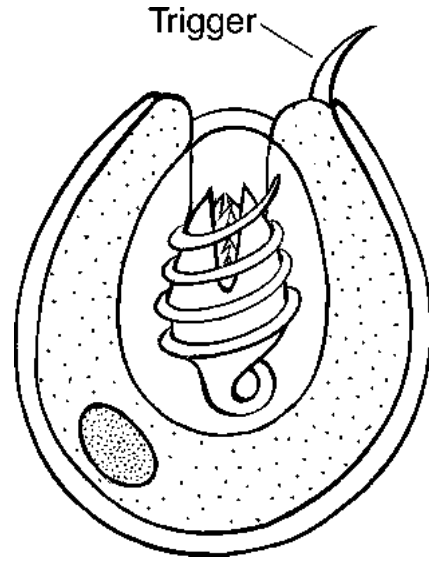


Fig. 1 Nematocyst before discharge (From Ref. [133], p. 1454)

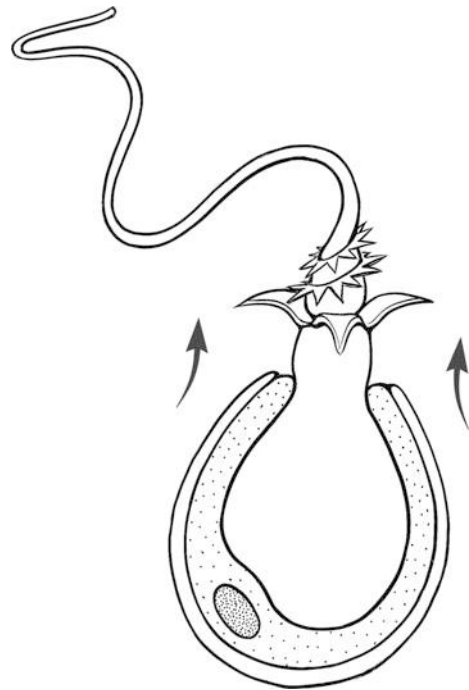


Fig. 2 Nematocyst after discharge (From Ref. [133], p. 1455)

mere 2.5 cm in diameter and tentacles the reach up to 100 cm from the bell. Given its small size, this jellyfish is not only elusive to the unsuspecting swimmer, but historically proved elusive to investigators. Hugo Flecker originated the term “Irukandji syndrome” in 1952 which is used to describe a set of clinical manifestations associated with, though not specific to, the sting of *Carukia barnesi* [2]. While its range was initially thought to be fairly wide, the “Irukandji jellyfish” is probably limited to Queensland waters [2] and the assumption of a wider distribution may be from envenomations from other members of the carybdeid family (i.e., *Carukia shinju*).

Interestingly, in 1964 a volunteer lifesaver by the name of Barnes cemented his place in history when he captured a specimen of a previously unnamed jellyfish and intentionally stung himself, and his own son, who were treated on site and survived. The offending jellyfish was named *Carukia barnesi*, sometimes referred to as the “Barnes’ jellyfish” [3]. Despite the lore around this species of box jellyfish, there has only been one death worldwide attributed to its sting.

Malo kingi (formerly *Chiropsalmus quadrigatus*), a species of box jellyfish, is also found in the Indo-Pacific region, particularly off the Philippian coast. This species has a bell measuring 7 cm in diameter and may have upwards of 60 tentacles, reaching as long as 3 m.

The Hydrozoa class contains two important species of jellyfish (*Physalia physalis* “Portuguese Man O’War” and *Physalia utriculus* “Pacific Man O’War”) and several species of medically important organisms (discussed below). An interesting feature of these two jellyfish is that rather than being a single self-sustaining organism, the creatures are a mass of hydroids living as a single colony. The floating colony is easily recognized by the characteristic sail, usually blue, which floats above the water’s surface. These hydrozoa can be found anywhere on the open ocean, but are more commonly found in tropical/subtropical regions of the Atlantic, Indian, and Pacific Oceans.

Scyphozoa, or true jellyfish, are home to a few medically important jellyfish such as *Cyanea*

capillata (lion’s mane jellyfish), *Chrysaora quinquecirrha* (sea nettle), and *Linuche unguiculata* whose larvae may cause a condition known as sea bather’s eruption. *Cyanea capillata* is considered one of the longest animals in the world, its combined length of the tentacles reaching as long as 63 m. Both *Cyanea* and *Chrysaora* spp. are found in tropical and temperate waters including, in particular, the Chesapeake Bay.

Pharmacology

Cnidaria venom is a complex, proteinaceous mixture capable of causing dermatonecrosis, myonecrosis, and cardiotoxicity and is species dependent.

Chironex fleckeri is considered one of the most venomous creatures in the world [4]. In 1959, Southcott and Kingston described a triad of basic toxicologic manifestations, cardio-respiratory failure, dermatonecrosis, and hemolysis. Over the last five decades, further in vitro and in vivo animal research has provided some insight into the reasons why certain clinical features are observed. First, a biphasic blood pressure response (initial hypertension, then hypotension) is often observed. An initial vasoconstrictive phase is followed by subsequent hypotension, likely from reduction in coronary blood flow, heart rate and contractility, arrhythmias, and baroreceptor stimulation [5]. Furthermore, there is an irreversible increase in intracellular calcium in rat myocytes which is speculated to correlate to atrio-ventricular block and systolic dysfunction in human cardiac tissue. This ion influx may result from pore-forming properties from two of *Chironex fleckeri*’s most abundant venom components, CfTX-1 and 2 [6].

The pain following envenomation may arise from modulation of nonselective cation channels expressed in nociceptive neurons [7]. There at least two myotoxins in the venom, both of which are capable of inducing skeletal muscle contractions in rat models [8]. Hemolytic effect, which may be a surrogate marker for venom-induced

cell-permeability and ion pore formation, is a rarely reported finding in humans [4].

Carukia barnesi is capable of inducing “Irukandji syndrome,” a series of signs and symptoms common in excess catecholamine states. Crude venom extract has been shown to cause the release of catecholamines in both in vitro and in vivo experiments [9]. The catecholamine release is likely, at least in part, from a prejunctional neuronal sodium channel activator which may be attenuated in the presence of tetrodotoxin or conotoxin. There is also, however, concentration-dependent contraction in rat mesenteric arteries that is not inhibited by tetrodotoxin. In isolated, human right atrial muscle, exposure to crude venom extract initially reduced contractile force, but was followed by a more sustained force of contraction. Sustained tachycardia and pulmonary hypertension has been demonstrated in in vivo piglet experiments where elevations of circulating noradrenaline and adrenaline were measured [9]. Winkel et al. have also noted that while the clinical manifestation is that of sympathetic nervous system activation, parasympathetic activation may play a role in the overall autonomic dysregulation that occurs following envenomation.

In vivo and in vitro studies on *M. kingi*, a box jellyfish smaller than *C. fleckeri*, have demonstrated extra-cellular calcium-dependent vasoconstriction and positive inotropic actions, which, at high concentration, become cardiodepressive [10–12].

Physalia physalis venom contains numerous proteins capable of myriad effects. Physalitin, a potent hemolysin, comprises about 28% of the total protein composition of the venom [13]. The venom most likely damages target cells by insertion into plasma membranes with subsequent pore formation, potassium efflux, and colloid osmotic lysis [14]. Intracellular calcium influx, induced through toxin induced pore formation, may occur at in vitro exposure as low as 10 ng/ml [15]. The influx of calcium is associated with a release of intracellular lactate dehydrogenase (LDH). In a canine model, intravenous administration of *Physalia physalis* venom induced

arrhythmias, hypertension, hyperkalemia, hyponatremia, and hemolysis [16].

Pathophysiology

Chironex fleckeri is probably the most medically important jellyfish and is one of the most dangerous animals on the planet. Reports are variable, but over 70 deaths have been reported from *C. fleckeri* envenomation [17]. Swimmers may not observe the jellyfish prior to or even after a sting. Most stings are innocuous and prospective studies have demonstrated that the majority of victims will not experience life-threatening symptoms [18]. For severe envenomations, symptoms begin with severe, unrelenting pain. Autonomic dysfunction, manifest as hypertension, may progress to hypotension, apnea, and cardiovascular collapse. Dysrhythmias have been reported in piglet models [5]. Coma may occur after the sting, which, when in the marine environment, may lead to drowning. Death is more likely if the length of cutaneous exposure exceeds 3 m [19].

Carukia barnesi is capable of inducing the “Irukandji syndrome.” In fact, *C. barnesi* was once referred to as the Irukandji jellyfish, but other members of the carybdeid family (*M. maxima*, *C. shinju*) are also capable of inducing this syndrome. Like envenomation from *C. fleckeri*, the victim of a *C. barnesi* sting may never see the offending organism. The sting is generally felt within a few moments of contact. The pain is not usually as severe as that of the big box jellyfish. Systemic features may begin within minutes and are manifest as muscular pain (in particular low back) and cramping (abdominal wall and limb), vomiting, diaphoresis, agitation, and hypertension [2]. In one case series, the symptom/sign frequency was abdominal cramps (40%), hypertension (50%), back pain (39%), nausea/vomiting (39%), muscular cramping of the limbs (34%), chest tightness (26%), and distress (24%) [20]. Troponin elevation, EKG abnormalities, and echocardiographic findings ranging from mild systolic dysfunction to global myocardial dysfunction were reported in another large series of *C. barnesi* envenomations [21]. Fatal

intracranial hemorrhage has been reported in one case of an extreme sequela of envenomation [22].

Envenomation from *Malo kingi* is reported to occur hundreds of times annually with at least three reported deaths [23]. The jellyfish can be found throughout the Indo-Pacific region, but is more commonly reported around the Philippines and Japan. Contact with *Malo kingi* is generally less severe than that of *C. flexeri*, though immediate, severe pain, cardiovascular collapse, and pulmonary edema are described [17].

Physalia physalis envenomations are common occurrences along the Atlantic Coast of the USA but are not limited to these waters and cause major stings worldwide. Symptoms of envenomation are generally immediate and localized, but delayed symptoms and systemic features can occur. Common symptoms include localized pain (mild to severe) and paresthesias and often accompany a linear, papular, or bullous rash or urticaria. Systemic features include diaphoresis, tachycardia, nausea, vomiting, muscle pain, headache, chills, and transient paralysis of the affected limb [24]. Hemolysis and renal failure has been reported [25]. Immediate, severe pain/distress followed by apnea and cardiac arrest has been reported (Irukandji syndrome) [26].

Dermatologic effects from jellyfish envenomation may arise from distinct toxins. Immediate dermatitis, skin discoloration, and local pain are the most common syndromes following cnidarian envenomation [27]. The local immediate and persistent wheals following sea nettle stings are likely an effect of leukotrienes, histamine, and neutrophil chemotactic activity [28]. Prolonged lymphokine responses have been demonstrated following jellyfish antigens, suggesting a T cell function may be a driving factor in the pathogenesis of skin lesions [29]. Erythema nodosum has been reported following a sting from *Physalia physalis* [27].

Clinical Presentation and Life-Threatening Complications

The majority of people envenomated by jellyfish will experience mild to moderate pain with or without cutaneous manifestation. Many victims

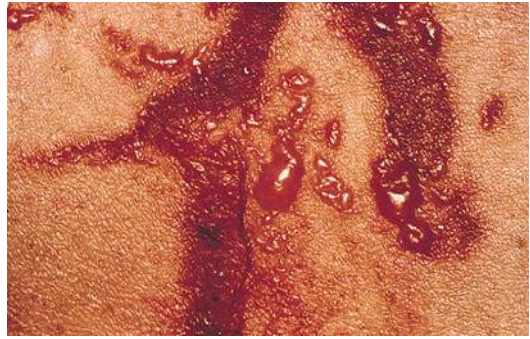


Fig. 3 Incipient necrosis and blistering within 24 h of box jellyfish (*Chironex fleckeri*) envenomation (Courtesy of John Williamson, MD. From Ref. [133], p. 1469)

may never seek medical attention. Nonspecific symptoms include nausea/vomiting, diaphoresis, and malaise. The severity of the toxidrome is variable and marked most commonly by dermatologic, cardiopulmonary, and neurologic effects.

Dermatologic manifestation can include skin discoloration, bullae, and urticaria. The clinical findings following contact with *C. fleckeri* are reported to be “distinctive” and described as heavily marked in a crisscross pattern, with transversely barred wheals which may be 8–10 mm wide (‘frosted ladder’) [17] (Fig. 4a, b). Delayed hypersensitivity reactions, characterized by a maculopapular rash, can occur 1–2 weeks after exposure. Necrosis of the skin can occur (Figs. 3 and 4).

Cardiovascular effects may include tachycardia, hypotension, and cardiogenic shock.

Neurologic manifestations generally begin with localized pain at the site of envenomation. Headaches, syncope, vertigo, ataxia, and altered mental status (agitation, delirium) may occur. Local paresthesia and transient limb paralysis are reported after *P. physalis* stings [24]. One death from intracerebral hemorrhage has been described following envenomation from *C. barnesi* [22].

The “Irukandji syndrome” is a serious form of envenomation from the carybdeid family of jellyfish, most notably *C. barnesi*. The syndrome begins rapidly, usually within 30 min, and consists of severe muscle pain/cramps, vomiting, diaphoresis, agitation, hypertension, and potentially acute heart failure or intracranial hemorrhage.

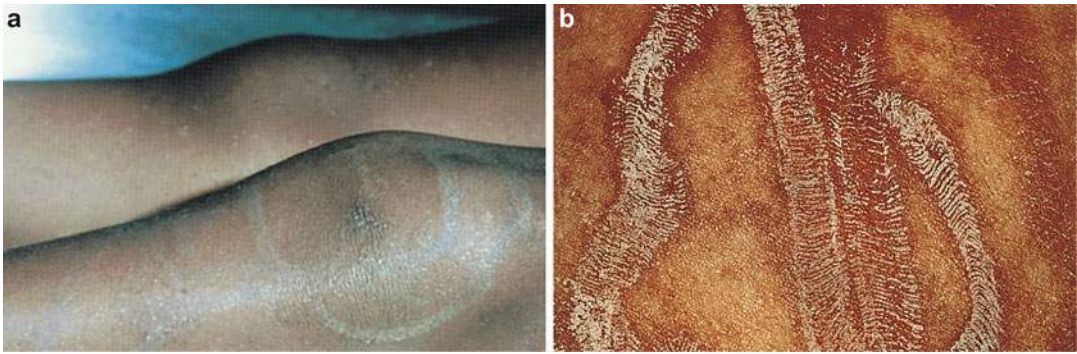


Fig. 4 (a) Frosted crosshatched pattern pathognomonic for a box jellyfish envenomation. The victim of this sting died rapidly. (b) The enhanced frosted appearance is a

result of application of a spray of aluminum sulfate (Courtesy of John Williamson, MD. From Ref. [133], p. 1469)

Toxin-induced neuronal sodium channel modulation leading to excessive catecholamine release is the postulated mechanism for this toxidrome [2].

Diagnosis

The constellation of sudden severe pain in a swimmer/bather/diver with cutaneous findings is suggestive of a jellyfish envenomation. Visualization of the jellyfish is obviously a helpful diagnostic clue; however, the small size or transparency of some species may limit visual detection. Examination of shed tentacles left on a victim may be a helpful work up to definitively identify a jellyfish sting, otherwise skin scrapings may be helpful for identifying the species of jellyfish responsible for the toxidrome. Diagnostic tests should be used to identify/follow potentially serious effects from the envenomation (i.e., serial troponins, EKG, echocardiogram, head CT, creatinine).

Treatment

As all envenomations will occur while the victim is in the water, first priority should be to remove the person from the marine environment and onto land or a boat to avoid drowning. There is a lack of data, suggesting a benefit to pressure dressings, and some in vitro evidence, suggesting a harmful effect [30]; therefore, there is no support for their

routine use. Patients should be kept calm and still, if possible. Physically removing tentacles should take place, but cautiously. Seawater irrigation and using an instrument to remove the tentacles is often suggested, but there are no data to support this. Health care workers need to don protective gear until complete decontamination is achieved. Tetanus prophylaxis is generally recommended when applicable (i.e., previously unvaccinated or out of date), although these envenomations do not pose a tetanus risk.

There is an exhaustive list of chemicals anecdotally used to neutralize undischarged tentacles left on the bodies of victims. There is no uniform approach or consensus on the protocol for such treatment, and evidence is often lacking or conflicting regarding topical neutralization. A 5% solution of acetic acid has been suggested to reduce nematocyst discharge from *C. fleckeri* and *C. barnesi* [31] envenomations. There are conflicting reports regarding the benefit of acetic acid for *P. physalis*. Some reports describe pain relief after the topical application of acetic acid [32], while others report immediate nematocyst discharge in both *P. physalis* and *C. quinquecirrha* [33]. Hypotonic solutions (fresh water), ethanol, isopropyl alcohol, and meat tenderizer are not likely beneficial and may increase nematocyst discharge and therefore should be avoided. Aluminum sulfate surfactant (Stingose [Pfizer], West Ryde, Australia) has been shown to reduce pain following *P. physalis*



Fig. 5 Box Jellyfish Antivenom (Courtesy of John Williamson, MD. From Ref. [133], p. 1470)

[32]. Lidocaine 4% topical solution with or without acetic acid reduced nematocyst discharge from *C. quadrumanus* and *C. quinquecirrha*. Heat application has been used to treat Irukandji syndrome and has been shown to reduce pain following *Physalis spp.* and *C. alata* envenomations [34]. Parenteral opiate analgesia may be the only necessary intervention to control pain.

The only currently available antivenin for jellyfish envenomation is the Box Jellyfish Antivenom (Commonwealth Serum Laboratories, Melbourne, Australia) (Fig. 5). Indications for treatment include envenomation from *C. fleckeri* with manifestations of systemic envenoming or in those who have extensive local involvement causing extreme pain which does not respond to routine analgesic therapy. Each vial contains 20,000 units of antivenin, and current treatment recommendations are to administer 1–3 vials (same dosing for adults and children) intramuscularly or intravenously (preferred when feasible), though it has been suggested that higher doses may be required to achieve venom neutralization [4, 35, 36]. There also seems to be a time-dependent

component to efficacy, with studies indicating that antidote efficacy may be augmented with a prophylactic approach rather than waiting for symptoms to occur [35]. This approach is problematic because most envenomations are mild, and the antivenin is derived from animal plasma; thus, there is a risk for anaphylaxis and serum sickness. Anaphylactic reactions should be treated in the standard manner. Human randomized trials are lacking, and the use of the box jellyfish antivenin remains a controversial point.

Management of serious Chironex envenomations, using verapamil, a calcium channel blocker and smooth muscle relaxant, is controversial and potentially harmful. While some studies have found that death was delayed in mice treated with verapamil before and after administration of venom [37] and lethality could be reduced from 21 of 21 to 16 of 22 mice treated with venom obtained from tentacle extract [38], others have shown that verapamil failed to prevent any effects of the venom and worsened cardiovascular collapse and increased mortality [5]. Currently, it is not recommended to use verapamil in the seriously envenomated patient [17].

There is no specific antidote for “Irukandji syndrome.” Painful toxidromes can be managed with opiate analgesics, usually parenterally. The “Irukandji syndrome” may exhibit direct myocardial effects; therefore, fentanyl may be a reasonable opiate to start with (pure narcotic receptor action without myocardial effects or toxic metabolites) [20]. Intravenous magnesium has been used in cases of severe envenomation and has a theoretical advantage because it may decrease vascular resistance in hyperadrenergic states [2]. In one case series, blood pressure reduction and pain improvement were observed in patients treated with IV magnesium (10–20 mmol boluses) [39]. However, a randomized trial comparing IV magnesium to placebo in the management of Irukandji syndrome failed to prove a benefit [40]. Though not without controversy, the authors of this randomized trial suggested reconsideration of the use of magnesium in the management of Irukandji syndrome. The Box Jellyfish Antivenom is not

expected to provide benefit from carybdae jellyfish envenomations causing the “Irukandj syndrome,” and given the potential harm, it should be avoided if the culpable jellyfish is known. Phentolamine and nitroglycerine have been used in case reports to treat the severe hypertension associated with this syndrome. Cardiovascular collapse may require inotropic support and pulmonary edema should be treated in the standard fashion. Patients who are asymptomatic without medications for 6 h after exposure may be discharged home with follow-up and careful discharge instructions.

With *Physalia spp.*, there is also no specific antidote. Treatment is supportive with focus on decontamination and pain control. As mentioned previously, there is conflict regarding the use of acetic acid, but given the concern for increasing nematocyst discharge, acetic acid might be best avoided. Though not well studied, severe muscle spasm may respond to 10% calcium gluconate (5–10 mL slow intravenous push), diazepam, or methocarbamol [25, 41]. Delayed cutaneous reactions, which may coincide with fever, weakness, joint pain/stiffness, can be managed with a 10- to 14-day oral prednisone taper starting at 1–2 mg/kg/day [42]. Topical anesthetics, such as benzocaine spray and lidocaine ointment and oral antihistamines, may be soothing.

Since the majority of patients who suffer jellyfish envenomation will experience only mild symptoms, most patients will be appropriately discharged from urgent care or emergency department settings. Hospital, and more specifically intensive care admission, should be reserved for those patients who experience the life or limb threatening problems. This applies to situations where a severe toxidrome requires: Box Jellyfish Antivenom, high dose opiates where respiratory compromise is a concern, evidence of ongoing ischemia (i.e., troponin elevations), intracranial hemorrhage, need for mechanical ventilation, malignant hypertension and end-organ injury, pulmonary edema, anaphylactic reactions, acute heart failure or following resuscitation from cardiopulmonary arrest.

Other Hydrozoa

Approximately one-third of the 10,000 species within the phylum Cnidaria belong to the class Hydrozoa. The medically important hydrozoans are *Millepora spp.* (fire corals), *Physalis spp.* (discussed above in the jellyfish section), and *Lytocarpus spp.* (fire weed or fern weed).

Fire corals are found in the tropical and subtropical waters of the Caribbean Sea and Indian, Pacific, and Atlantic Oceans. They tend to habitat in shallow water. Nematocysts found on tentacles which protrude from pores of the coral can envenomate divers and swimmers who may mistake the fire coral for rocky structures. Fire coral often have brightly colored structures and are brittle and thus easily fracture.

Pharmacology

At least 13 different species of *Millepora* exist and there are reports of various toxic components. Purified components of *M. alcicornis* and *M. tenera* have been shown to elicit hemolytic and dermonecrotic effects [43, 44]. *Millepora* cytotoxin-1 (MCTx-1), from *M. dichotoma var. tenera*, was the first proteinaceous toxin to be characterized [45]. MGTx-1 belongs to the dermatopontin family and is cytotoxic and hemotoxic in animal studies. Phospholipase A2, isolated from *M. complanata*, is a vasoconstrictive and hemolytic compound in rats [46]. Milleporin-1, a distinct toxin from MCTx-1, has been isolated from *M. platyphylla* and is also hemolytic to human red blood cells in vitro [47].

Clinical Presentation and Life-Threatening Complications

Contact with *L. philippinus* induces painful and pruritic wheals. Symptoms following contact with fire coral generally begin within 30 min of contact. There is often burning and stinging at the site of contact. A pruritic, erythematous, vesicular, or raised rash develops soon afterward. Violaceous papules and plaques may be replaced by blisters



Fig. 6 Hydroid sting on arm of a diver (Photo by Neville Coleman. From Ref. [133], p. 1461)



Fig. 8 Fire coral sting (Photo by Kenneth Kizer, MD. From Ref. [133], p. 1462)



Fig. 7 Fernlike hydroid print on the knee of a diver (Photo by Paul Auerbach, MD. From Ref. [133], p. 1461)

once resolved [48] (Figs. 6, 7 and 8). Though brittle, the backbone of the fire coral is sharp enough to cause lacerations or local trauma to the skin of those who contact it. Allergic and anaphylactic reactions would be suggested if systemic symptoms such as angioedema, bronchospasm, or diffuse erythema develop. Like all wounds from marine sources, secondary infections can occur. There is at least one case report of delayed nephrotic syndrome, pulmonary edema, and renal failure following exposure to fire coral [49]. Contact with *M. dichotoma* was reported to cause a full-thickness burn requiring admission to a burn unit [50].

Diagnosis

There is no routine or specific diagnostic testing to confirm fire coral or fire weed stings. The

differential diagnosis would include jellyfish stings or trauma from non-Cnidaria coral. There is no role for routine diagnostic testing to investigate systemic injury in the context of minor, local symptoms. However, if systemic features occur, renal function testing, chest radiography, and complete blood counts may be beneficial.

Treatment

Like treatment for jellyfish stings, treatment for fire coral or fire weed envenomations begins with removal from the water environment. Rescuers should put on gloves and carefully remove any remaining tentacles with an instrument such as forceps. The skin should be rinsed with salt water. Hot water immersion may be helpful in control of pain (Table 5) Acetaminophen or non-steroidal anti-inflammatory medications are generally sufficient enough to treat the pain associated with the sting, though in severe cases, opiates may be indicated. Application of ice packs is recommended for *L. philippinus* stings, but not dousing with urine, vinegar, or methylated spirits as these may increase nematocyst discharge [51]. Topical steroids and oral antihistamines reduced the severity of symptoms, but not skin manifestation in one case series of Red Sea Coral stings [48]. Allergic reactions and anaphylactic reactions should be treated in the standard fashion. In the reported case of nephrotic syndrome, a single-dose intravenous methylprednisolone

(120 mg), followed by oral prednisone (75 mg/d), was used [49]. Surgical debridement may be necessary if necrosis complicates the dermal effects. Tetanus prophylaxis should be employed in the appropriate circumstances.

ICU admission is indicated in the rare instance of severe anaphylaxis, sepsis complicating envenomation, or pulmonary edema.

Stingrays

Stingray point in the US state of Virginia gets its name from an event that occurred during Captain John Smith's exploration near Jamestown. He sustained a serious stingray injury while exploring Chesapeake Bay near the Rappahannock River, but he recovered and later ate the stingray for dinner (Stingray Point historic marker N 76).

Stingrays inhabit the oceans, bays, inlets, and rivers of temperate and tropical climates around the world [52]. Rivers around the world with species of stingrays include the Amazon, Niger, Mekong, and those in Australia [52–54]. Stingrays are flat fish that have wide muscular wings to swim, but they often burrow into sandy ocean bottoms and await their prey. They are cartilaginous similar to sharks; however, they will not attack or pursue a human diver or bather, and most injuries occur when they are accidentally stepped upon and the stingray reflexively flex their whip-like barbed tail producing a deep penetrating injury likened to a knife wound [53].

Some 2000 stingray injuries occur in the USA each year and many more worldwide [52]. One of the more tragic occurrences was the 2006 death of Steve Irwin, an Australian naturalist and TV personality known as the "Crocodile Hunter," when he sustained a cardiac wound from a stingray, emphasizing how quickly these encounters can turn deadly. His was not the first such fatal cardiac wound reported, a young woman died in New Zealand from a similar wound in 1939 [53]. A report in 1988 described a 12-year-old boy who sustained a penetrating chest wound from a stingray, received medical care, but died 6 days later at home from sudden cardiovascular collapse due to pericardial tamponade [54].

Table 1 Stingray families

True stingrays	True rays
<i>Dasyatidae</i> (Whiptail stingrays)	<i>Myliobatidae</i> (Eagle rays, Manta rays)
<i>Urolophidae</i> (Round stingrays, "stingarees")	<i>Gymnuridae</i> (Butterfly rays)
<i>Potamotrygonidae</i> (Freshwater stingrays)	<i>Rhinopteridae</i> (Cow nose rays)

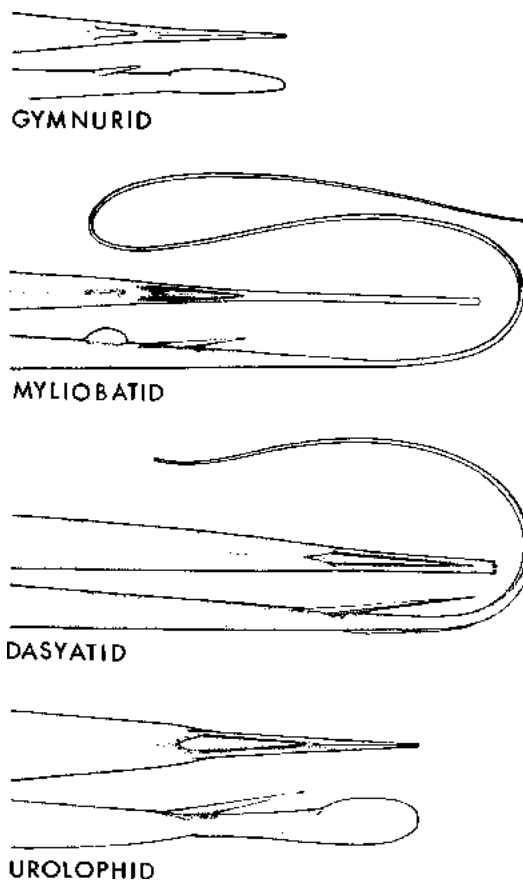


Fig. 9 Four anatomic types of stingray venom organs (From Ref. [133], p. 1489)

Stingrays, and the less injurious rays, are represented by 150 species within three families (Table 1). Each family has a distinguishing tail with one to four serrated spines (Fig. 9). The most dangerous is the *Dasyatidae* family due to the location of the spine and the length (37 cm) of its tail increasing penetrating efficiency [52]. This sharp serrated spine, with rear-facing barbs, acts

like a knife that can impale itself in a human when the stingray is disturbed and then reflexively arches its tail in self-defense. The spines often break off in the victim, but this does not kill the stingray. The spine can penetrate neoprene boots worn by divers. The spine's sheath contains two longitudinal grooves that contain venom [52].

Pharmacology

The venom is poorly characterized but contains 5'-nucleotidase, phosphodiesterases, and other tissue spreading factors [52]. Some as yet uncharacterized component of the venom may have direct cardiotoxicity [52, 55].

Clinical Presentation and Life-Threatening Complications

Stingrays inflict a penetrating wound from which the barb spine cannot be easily removed. The venom itself has low toxicity but plays a role in the inflammatory response and pain felt at the wound site [52]. Wounds to the heart, liver, spine, femoral artery, and extremities have been reported [52–54, 56–60]. Potential complications include cardiac tamponade and internal bleeding, and the victim may present in decompensated shock requiring emergent resuscitation. Arrhythmias possible due to the venom in the absence of a cardiac wound have been reported [55]. The most common wound from stepping on a stingray is a wound to the foot or lower leg (Figs. 10 and 11). Pain from any of these wounds is often excruciating and lancinating in character, peaking in 15–90 min and lasting up to 2 days [52]. Pain can extend up the entire limb, and a variety of systemic effects including nausea, vomiting, seizures, muscle spasms to the degree where the individual cannot continue to swim, and hypotension may occur [52].

Treatment

Critical attention to the resuscitation from penetrating trauma is the key management for stingray

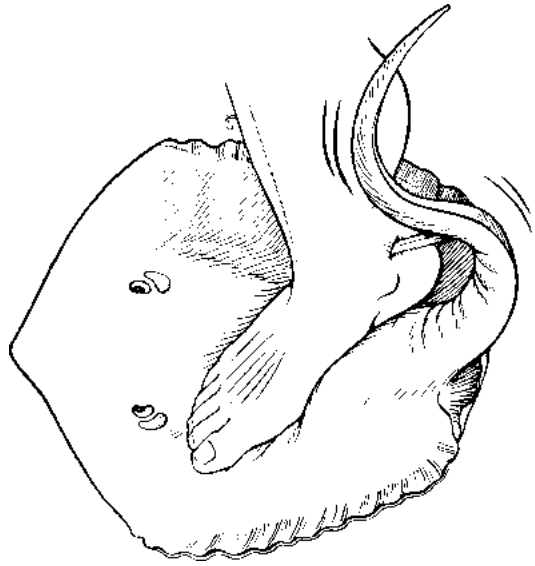


Fig. 10 The stingray lashes its tail upward into the leg and generates a deep puncture wound (From Ref. [133], p. 1490)



Fig. 11 Stingray spine tip broken off into the heel of a victim (Photo by Robert D. Hayes. From Ref. [133], p. 1490). See Color Fig. 11

injuries. Injuries to the head or torso may require airway management, fluid resuscitation, and potential need for chest thoracostomy or operative exploration in an operating room. Embedded chest and abdominal spines should not be pulled out blindly. Extremity injuries should be evaluated for vascular and nerve lacerations. Pain control in a stable patient will require immersion of an affected limb in hot water (45 °C/113 °F) [52]. Wounds may appear cyanotic centrally. Wounds should be both x-rayed and explored for retained foreign bodies which should be removed. Plain radiography may miss these thin spine structures, and direct wound exploration is mandatory [60]. Often local or regional anesthesia is needed to achieve adequate wound exploration and debridement [52]. Antibiotics are usually given for penetrating traumatic injuries from the marine environment and should be broad-spectrum to cover for organisms such as *Vibrio damsela* (now *Photobacterium damsela*) [52, 61]. Penetrating wounds to bowel should receive antibiotics to cover gram-negative and anaerobic bacteria.

Delayed complications from these wounds may include risk of cellulitis, septic arthritis, necrotizing fasciitis, and osteomyelitis. A pseudoaneurysm of the superficial femoral artery has been reported [62].

Scorpaenidae

The bony fishes of the family Scorpaenidae (Table 2) represent a diverse group of fish, from both freshwater and seawater habitats throughout the world (Fig. 12). They all have a bony plate

across their back from their eye to their gill, with spines that cover a venom gland. When pressure is applied to these spines, as when the fish is stepped on, they release their venom into the wound created by the sharp spine. A few species have importance in human envenomation, the most severe of which is the stonefish. Other species of spiny fish have also been implicated in less common instances of envenomation (Table 3).

The stonefish are the most toxic of this group of marine envenomations. These are bottom-dwelling fish, which have a natural camouflage to appear like a rock or coral. Additionally they can burrow into sand and lay motionless for long periods of time so to give the appearance to an inattentive diver that they are part of the coastal rocky bottom. At times algae overgrowth on their skin adds additional camouflage to their appearance. Most stone fish are found between the Tropics of Cancer and of Capricorn in Australian coastal waters, in the Indian and Pacific Oceans. They do not naturally live along North American shorelines. While envenomation can cause hypotension, muscle paralysis, acute pulmonary edema, and cardiac dysrhythmias, it is not usually lethal. Although some resources claim that stonefish envenomation could potentially be fatal, the only fatality in Australia is that of Dr. Joseph Wassell, which occurred in 1915 on remote Thursday Island in the Northern Territories [63]. Two other fatalities occurred in the Indian Ocean in the Seychelles and on Mozambique in the 1950s [63]. With modern supportive care, envenomations from this group of marine life are treatable and victims should survive with access to medical care [64].

Table 2 Scorpaenidae: bony fishes

<i>Synanceja</i> : Pacific and Indian Oceans, North or Tropic of Capricorn	<i>Scorpaena</i> : Pacific and Atlantic Oceans, Caribbean Sea	<i>Pterois</i> : Pacific Ocean including North American West Coast
Stonefish (<i>Synanceia verrucosa</i>)	Scorpionfish (<i>Scorpaena plumieri</i>)	Lionfish (<i>Pterois volitans</i> , also: <i>Pterois radiata</i> , and <i>Pterois russellii</i>)
Indian Stone fish (<i>Synanceia horrida</i>)	Soldierfish (<i>Gymnapistes marmoratus</i>)	Turkeyfish (<i>Pterois mombasae</i> , <i>Pterois sphex</i>)
Australian estuarine stonefish (<i>Synanceia trachynis</i>)	Sculipin: (<i>Scorpaena guttata</i>)	
Midget Stonefish (<i>Synanceia alula</i>)	Bullrout (<i>Notesthes robusta</i>)	
Red Sea Stonefish (<i>Synanceia nana</i>)	Red Rock Cod (<i>Scorpaena ergastulorum</i>)	

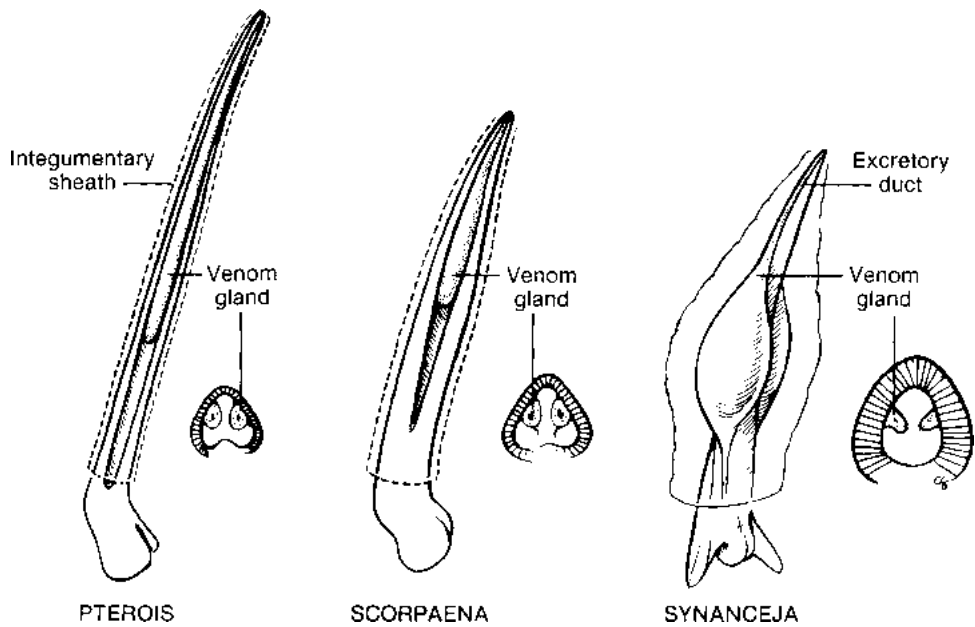


Fig. 12 Lionfish, scorpionfish, and stonefish spines with associated venom glands (From Ref. [133], p. 1495)

Table 3 Other spiny venomous fish

<i>Thalassophryne nattereri</i> (Atlantic Toadfish)
<i>Thalassophryne maculosa</i> (Cano Toadfish)
<i>Hydrolagus coliei</i> (Pacific Ratfish)
<i>Chimaera monstrosa</i> (European Ratfish)
<i>Kathetostoma avarruncus</i> (Stargazer)
<i>Scatophagus argus</i> (Spotted Scat, Butterfish)
<i>Selenotocota multifasciata</i> (Silver Scat, Stripped Butterfish)

There are over 80 species of *Scorpaena*, but only a few have documented human envenomations, and none have been lethal. Like stonefish they are well camouflaged. They are in both the Pacific and Atlantic Oceans and are one of the most common venomous fish along the coast of Brazil [65]. The venom apparatus varies between species that may possess 10–15 dorsal spines, and 2 pelvic and 3 anal spines, each with venom glands.

The least toxic of the scorpaenidae group are the lionfish (*Pterosis spp*), which go by a variety of names including zebrafish, dragonfish, firefish, and turkeyfish [66–70]. They are endemic to southern hemisphere coral waters but have been introduced in the Atlantic and Caribbean and are

considered an invasive species along the US East Coast [71]. These are a favorite for aquarium hobbyists, as they are free-swimming fish with thin ornate spines and coloration. In aquarium owners, they have been responsible for envenomations of the hands and fingers due to efforts to handle the fish or clean the aquarium [66–68]. Even handling a lionfish which had been dead for 1 or 2 days can result in envenomation [66].

Pharmacology

The venom apparatus is contained in its grooved dorsal spines and pelvic and anal spines. The spines are covered with an integumentary sheath over a venom gland. Each venom gland may contain 5–10 mg of venom [64, 72]. These venoms present a complex mixture of substances when injected into the skin, but the end result is severe pain, tissue destruction, hemolytic activity, and systemic effects. Components of the venom include hyaluronidase as a tissue spreading factor, and the toxic components, stonustoxin, verrucotoxin, and trachynilysin. Stonustoxin, a

heat-labile protein purified from *Synanceia horrida*, is composed of alpha and beta subunits and has a molecular weight of 148,000 Da [72, 73]. In animal models, stonustoxin causes hemolysis and edema, through local vasodilation, but this is generally not seen in human envenomations [72]. Verrucotoxin, from *Synanceia verrucosa*, has two alpha and two beta subunits, with a molecular weight of 322,000 Da [74]. The beta subunit has a 96% homology with the beta subunit of stonustoxin [72–74]. Verrucotoxin inhibits calcium and activates potassium channels in frog atrial tissue, but human cardiac effects are rare [74]. Trachynilysin, from *Synanceia trachynis*, has a molecular weight of 158,000 Da. It causes release of acetylcholine at the neuromuscular junction and causes negative inotropy and cholinergic effects, possibly through calcium influx [72–74]. Other vasogenic amines norepinephrine, serotonin, dopamine, and tryptophan, and enzymes acetylcholinesterase, phosphodiesterase, arginine esterase, and 5'-nucleotidase are also present in these venoms [64].

Clinical Presentation and Life-Threatening Complications

When a stonefish is stepped on, and a diver is envenomated, the clinical effects include severe pain, which peaks within 60–90 min after envenomation, and may persist for up to 12 h [72–76]. It is often described as severe burning in nature [76]. Other symptoms may include headache, muscle aches, diaphoresis, vomiting, diarrhea, restlessness, delirium, seizures. A variety of both tachydysrhythmias and bradydysrhythmias have been reported, as have acute pulmonary edema, hypotension, syncope, and pericarditis [75, 76]. The wound is painful, may bleed due to venom components with anticoagulant activity, and will appear cyanotic or ischemic centrally with a perimeter of erythema [64]. Local vesicles and bullae may form, and local lymphangitis may occur. Wound healing is very slow, taking months to heal, with possible secondary complications such as deep abscess formation, granuloma formation, and neuropathy.

Envenomation from the *Scorpaena* species, and related spiny fish, causes similar signs and symptoms as stonefish but are less severe. Since some of these species, such as sculpin, are harvested for food, hand injuries in fisherman are more common in this group of fish. In rat models of envenomation, hypertension and tachycardia occur first, followed by vasodilation, hypotension, and bradycardia prior to death [77]. Some other species such as bullrout and soldierfish are often grouped with these fish as potential venomous species [77–80]. Stonefish antivenom has been shown in vitro and in animal models to have activity for some *Scorpaena* and soldierfish venom [77, 78]. Studies of bullrout venom, however, show its venom has no hyaluronidase or phospholipase activity and has no antigenicity with stonefish antivenom [80].

The envenomation from the lionfish is described as throbbing, but systemic signs or symptoms rarely occur [67]. Reviews of cases from North American poison centers show mild to moderate pain at the envenomation site, radiating up the affected extremity [66–68]. Local edema usually occurs, but vesicles and bullae formation are possible local effects of lionfish envenomation [66–68] (Fig. 13). Diaphoresis, chest or abdominal pain, and jaw tightness have occurred in a few cases [66, 67, 81].

Treatment

Treatment consists of basic first aid with immersion of the envenomated extremity in water as hot as can be tolerated without causing burns or scalding injury. This is to deactivate the heat-labile components of the venom. Hot water as high as 45 °C / 113 °F has been used but can give rise to first degree burns. Therefore, water temperatures should not exceed 43 °C (Table 5). Recommended immersion times range from 30 to 90 min. If recurrent pain occurs a repeat heat immersion can be tried. Appropriate level of analgesics should be given. Local or regional anesthetic blockade may be warranted, especially if embedded spines are present, and these need to be removed and the wound debrided and irrigated. Deeply penetrating spines



Fig. 13 Vesiculation of the hand 48 h after the sting of a lionfish (Photo by Howard McKinney. From Ref. [133], p. 1495)

especially in the soles of the foot or the palm of the hand may require surgical exploration and removal in the operating room. Radiographs to find retained foreign body are often needed. There is no support for the anecdotal use of folk remedies, meat tenderizer, antiseptics, or dyes to aid in local wound care. Cold immersion though should never be done. Antibiotics have been used as for any penetrating wound.

Stonefish antivenom is available in Australia through Commonwealth Serum Laboratories (CSL) of Australia (Fig. 14). It is indicated for severe envenomation. Each 2-ml vial contains 2000 units of equine-derived F(ab')₂ antivenom against *Synanceja trachynis*, but has been used for all stonefish envenomations. Dosing is based on the number of spinous puncture wounds as an approximation of venom load. If there are one or two puncture wounds, one vial of antivenom intravenously is recommended, if there are three or four puncture wounds then two vials can be used, and for cases with greater than four puncture wounds three vials have been used. If recurrent pain occurs, addition vials may be given [71]. Aquaria in other countries with stonefish may stock the antivenom even if unapproved locally. For example, major US aquaria that house these species may have the CSL antivenom for use with investigation new drug status. In the US consulting, the antivenom index may help locate which facilities carry the antivenom: (<http://www.aza.org/antivenom-index/>).



Fig. 14 Stonefish antivenom (Courtesy of John Williamson, MD. From Ref. [133], p. 1496)

Envenomation by *Scorpaena* should be treated as stonefish envenomation with hot water immersion, pain control, local wound exploration with removal of spines, and ongoing wound care. Wound infections with *Vibrio vulnificus*, *Aeromonas Hydrophilia*, *Edwardsiella tarda*, *Streptococcus iniae*, *Erysipelothrix rhusiopathiae*, and *Mycobacterium marinum* have been associated with marine infections including necrotizing fasciitis [64].

The symptoms from lionfish envenomation can be treated with warm water immersion and analgesia alone (Table 5). Cold therapy can worsen symptoms and is to be avoided [66]. Stonefish antivenom, although demonstrated in animal models to neutralize the cardiovascular effects of lionfish venom, is not used for these less symptomatic human envenomations [66, 78]. Wound exploration and radiographs to see if there is a retained spine may be needed [68], otherwise antibiotics should be reserved for cases which progress to cellulitis, lymphangitis, and tenosynovitis [66].

Catfish

Catfish are a diverse group of fish inhabiting both fresh and salt water environments. Notable for their barbels (“whiskers”), catfish lack scales, dwell at the bottom of rivers, lakes, streams and oceans, and may grow to 350 kg (*Pangasianodon gigas*). Eight families of catfish live underground, four families live in salt water. Some species of catfish have as many as four pairs of barbels (maxillary, nasal, and two chin), while others have none. The barbel is a special sensory organ, aiding in chemoreception and detection of food, and is not the organ responsible for envenomation. Catfishing is an important source of commerce, and important freshwater species include the channel catfish (*Ictalurus punctatus*), brown catfish (*Ictalurus nebulosus*), and black bullhead (*Ictalurus melas*).

All catfish, except the electric catfish, contain a hollow spine along their dorsal and pectoral fins. These three spines are covered with glandular tissue within an integumentary sheath and some contain barbed retrorse teeth [42]. The spines normally lie flat against the fin, but the animal may extend the spine in defense when it feels frightened. While the common route of envenomation is following puncture from one of these spines, there are reports of envenomation following handling of just the tail of some species (Arabian Gulf catfish and some Mississippi River species) [82, 83]. This is thought to occur through epidermal secretion of venom. Puncture wounds are more common than lacerations, though both occur. Hand injuries are commonly reported among those who handle catfish [82].

Pathophysiology

Catfish venom is species dependent, but in general, is a complex composition of hemolytic, dermonecrotic, and vasogenic proteins [84]. The potency is inversely proportional to the size of the fish [84]. When the integumentary sheath of the spine is broken, the heat-labile venom is injected into the wound. Crinotoxin, identified in *Arius thalassinus* and *Plotatus lineatus*, is secreted from the epidermis when the fish feels threatened

and can enter humans through broken skin. Smooth muscle contraction and prostaglandin release are two effects from envenomation from crinotoxin. Salt water catfish have reputedly more severe envenomations.

Clinical Presentation and Life-Threatening Complications

In general, there is little morbidity following catfish envenomations and death is a rare complication. The majority of injuries occur following handling of the fish. There can be lower extremity injuries from stepping on or brushing up against a catfish spine. In the case of *Arius thalassinus* and *Plotatus lineatus*, envenomation can occur from skin exposure to epidermally secreted toxin. The effects of catfish envenomation generally occur soon after the puncture or laceration from the spine. Pain may be intense and seemingly out of proportion to the exam and may extend centripetally. Left untreated, symptoms generally resolve within an hour. A robust inflammatory reaction leads to erythema, edema, local hemorrhage, and potentially skin necrosis [84]. Systemic findings, such as tachycardia, weakness, hypotension, nausea, vomiting, dizziness, paresthesias, loss of consciousness, and respiratory distress can occur, but are not common. Crinotoxicity is manifest by throbbing pain, tissue necrosis, and muscle fasciculations.

The major morbidity from catfish envenomation stems from secondary infections. Following injury from fresh water species, *Aeromonas hydrophila* inoculation is reported, while *Vibrio spp* infection may complicate envenomation from salt water species [84]. Other infectious considerations include *Mycobacterium terrae*, *Corynebacterium spp*, *Staphylococcus* and *Streptococcus spp*. [82] as well as *Edwardsiella tarda*, *Klebsiella*, *Erysipelothrix*, *Nocardia*, *Chromobacterium*, *Sporothrix* and *Actinomyces* [84].

Diagnosis

There is no specific diagnostic test for catfish envenomations. Given the potential for spine

dislodgement, routine use of radiographs seems appropriate to exclude foreign body. Secondary infections may resemble streptococcal cellulitis [82], though gram-negative cellulitis should be considered. Wound cultures may be a challenge to obtain given the small puncture size.

Treatment

There is no specific antidote for catfish envenomations. Treatment is primarily supportive and effectiveness may be time dependent. Hot water immersion is the most commonly utilized method to reduce pain. Catfish venom is heat-labile, and hot water immersion may inactivate venom proteins and limit local sequestration. Immersion in nonscalding water at 43 °C for 30–90 min or until analgesia is achieved is one approach (Table 5). Folk remedies such as pouring hot coffee over the wound, applying mineral salts, solvents, or other chemicals have no proven benefit. Another folk remedy, of doubtful value, is rubbing the wound with the gel-like material secreted from the skin of the traumatized fish. This is thought to act as a local vasoconstrictor and pain reliever. Local infiltration with an anesthetic such as lidocaine or bupivacaine may be a helpful adjunct.

Local wound exploration is paramount as retained spines may act as a source for infection and persistent pain. Radiographs are a reasonable adjunct to evaluate for a deeply penetrating spine or fracture. Like most puncture wounds or dirty lacerations, suturing should not be employed. Allowing the wound to heal by secondary intention is a more appropriate strategy. Tetanus prophylaxis is indicated in the previous unimmunized or if previous immunization is out of date. Careful observation and return for wound checks are important. Routine use of antibiotics empirically in high risks wounds (deeply penetrating hand or foot punctures) seems appropriate. Recommended oral regimens include ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, or IV carbapenems or cefepime. For cellulitis associated with bullae, vesicles or ulcers where *Vibrio vulnificus* is suspected, IV

ceftazidime, fluoroquinolones, plus doxycycline is recommended [64].

It is unlikely that ICU level care would be expected following a catfish envenomation. The most likely scenario would be sepsis in a susceptible host (immunocompromised or cirrhotic)

Amazonian Parasitic Catfish

Within the waters of the Amazon valley lives a strange creature with a reputation to swim into the urethra of unsuspected bathers, particularly during micturition. This catfish is known by several names including candiru, canero, vampire fish, toothpick fish, and urethra fish and is a member of the genus *Vandellia*. In addition to urethras, this transparent, parasitic fish has been reported to swim into vaginas, ears, noses, and anuses [85]. Adults may reach 40 cm (16 in.) in length, though most species are much smaller.

There is controversy regarding the legitimacy of human penetration by this fish, and the stories remained largely folklore over the last one hundred years. The fish has umbrella-like spines near its small head, which may extend and penetrate human tissue, thereby making removal difficult (much like the barb in some fish hooks). It naturally preys on fish, swimming against the stream into the gills of other fish where it attaches itself for a blood meal. Human “attacks” are likely accidental. While not venomous, the tissue damage and lacerations that occur from forceful removal have been reported to cause death from massive hemorrhage [86].

Treatment

While penile amputations and forceful extractions are documented treatments for human exposures [86], prevention with tight fitting bathing suits may be a more practical approach. High-dose vitamin C and fresh juice from the unripen fruit of the jagua tree (*Genipa americana*) may be used by locals in remote settings as citric acid is reported to soften or dissolve the spines of the fish and facilitate removal. In modern health care

settings, removal should involve a specialty trained surgeon (i.e., urologist). Unless severe hemorrhage or sepsis has occurred, ICU admission is unlikely.

Weeverfish

Nine species of weeverfish belong to the family *Trachinidae*, although a number of other fish are sometimes referred to as “weeverfish.” The weeverfish has venomous spines located on its first 5–6 dorsal fins and gills. The name *weever* is from the Old French (*wivre*, *guivre*, *vivre*) for “viper.” *Trachinus vipera* (the lesser weever) and *Trachinus draco* (the greater weever) are the most well-known. Other English names for the weever fish include adder pike, sea dragon, sea cat, black fin, scorpion fish, and stang. The weeverfish can reach up to 50 cm in length and are yellow-gray with a white belly. They are rugged animals, capable of surviving several hours out of water.

The weeverfish does not have a swim bladder. Therefore, it sinks to the bottom of the ocean when not actively swimming. Here, it buries itself under the sand and waits in ambush for unsuspecting prey to swim by. The spines of the weeverfish are associated with venom-containing glandular tissue. When the integrity of the glandular tissue is disrupted, after puncture, for example, venom is released through the spine and driven into the victim. The fish is easily provoked [87], but most injuries occur when the spines are accidentally stepped on by bathers or mishandled by fisherman. The lesser weeverfish is the most dangerous of all the weeverfish and is considered the most venomous of all fish in the temperate waters of the Eastern Atlantic, Mediterranean, Baltic, North, and Black Seas [87].

Pharmacology

The venom from the weeverfish is clear gray with an odor of ammonia. It contains several heat-labile, high molecular weight proteins, 5-hydroxytryptamine, and a protein responsible for releasing histamine in victim tissue, kinin-like

proteins, and several catecholamines [88, 89]. *Trachinus draco* venom (dracotoxin) contains large amounts of catecholamines and histamine and has cholinesterase activity [90] and hemolytic properties [91]. Trachinine, one of the two lethal fractions from *T. vipera*, has been described as the most lethal venom ever derived from fish venom [87], but is labile and loses its toxicity after an hour at room temperature. Serotonin (5-HT) is found in the venom of other animals (cone snail, box jellyfish, Portuguese man-of-war, etc.) as well as the weeverfish and is potent pain-inducing substance.

Pathophysiology

Release of serotonin into the victim’s tissue produces the characteristic pain associated with weeverfish envenomation. The histamine component is capable of producing wheal reactions, edema and erythema [87]. Central and autonomic system effects may be a sequela of the catecholamine component of venom.

Clinical Presentation and Life-Threatening Complications

Severe pain, immediately after the puncture, is the expected reaction. The pain, which is initially local, may radiate throughout the limb, becoming progressively more intense over about 30 min when symptoms peak. The pain has been described as burning, crushing, stabbing, and “neuralgic” and can be out of proportion to the exam and difficult to control [87]. The pain generally resolves within 12 h, though may persist for up to a year [42]. Edema, erythema, cyanosis, and necrosis may be associated cutaneous findings. Systemic effects such as paresthesias, diaphoresis, convulsions, syncope, bradycardia, chest pain, respiratory distress, and delirium have been reported [87]. Weeverfish envenomation has been associated with spontaneous abortions [92]. Death is a rarely reported complication and may be from sepsis rather than a toxin-mediated process [93].

As with all puncture wounds, secondary bacterial infections can complicate the toxidrome.

Gangrene, skin necrosis, and abscesses have been reported [87].

Diagnosis

There is no specific diagnostic test for weeverfish envenomations. Given the potential for spine dislodgement, routine use of radiographs seems appropriate to exclude foreign body. An accidental sting from a weeverfish should be in the differential diagnosis for any bather or fisherman who presents with severe pain and puncture wound if weeverfish are local species.

Treatment

There is no commercially available antidote for the treatment of weeverfish envenomations. The mainstay of treatment is geared toward analgesia. While the pain will generally resolve if untreated, the degree of pain can be severe. Immediate immersion in nonscalding hot water (43 °C) for approximately 30–90 min or until analgesia is obtained should be the initial treatment (Table 5). This may inactivate heat-labile proteins in the venom and limit local sequestration. Local anesthetic infiltration, for example, 1% lidocaine without epinephrine, can be considered. Application of cold packs may worsen the pain and therefore should be avoided [88]. Intravenous calcium gluconate has been reported to help alleviate refractory pain [94]. While nonsteroidal anti-inflammatory drugs may be sufficient for pain relief, opiates would be a reasonable option if the pain is severe and refractory to hot water immersion. Anaphylaxis should be treated in the standard fashion.

Dislodgement of the spine is unusual, but radiography seems a reasonable tool to exclude spine foreign body. Local wound exploration and copious irrigation is important, though wide incision and drainage is not advocated given that this spine rarely breaks off into the victim and there is morbidity associated with further destruction of tissue [95]. Treatment for limb edema is probably best handled by elevation of the affected limb rather than pressure bandaging [95].

Tetanus prophylaxis is indicated in the previous unimmunized or if previous immunization is out of date. Prophylactic antibiotics should be considered in deeply penetrating wounds particularly in the hands or feet, though some have advocated that routine antibiotic use is unnecessary [96]. If antibiotics are to be used, consider coverage for *Vibrio spp* given the salt water environment.

Requirements for admission to an ICU are unusual following envenomation from a weeverfish, though consider this for situations where large doses of opiates are needed to control pain, anaphylactic reactions, secondary sepsis, or septic shock.

Starfish and Sea Cucumbers

Only one of the roughly 1,500 species of starfish is medically important. *Acanthaster planci*, the crown-of-thorns, is widely distributed in the Indo-Pacific Ocean, as well as tropical and subtropical zones of the Red Sea and the east coast of Africa across from the Indian Ocean. A known predator of coral, the crown-of-thorns starfish can decimate coral reefs [97]. *A. planci* is one of the largest sea stars, reaching diameters up to 60 cm, and is the only sea star which contains venom in its spines [98]. Injury occurs when one of the many spines of the sea star punctures and penetrates human tissue; thus, it is important to wear protective gloves when handling them.

Sea cucumbers (*Synapta maculata*), members of the phylum Echinodermata, are found on the sea floor and have a worldwide distribution. They have a soft, elongated body and can reach upwards of 3 m. Several species are collected for aquarium habitats, while other species are cultivated for human consumption. While it would appear to be an easy target for prey, the sea cucumber contains holothurin, a neurotoxic substance to some marine organisms, and is also capable of ejecting a soap-like substance from its cloaca which can entangle would-be predators.

Pharmacology

Several in vitro experiments have demonstrated numerous effects of extracted *A. planci* venom.

Venom components have demonstrated hemolytic, antiproliferative, apoptotic, edema-forming, and capillary permeability-increasing activity [99, 100]. Mice injected with lethal factor extract from *A. planci* have developed hepatocellular necrosis [101]. Holothurin A and B, produced by the sea cucumber, is a saponin which acts as an anionic surfactant. In isolated canine cardiac sarcolemmal vesicles, holothurin seems to interact with membrane permeability and can influence calcium and sodium exchange [102].

Clinical Presentation and Life-Threatening Complications

While *A. planci* is predacious to coral reefs, human envenomation is accidental, generally the result of mishandling or stepping on the sea star. Pain (ranging from mild to severe), erythema or discoloration, bleeding, and edema are the typical manifestations [103]. The pain is often self-limited and may last upwards of 3 h. While local symptoms predominant, systemic effects such as paresthesias, nausea/vomiting, and muscular paralysis may occur and are likely the result of multiple puncture wounds [42]. Subcutaneous granulomas and induration as well as tenosynovitis have been reported [42, 98]. To date, there is just one case of fatal anaphylactic shock which manifest within minutes following a single-puncture wound from *A. planci* [103].

Handling sea cucumbers without protective gloves may cause contact dermatitis [42]. The major risk from exposure to sea cucumber toxin is ocular injury which may cause severe conjunctivitis and blindness [42]. Holothurin is reported to cause severe illness or death if ingested [42]. All species of sea cucumbers are poisonous if ingested.

Diagnosis

There is no specific diagnostic marker for exposure to either the sea cucumber or sea star. Because spine fragmentation into soft tissue has been reported, x-rays following puncture wounds from *A. planci* is reasonable.

Treatment

Earlier reports suggest rapid and dramatic report of sudden collapse following *A. planci* envenomation; however, these are of questionable validity. Nevertheless, the priority for treatment following exposure to the crown-of-thorn sea star should be prompt removal/retreat from the aquatic environment. Once out of water, immediate immersion of the affected body part in hot, but nonscalding, water should take place until analgesia is obtained. Local anesthetics can be used for pain control if hot water immersion has failed to provide significant relief. Opiate analgesics may be useful for refractory pain. Surgical excision may be necessary for retained spines [98]. Repeated steroid injections (2 mg triamcinolone acetonide diluted fivefold with 1% Xylocaine weekly) has been reportedly used for persistent subcutaneous induration from retained foreign bodies following *A. planci* envenomation. Anaphylaxis should be treated in the standard fashion.

The dermatitis from sea cucumber exposure can be treated with topical steroids or for severe reactions, systemic steroids [42]. Topical analgesics may facilitate exam and irrigation. Careful inspection for any signs of a foreign body and, if there is suspicion of ocular exposure, fluorescein examination to exclude a corneal abrasion is indicated. Prompt ophthalmology referral is appropriate if there is ocular involvement. Though not well studied, cycloplegic, mydriatic, and corticosteroid ophthalmic solutions have been suggestive as treatments for inflammatory keratitis in the absence of appreciable infection [42].

Octopuses

All species of octopus are venomous; however, the most poisonous mollusca species are the southern blue-ringed octopus (*Hapalochlaena maculosa*) and greater blue-ringed octopus (*Hapalochlaena lunulata*) [71]. These are found in warm semi-tropical waters of the Pacific Ocean around Australia, New Zealand, the Philippines, and as far north as Japan, and in the Indian Ocean with distribution in New Guinea, Malaysia, and Sri Lanka [71].

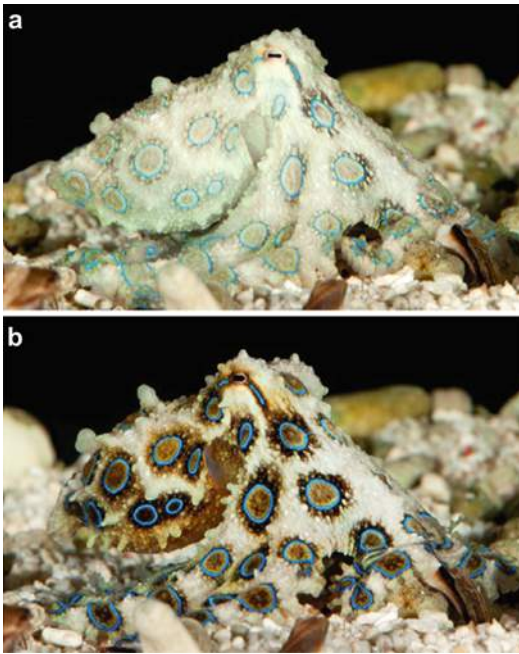


Fig. 15 Blue-ringed octopus (*H. lunulata*) with exposed blue rings, showing how varying states of expansion of chromatophores surrounding each ring can dramatically change the conspicuousness of the blue rings from relatively pale (a) to very conspicuous (b) (Photo by Roy Caldwell from: Ref. [104])

These are small creatures, usually less than 20 cm long even with its tentacles extended, and tend to prefer a habitat of shallow water tide pools. They are usually not found deeper than 10 m of seawater. This habitat makes them easily found by sea bathers, curious children, snorkelers and shoreline divers. While at rest and undisturbed, they have bands that are a yellow color; however, when agitated the body darkens and its rings, which contain chromatophores, turn bright blue [104]. A typical blue-ringed octopus may have 50–60 such brightly colored rings. Unfortunately in this state they become more fascinating to children and adults unwary of its toxic potential (Fig. 15).

Pharmacology

The venom of the blue-ringed octopus contains tetrodotoxin, the same toxin found in puffer fish,

the Oregon rough-skinned newt, and poison dart frogs. It is found throughout the blue-ringed octopus's body, but the venom delivery is via its salivary glands, and a strong ventral mouth and piercingly strong jaws [105]. They can inject their venom deep into muscle fascia. The purpose of the toxin is for the octopus to use to overcome its prey, usually crabs and shrimp, and with its' adjacent suckers can hold its food, while the tetrodotoxin is delivered via an injection through the skin. Other tissue spreading factors in the venom include hyaluronidase and vasogenic constituents such as histamine, tyramine, and serotonin. These substances may cause hypotension in experimental animals, but hypotension in human envenomation is not likely to occur.

Tetrodotoxin blocks peripheral voltage-gated sodium channels and produces rapid onset of weakness and paralysis in all motor nerves [42, 106]. Central nervous system effects are absent, and consciousness is maintained throughout in human victims.

Clinical Presentation and Life-Threatening Complications

The blue-ringed octopus does not envenomate while freely swimming. When a human gives the small blue-ringed octopus, a ride on an arm or hand the octopus can bite and envenomate [42]. This should never be done, unless the diver wears impermeable rubber gloves. At the bite site, usually two small puncture wounds are seen. Only minimal pain occurs at the time of the bite itself. Muscle aches and a stinging sensation ensue, followed by slight anesthesia at the bite site within 5–10 min. From the envenomation site, the sensations spread to the whole limb. Within a half hour, the bite site becomes red and swollen [42, 107–111]. Nausea, vomiting, hives, and itching all can occur. As the sodium channel blocking effect of the tetrodotoxin becomes systemic, perioral and tongue numbness occur. Subsequently, muscle weakness begins and can progress rapidly to complete paralysis. Bulbar palsies with diplopia,

dysarthria, and blurred vision occur. Inability to stand and walk occurs as larger muscles are affected, and deep tendon reflexes are lost [42]. As the muscles of respiration are affected, chest tightness and breathlessness occur. Progression to respiratory failure, complete flaccid paralysis, and death may occur unless medical intervention is delivered [42, 110]. Pupils may dilate and become unresponsive to light reflex, causing the physician to misdiagnose brain death.

Treatment

Treatment includes rapid recognition of the effects of the blue-ringed octopus bite and summoning of advance first aid. Early mouth-to-mouth respiration or bag-valve-mask ventilation to preserve ventilation may be necessary. In rare cases, endotracheal intubation with ventilator management is required [108, 109]. The duration of venom effects is quite variable but may last up to 10–12 h [71]. Complete recovery may require a few days. Unfortunately there is no antitoxin or antidote. Wound care for the bite site is also important [111]. Granuloma annulare has occurred with other octopus bites [112]. A light pressure immobilization bandage to occlude lymphatic flow might temporize the systemic spread of the toxin until definitive airway skilled personnel arrive [42].

Indications for ICU admission are generally related to cardiovascular and nervous system effects and would include progressive muscular weakness, respiratory insufficiency/arrest, and significant alteration of mental status or cardiac dysrhythmias.

Cone Snails

On display in the Pergamon Museum in Berlin is a 5000-year-old necklace of cone shells excavated from a tomb in the Mesopotamian city of Uruk, proving that the attraction for these beautiful shells dates back centuries [113] (Fig. 16). The *Conus* species contains many beautiful appearing

shells in which a living snail resides with an effective stinging apparatus for capturing its prey. Smaller *Conus* species feed on worms (vermivores) but are less toxic, while mollusk hunting (molluscivores) and fish-hunting (piscivores) are potentially toxic when they envenomate humans [113]. Over 700 individual *Conus* marine snails exist in the *Conus* species. While stings are rare, they are potentially fatal due to the unique and complex nature of the conotoxins in its venom [71, 114–122]. Most cases occur along the coastlines of the Pacific Ocean, and fatalities have mostly been due to *Conus geographus* [114, 115]. However, other *Conus* species are capable of a painful envenomation [71, 115] (Fig. 16).

Cone snails tend to burrow into the sand during the day and emerge at night to feed on fish or mollusks [71, 114]. The stinging apparatus of snail cones is shown in Fig. 15. The harpoon-like radular tooth is launched by the proboscis. Conotoxin venom is stored in the venom bulb which pumps it through the venom duct into the hollow barbed radular tooth. Since the snail itself is slow moving, this rapidly firing harpoon is effective at striking its prey, and the conotoxins secreted into its hollowed barbed tooth are effective at immobilizing it [71].

Pharmacology

The conotoxins are actually several hundred peptides, which share a disulfide bridge, but have great variation in their activity between species and even within the same species [113, 115–117]. The common mechanism of action is through ion channel blockade at different receptors including calcium, sodium, potassium, and acetylcholine channels (Table 4). Blockage of the nicotinic acetylcholine receptor subtype results in paralysis, usually only in the snail's prey, but human envenomation can produce diffuse muscle weakness. The alpha-conotoxin, which blocks neuromuscular acetylcholine receptors, is mechanistically similar in action to alpha-bungarotoxin. The mu-conotoxins, which block sodium channels, are mechanistically similar to tetrodotoxin



Fig. 16 Seven *Conus* species are shown. The large specimen at the extreme left is *Conus marmoreus*, the marble cone, the type species of the genus *Conus*, and at the extreme right is the geography cone, *Conus geographus*, the species causing the majority of human fatalities. The large specimen on top is the glory-of-the-sea cone, *Conus gloriamaris*, one of the most prized and valuable natural history objects of the eighteenth and nineteenth century. The four smaller shells on the bottom row are, from left to

right, *Conus cedonulli*, the matchless cone, a specimen of which once outsold a masterpiece by Vermeer; *Conus imperialis*, the imperial cone; *Conus purpurascens*, the purple cone; and *Conus magus*, the magician's cone. *C. cedonulli* and *C. imperialis* are vermivorous (worm-hunting) species; *C. gloriamaris* and *C. marmoreus* are snail-hunting species; and *C. purpurascens*, *C. magus*, and *C. geographus* are piscivores (fish-hunting cone snails) (Photo from: Ref. [113])

and saxitoxin. Both of these produce neuromuscular paralysis. One conotoxin peptide, an omega-conotoxin derivative, from the species *Conus magus*, the magician's cone, has been developed into the pharmaceutical agent ziconotide, used for intrathecal injection for central neurologic pain control [116, 118, 119]. It blocks the N-type calcium channel [119]. Other nonconotoxin peptides lack a disulfide bond and have other physiologic actions (Table 4). The conopeptide conantokin-G was originally called the "sleeping peptide," as it put young mice into a trance like state, when injected directly into the CNS, via its blocking action on the NMDA receptor [113].

Clinical Presentation and Life-Threatening Complications

Human envenomation occurs when a diver handles the shell unaware it is home to the snail. Slight pressure on the proboscis causes the radular tooth to penetrate the skin and may break off. The initial pain is similar to a bee sting, but may include localized edema or cyanosis. Depending on the

species involved, symptoms may be localized to pain, or spreading paresthesia with limb heaviness or numbness, and constitutional symptoms such as nausea and malaise [120, 121]. Serious *Conus geographus* envenomations can cause generalized motor weakness, bulbar palsy symptoms (diplopia, ptosis, dysarthria, dysphagia, aphonia), respiratory arrest, coma, and cerebral edema [120, 122]. Death may occur if medical intervention is unavailable or delayed onset paralysis occurs with respiratory insufficiency. The severe effects can last for several hours and take a few weeks before complete recovery occurs [71, 122].

Treatment

Careful attention to respiratory support is essential for patients with paralytic symptoms. Intubation and ventilator support is critical once signs of diaphragmatic weakness and impending paralysis occur. As with other heat-labile venoms immersion of the envenomated limb in hot water up to 45 °C/113 °F may provide pain relief, but analgesics may also be necessary (Table 5). One source has recommended

Table 4 Physiologic actions of some conotoxins

Omega-conotoxin	Voltage-gated calcium channel N-type blockade
Mu-conotoxins	Voltage-gated sodium ion channel blockade
Delta-conotoxin Iota-conotoxin	Voltage-gated sodium ion channel enhancer
Kappa-conotoxins	Voltage-gated potassium ion channel blockade
Alpha-conotoxin Psi-conotoxin	Ligand-gated nicotinic acetylcholine receptor antagonists
Sigma-conotoxin	Serotonin receptor 5-HT3 blockade
Rho-conotoxin	Alpha-1 adrenoreceptor blockade
Chi-conotoxin	Noradrenaline transporter blockade
conantokin	NMDA (<i>N</i> -methyl D-aspartate) receptor blockade
conopressin	Vasopressin release modulator/agonist
contulakin	Neurotensin receptor agonist

edrophonium, 2 mg IV as a test dose, similar to a tensilon test, with up to 10 mg IV in an adult, as a reversal agent for the neuromuscular blockade at the nicotinic acetylcholine receptor [71].

Indications for ICU admission are primarily related to neurologic or respiratory system effects and would include progressive weakness, respiratory insufficiency or arrest, coma, or significant altered mental status.

Sea Urchins

Roughly 950 species of sea urchins inhabit all the world’s oceans but are often found among coral reefs. Most sea urchins have spines measuring upwards of 3 cm, though some may reach 30 cm. Spines are a defense mechanism for the sea urchin and act as a physical barrier capable of inflicting an uncomfortable puncture to predators.

Not all sea urchins are considered venomous, given only those in the family Diadematidae and

Table 5 Hot water immersion as initial treatment for Marine envenomation

Stingray	Sea Urchin
Stonefish	Scorpionfish
Lionfish	Blue-ringed Octopus
Cone snail	Weeverfish
Catfish	Starfish
Fire Coral Physalia	Crown-of-thorns

Echinothuriidae have a venom apparatus. Venom is contained within the spines of the sea urchin or within pedicellariae, small clamp-like organs that can capture and hold onto prey (Fig. 17). Sea urchin spines can be broken after impaling humans, often as a result of mishandling or stepping on the creature. Regeneration of dislodged spines by the sea urchin is possible [123].

Pharmacology

Sea urchin venom contains several biologically active components including steroid glycosides, serotonin, hemolysin, protease and acetylcholine-like substances [124]. Cathepsin B/X, present in the *Echinometra lucunter* sea urchin, is thought to contribute to the painful, inflammatory process following envenomation [123]. *Toxopneustes pileolus* causes histamine release from rat mast cells, whereas contractin A induces contraction of tracheal smooth muscle in guinea pigs [125, 126]. The venom of the Pacific *Tripneustes* urchin contains a neurotoxin that targets facial and cranial nerves [42].

Clinical Presentation and Life-Threatening Complications

Local inflammatory reactions, edema, local sensory loss, or pain are common features shortly following envenomation by sea urchins [127, 128] (Fig. 18). The pain associated with envenomation is moderate to severe in intensity and has been described as burning or aching. Spines may

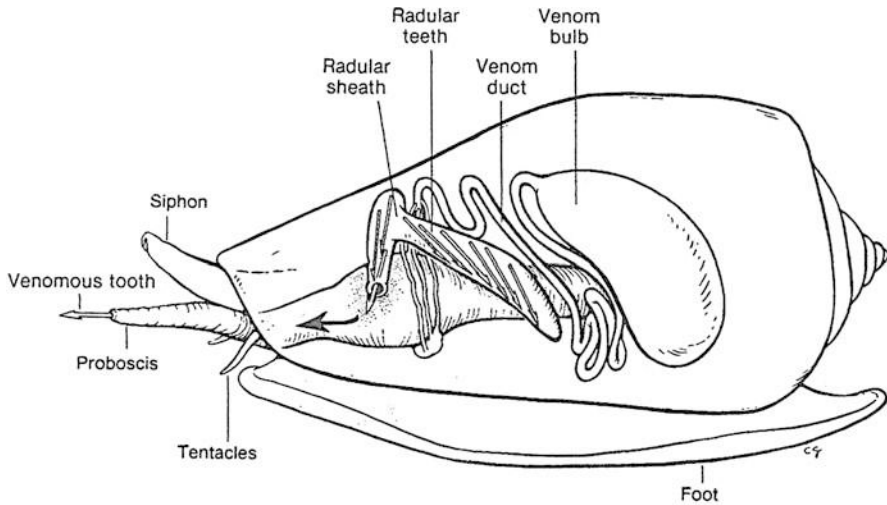
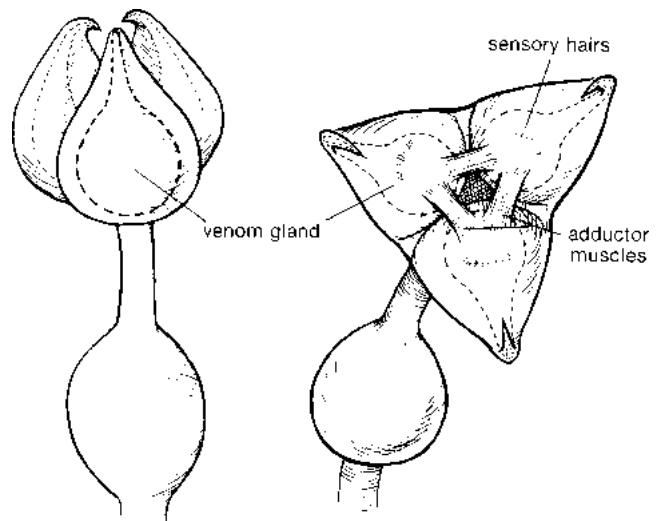


Fig. 17 Venom apparatus of the cone snail. (From Auerbach PS: Envenomation by aquatic invertebrates. In Auerbach PS [ed]: Wilderness Medicine, 4th ed. Philadelphia, Mosby, 2001, p 1481.)

Fig. 18 Globiferous pedicellaria of a sea urchin, used to hold and envenom prey (From Ref. [133], p. 1476)



be visible underneath the skin and those from *Diadema setosum* or *Strongylocentrotus purpuratus* may appear purplish [129]. Systemic features including nausea/vomiting, abdominal pain, paresthesias, muscular paralysis, syncope, delirium, hypotension, and respiratory distress may occur but appear to represent a minority of cases [130]. Osteoarthritis, tenosynovitis, fasciitis, and bursitis were reported in a cases series of envenomations from Reunion Island [131]. Urchin

granulomas may develop months after the injury [132]. Two cases involving multiple stings from a black sea urchin in Hawaii presented with bulbar polyneuritis and respiratory insufficiency 6–10 days after envenomation. One patient developed magnetic resonance imaging-documented meningoencephalitis, whereas the other had signs and symptoms mimicking Guillain-Barré syndrome, with hyporeflexia and elevated cerebrospinal protein levels [71]. Envenomation from the

pedicellariae may cause more severe symptoms and, in addition to severe pain and the systemic features described above, aphonia, hypotension, and death [71].

Diagnosis

There is no specific diagnostic study in the management of sea urchin envenomation. Differential diagnosis would include envenomation from other stinging fish or simple punctures wound from nonvenomous animals, corals. Given the possibility of spine fragmentation, x-rays should be considered for all envenomations. Consider ultrasound, CT or MRI if negative x-rays but strong suspicion for embedded spine.

Treatment

There is no specific therapy or antidote for sea urchin envenomation. Treatment should begin with immediate hot water immersion (nonscalding) for 30–90 min or until anesthesia is achieved (Table 5). Easily reachable spines or pedicellaria should be removed as persistent envenomation may continue. Analgesics, including opiates in severe cases, should be considered. Presumptive wound exploration without evidence of spine fragmentation should be avoided, as spine localization is unlikely. Some species of sea urchins contain a dye that stains tissue and may confuse the practitioner for retained foreign body, though this dye should fade in 36 h.

Surgical consultation, by either an orthopedic, plastic, or general surgeon, is indicated for deeply penetrating spines that are causing persistent pain, synovitis, or are the source for infection. Splinting the affected structure to avoid further fragmentation may be beneficial. There is no consensus on the routine use of prophylactic antibiotics or anti-inflammatories in the management of these injuries. Tetanus prophylaxis should be instituted when applicable (i.e., previously unvaccinated or out of date) (Fig. 19).



Fig. 19 Finger swelling from sea urchin puncture. A single spine entered the palm over the third metacarpal bone. Swelling was severe in the second and third digits (Photo by Paul Auerbach, MD. Courtesy of John Williamson, MD. From Ref. [133], p. 1478)

Intervention	Organism	Level of evidence
Acetic acid 5%	<i>C. fleckeri</i>	III
Stingose	<i>P. physalis</i>	III
Box Jellyfish Antivenom	<i>C. flexeri</i> <i>C. quadrigatus</i>	III
Magnesium sulfate	Carybdeid spp.	III
Hot water immersion	All stinging fish	III
Opiate analgesics	All painful envenomations	III
Stonefish antivenom	Synacea spp.	III
Prophylactic antibiotics	All penetrating envenomations	III
Surgical debridement	All penetrating envenomations	III
Corticosteroids	<i>Physalia</i> spp. <i>L. philippinus</i> <i>A. planci</i> <i>S. maculata</i>	III
Pressure immobilization	Hapalochlaena spp.	III
Edrophonium	<i>C. geographus</i>	III

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Seafood is a common cause of outbreaks of foodborne illnesses. Of these outbreaks, one report described scombroid poisoning as the most frequent [1]. In the United States and Europe combined, scombroid accounts for up to 40% of all reported seafood-borne food-poisoning outbreaks [1].

Scombroid poisoning has been recognized since the late 1700s and was first documented in 1830 [2]. It is also known as histamine fish poisoning because of the concentrations of histamine in fish causing the characteristic signs and symptoms described in this chapter. It is a foodborne illness that occurs in clusters worldwide, most commonly after the ingestion of improperly stored seafood, but has also been reported after the ingestion of cheese [3].

The term “scombroid” originates from the family of fish Scombridae and Scomberesocidae associated with the illness, although poisoning can occur after the ingestion of other types of fish, see Table 1 [5–7]. Scombroid fish are largely oceanic and distributed widely throughout all temperate and tropical seas, and some are found occasionally in Arctic and Antarctic waters (Fig. 1).

Scombroid poisoning has been reported in Europe, Asia, Australia, New Zealand, Africa, Canada, Europe, and the United States. Estimates of the incidence rate of scombroid poisoning in Denmark, New Zealand, France, and Finland range from two to five outbreaks per year per million people. However, in the United States,

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Table 1 Fish implicated in scombroid fish poisoning

Family	Common name	Genus and species
Arripidae	Australian salmon	<i>Arripis trutta</i>
Clupeidae	Pilchard	<i>Sardinops sagax</i>
Clupeidae	Spotted sardines	<i>Amblygaster sirm</i>
Coryphaenidae	Dolphin fish (mahi-mahi)	<i>Coryphaena hippurus</i>
Scomberesocidae	Saury	<i>Cololabis saira</i>
Scombroidae	Frigate mackerel	<i>Auxis thazard</i>
	Little tuna	<i>Euthynnus affinis</i>
	Little tunny	<i>Euthynnus alletteratus</i>
	Skipjack tuna	<i>Euthynnus pelamis</i> or <i>Katsuwonus pelamis</i>
	Striped bonito	<i>Sarda orientalis</i>
	Bonito	<i>Sarda sarda</i>
	Pacific mackerel	<i>Scomber japonicus</i>
	Atlantic mackerel	<i>Scomber scombrus</i>
	King mackerel	<i>Scomberomorus cavalla</i>
	Spanish mackerel	<i>Scomberomorus maculatus</i>
	Cero	<i>Scomberomorus regalis</i>
	Albacore	<i>Thunnus alalunga</i>
	Yellowfin tuna	<i>Thunnus albacares</i>
	Bigeye tuna	<i>Thunnus obesus</i>
	Bluefin tuna	<i>Thunnus thynnus</i>
Xiphiidae	Swordfish	<i>Xiphias gladius</i>

Data from Refs. [3, 4]

Hawaii reports a rate of 31 outbreaks per year per million people [1, 6].

Signs and symptoms of scombroid poisoning are variable in presentation and duration and are similar to other diagnoses such as allergic reactions, potentially leading to underreporting. In developing countries, the most common source of contaminated fish comes from recreational

fishing as opposed to commercially caught fish. This is likely due to inadequate refrigeration, which is more common in the recreational setting than in commercial fishing [6, 8].

In the United States, The Food and Drug Administration (FDA) requires fish importers to develop a plan to prevent spoilage and contamination. Along with the United States Customs and Border Protection, the FDA inspects thousands of seafood shipments annually for safety [9].

Biochemical Basis of Scombroid Poisoning

Fish causing scombroid poisoning contain high concentrations of the amino acid histidine [10]. When these fish are improperly stored, histidine is converted to histamine by bacterial contaminants in the flesh of the fish. This usually occurs when refrigeration is delayed or the fish are kept at or above 70–90 °F [21.1–32.2 °C], although spoilage can occur at lower temperatures (>45 °F [>7.2 °C]) [11].

The conversion of histidine to histamine occurs via bacterial histidine decarboxylase. Bacterial species associated with this enzymatic activity include *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus (Morganella) morganii*, *Serratia marcescens*, *Enterobacter intermedium*, and *Plesiomonas shigelloides* [12]. The skin, gut, and gills of affected fish may be normally colonized with these bacteria, which can overgrow during inadequate refrigeration, or through secondary contamination from fish handlers [13]. Figure 2 shows the pathways of biosynthesis and metabolism of histamine after conversion from histidine [14].

In fish, most histamine is produced in the flesh around the intestines, which then diffuses into other tissues. Concentrations of 5 mg of histamine/100 g of fish are regarded as normal [15]. Mild symptoms of scombroid poisoning may occur at concentrations of 20 mg of histamine/100 g of fish. Severe poisoning is reported after the consumption of fish containing histamine concentrations of more than 100 mg/100 g [16].

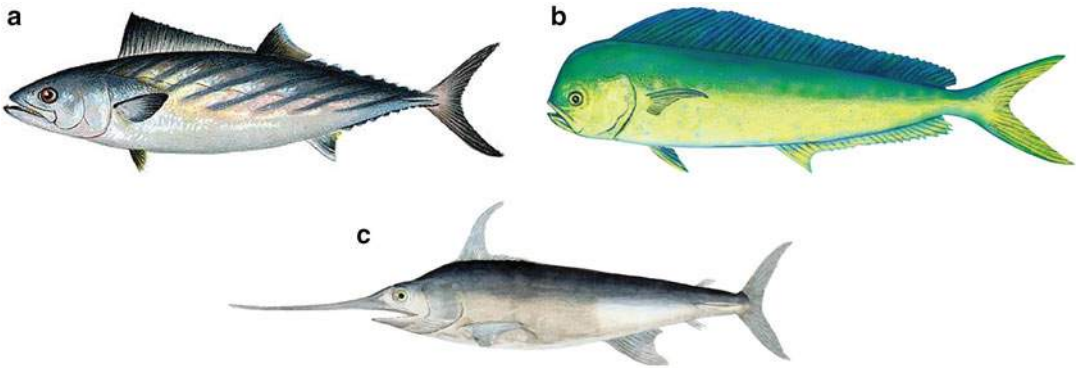


Fig. 1 (a) Bonito; (b) Mahi-Mahi; (c) Swordfish (Adapted from <https://commons.wikimedia.org>)

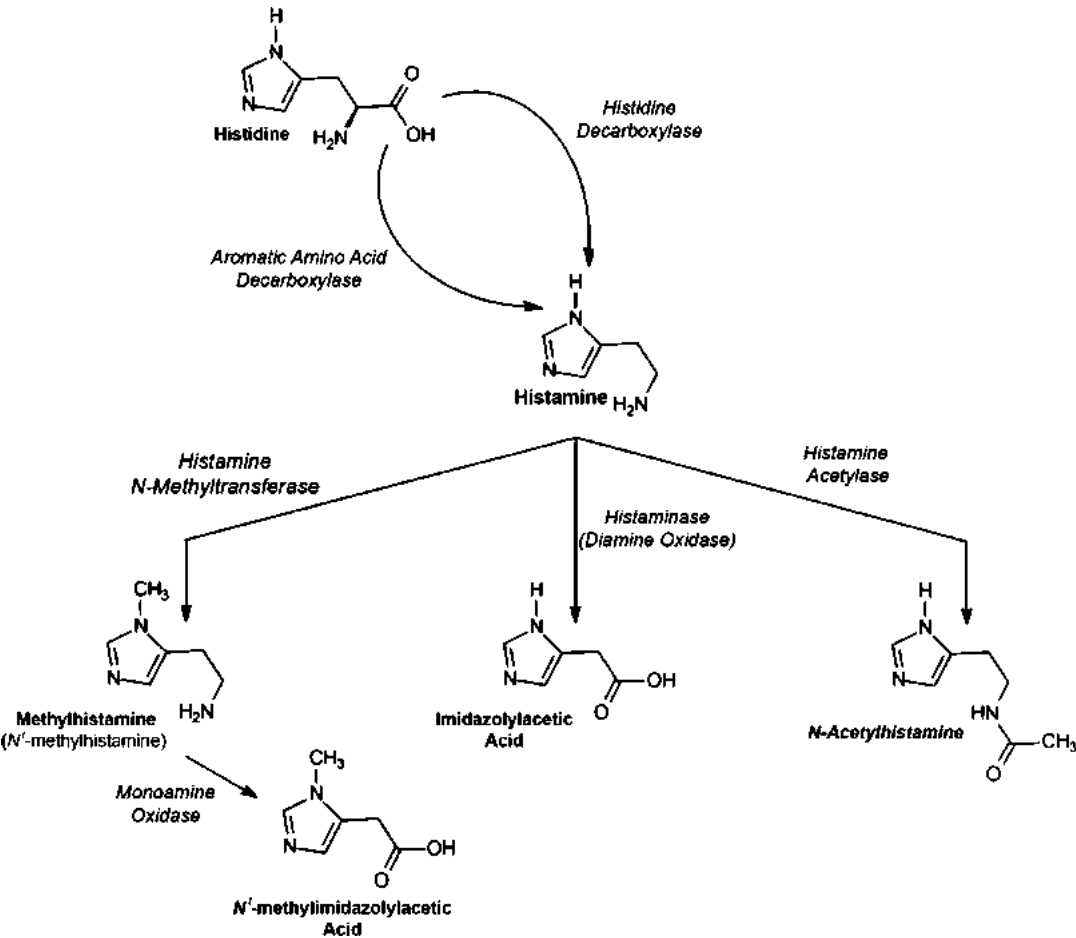


Fig. 2 Biosynthesis and metabolism of histamine

Rapid chilling or refrigeration of fish immediately after catching is the most effective way to prevent histidine-to-histamine conversion. In the United States, government regulations require storing the fish at $\leq 40^{\circ}\text{F}$ ($\leq 4.4^{\circ}\text{C}$). However, more recently there have been bacteria identified with the ability to form histamine at temperatures as low as 32°F (0°C), which could theoretically cause scombroid poisoning [17].

Implicated fish may not have a specific odor or appearance, nor is visible spoilage necessarily evident. Once histamine is formed, it is heat stable and the toxicity of contaminated fish is not reduced or eliminated by cooking.

Pathophysiology

In humans, histamine is a naturally occurring molecule. It is released from mast cells and enterochromaffin-like cells such as basophils, and from neurons as a neurotransmitter. The effects of histamine occur via its actions on histamine receptors (H1–H4) located in the gastrointestinal, respiratory, cardiovascular, nervous and hematologic/immunologic systems, and the skin [8]. Histamine agonism at H1 and H2 receptors causes hives, itching, flushing, and variable effects on the cardiovascular system. On the heart, histamine has positive chronotropic and inotropic effects. Histamine has also been known to be directly arrhythmogenic, which can lead to severe tachyarrhythmias. Its effects on the vascular system include vasodilation and increases in vascular permeability [18–20]. Histamine acts on the respiratory system causing bronchospasm, edema, and inflammation via its direct effects on the H1 receptor. Additionally, histamine mediates mucus secretion in the respiratory system through the H2 receptor [21]. Agonism at H3 receptors causes headache, nausea, and vomiting. Less is known about the role of H4 receptors in scombroid poisoning [5, 22].

There is some controversy as to whether scombroid poisoning is related to ingestion of exogenous histamine alone or simultaneous impairment of histamine metabolism in the consumer.

Interindividual variations in histamine tolerance may also play a role.

Histamine is metabolized by two enzymes in humans. Diamine oxidase (DAO) is directly excreted into the circulation and the gastrointestinal tract making it a major enzyme in catabolizing extracellular histamine. In the cytosol, histamine *N*-methyltransferase (HNMT) catabolyzes intracellular histamine [22].

Individuals with genetically determined reductions in the activity of DAO and HNMT may have a lower histamine tolerance, and along with variation in ingested histamine concentrations, this may explain some of the variable presentations in disease severity [6, 22, 23, 24]. The most common polymorphisms of DAO are Thr16Met, Ser332Phe, and His645Asp. Individuals with the His645Asp polymorphism may have atopic symptoms even without high concentrations of histamine [25]. For HNMT, there have been two polymorphisms described, Ile199Val and Thr105Ile, with the latter being the most common. The Thr105Ile variant of HNMT is associated with reduced thermal stability of the enzyme and decreased HNMT activity [26]. In theory, individuals with this polymorphism should be more susceptible to histamine-mediated symptoms, although studies have a mixed consensus in demonstrating an association between the Thr105Ile polymorphism and the development of histamine-mediated symptoms such as atopy and allergic diseases [26, 27].

Another hypothesized mechanism of scombroid poisoning involves the inhibition of DAO and HNMT [28–30]. In decomposed fish, lysine is decarboxylated to cadaverine, a potent DAO inhibitor [31]. This mechanism of scombroid toxicity is debatable as biogenic amine concentrations, such as cadaverine, are typically insufficient in most decomposed fish to cause inhibition of DAO and HNMT [32]. It has been suggested that the synergy between multiple substances can be enough to inhibit these enzymes and potentiate histamine toxicity [8]. Medications such as isoniazid (a potent inhibitor of DAO) [33] or monoamine oxidase inhibitors and chloroquine (potent inhibitors of HNMT) [29] can inhibit enzymatic activity and thus play a role in potentiating scombroid poisoning.

Another possible mechanism contributing to scombroid toxicity is that an unidentified toxin (“scombrot toxin”) in fish causes mast cell degranulation and histamine release. However, in a study of patients with scombroid poisoning where measured histamine and its metabolites were found to be elevated and prostaglandin-M concentrations were unchanged, suggesting that mast cell degranulation was not the histamine source [34]. Despite evidence against mast cell degranulation, some have suggested a yet-unidentified toxin that causes degranulation of either basophils, mast cells, or both, without the release of prostaglandins [32].

Clinical Presentation

The signs and symptoms of scombroid toxicity usually occur within an hour after the ingestion of a contaminated food source, usually fish [3, 6, 8]. The clinical presentation commonly includes swelling, flushing, and hives, especially to the face, neck, and upper torso. Symptoms such as oral paresthesias, numbness or burning, peppery or metallic taste, abdominal cramping, nausea, vomiting, and diarrhea may be reported. As histamine receptors are distributed throughout the cardiovascular system, tachycardia, palpitations, hypotension, lightheadedness, and, less frequently, dysrhythmias may occur. In severe cases, cardiac dysrhythmias, bronchospasm, respiratory distress, and shock may also occur. These patients present similar to those with severe allergic or anaphylactic reactions.

Elderly patients and individuals with preexisting cardiac or pulmonary diseases may be more vulnerable to the cardiopulmonary effects of scombroid poisoning [35]. Other potential risk factors for more severe and prolonged presentation of scombroid poisoning include those who are taking medications which interfere with histamine metabolism as mentioned above. However, severe presentations of scombroid poisoning are described in otherwise healthy young persons who progressed to hemodynamic instability and cardiogenic shock after initially presenting with mild symptoms [36–39]. In these rare cases, the electrocardiogram demonstrated diffuse ST depressions and elevations along with elevations in cardiac enzyme,

suggesting myocardial ischemia and necrosis. Additionally, an echocardiogram done in one case revealed left ventricular hypokinesis and a severely decreased ejection fraction [37]. Patients who underwent coronary angiography did not show evidence of coronary artery disease, suggesting that the mechanism for myocardial necrosis is secondary to coronary vasospasm [39]. These cases typically evolve within a few hours of presentation.

Signs and symptoms of mild scombroid poisoning are self-limited and usually resolve within 24 h if untreated and within an hour if antihistamines are administered. In severe cases, patients may be symptomatic for up to 48 h [3, 6, 8]. Shock and death have also been reported in the past but not in recent years.

A spectrum of presentations have been described, and these may be classified as mild, moderate, or severe (Table 2) [40].

The clinical presentation of scombroid poisoning may be difficult to distinguish from an allergic reaction to seafood. Retrospective epidemiological data are often the only differentiating factor. In particular, those affected by scombroid poisoning more often present in clusters rather than as isolated individuals. Recognizing clusters may be difficult as not all of these patients will present to the same emergency department and some may not seek care at all. This clinical cue, therefore, may not be readily available unless multiple patients present simultaneously after sharing the same meal. Information on clusters provides useful information to public health departments who can intervene to reduce subsequent exposures.

Diagnosis

There is no definitive diagnostic test for scombroid poisoning. The diagnosis is made based on history and clinical presentation. Scombroid is suggested when the presentation is scombroid poisoning in the setting of ingestion of the typical fish species. As mentioned previously, the presentation of similar symptoms among other individuals who ingested the same food suggests an outbreak. The lack of previous allergies to the implicated fish ingested supports the diagnosis

Table 2 Recommended classification and treatment of scombroid poisoning

Severity	Clinical features	Treatment
Mild poisoning	Rash only or brief flushing; tachycardia	Observe for 2 h
		Consider parenteral antihistamines if condition fails to improve or worsens
Moderate poisoning	Rash and persistent flushing; tachycardia; headache and/or gastrointestinal symptoms	Overnight admission if symptoms slow to resolve
		Basic life support (ABCs, oxygen) IV access
		Parenteral antihistamines (H ₁ and H ₂ antagonists); repeat if necessary
Severe poisoning	Any of the above	Hospital admission
	And/or bronchospasm	Basic life support (ABCs, oxygen) and/or advanced life support
	And/or hypotension	IV fluids
	And/or airway compromise	Epinephrine
	And/or angioedema	Parenteral antihistamine (H ₁ and H ₂ antagonists); repeat as necessary
		Nebulized bronchodilators

Adapted from Ref. [40]

ABCs airway, breathing, and circulation, IV intravenous

of scombroid poisoning, but does not definitively rule out allergic reaction [3].

Once a suspected index case occurs, the source fish may also be tested by some regulatory agencies for tissue histamine concentrations, which is a good indicator of fish spoilage, even when fish are not obviously decomposed. However, identified specimens must be properly stored and frozen prior to analysis to prevent ongoing histamine

production [3]. Regulatory agencies have determined specific values at which a batch or lot of fish may be rejected based on histamine concentrations. In the United States, histamine concentrations in fish found to be at 50 mg/100 g or greater are considered to be potentially hazardous to humans and are rejected prior to coming to market [41]. Suspected culprit fish with histamine concentrations exceeding this threshold suggest the diagnosis of scombroid poisoning. Bacterial counts in suspected fish are not useful because processing the flesh subsequent to spoilage may destroy the responsible organisms. Unfortunately, information on tested source specimens is rarely clinically available, and outbreaks may only be identified retrospectively. Reporting to the local poison control center may facilitate early identification of an outbreak when the diagnosis is presumed or suspected.

Treatment

The treatment of scombroid poisoning is symptomatic and supportive. Although signs and symptoms are self-limited, the use of antihistamines such as H₁ (e.g., diphenhydramine, hydroxyzine or promethazine) and/or H₂ receptor antagonists (e.g., ranitidine or cimetidine) may reduce the severity and duration of the clinical effects [4, 12] (Grade III evidence). The efficacy of cimetidine has been found to be equivalent to or to exceed that achieved with H₁ antagonists alone [12, 42] (Grade III evidence). H₂ antagonists are easy to administer and lack the sedating side effects of H₁ antagonists, reducing delay in hospital discharge [11]. Additional supportive measures can include antiemetics for nausea and intravenous fluids when signs of dehydration are present.

In rare occasions, when individuals present with moderate to severe scombroid poisoning, more aggressive treatments are warranted (e.g., epinephrine and glucocorticoids). In patients with respiratory effects such as bronchospasm or those with preexisting underlying respiratory diseases, β_2 bronchodilators may be indicated.

Those with cardiac complaints or preexisting cardiac diseases should be placed on a cardiac monitor. Progression of clinical signs to more severe presentations require escalation of care, as in the case for anaphylactic shock (e.g., intubation or vasopressors). In cases of moderate to severe presentations of scombroid poisoning, hospital admission or observation may be required. When the diagnosis of scombroid is suspected but overlapping with the potential diagnosis of seafood allergy, it is reasonable to treat specifically for anaphylaxis and discharge stabilized patients with treatments for allergy, including corticosteroids, diphenhydramine, and an epinephrine autoinjector, with instructions to avoid seafood until after appropriate follow-up with an allergist.

When clusters of patients present, in addition to the above therapies, the department of health or local poison control center should be notified.

Indications for ICU Admission in Scombroid Poisoning

- Any patient with underlying cardiac or respiratory disease who is severely symptomatic
- Any patient with severe bronchospasm and respiratory distress which does not promptly resolve
- Any patient in vasodilatory or cardiogenic shock
- Any patient with cardiac dysrhythmias as a result of scombroid poisoning

Criteria for ICU Discharge in Scombroid Poisoning

Discharge is indicated when the severe effects have resolved or have been treated successfully.

- Resolution of
 - Respiratory distress such as tachypnea, wheezing, or stridor
 - Cardiovascular instability
 - Dependence on mechanical ventilation

Special Populations

Scombroid poisoning is usually mild and self-limited. However, certain patient populations are at risk for more severe or prolonged disease. These include the elderly individuals with a history of allergic and atopic diseases (e.g., eczema, asthma), concurrent use of certain drugs that inhibit histamine metabolism (e.g., isoniazid, nonselective monoamine oxidase inhibitors), or those with preexisting cardiac or respiratory diseases [4, 35]. Patients included in these populations should be strongly considered for observation and/or hospital admission.

Scombroid poisoning in pregnancy is unlikely to affect the growth or development of the fetus. There are currently no data to suggest that children are more susceptible to scombroid poisoning, but this may be due to presumption of an allergic reaction as a misdiagnosis in this group.

Common Misconceptions about Scombroid Poisoning

1. It is an allergic reaction.
2. It is due to ingestion of a toxin.
3. It occurs only from scombroid fish.

Key Points in Scombroid Poisoning

1. It is not an allergic reaction.
2. It is caused by ingestion of food, usually fish, containing high concentrations of histidine which is converted to histamine via bacterial conversion.
3. The mechanism of illness may be multifactorial.
4. It may occur with nonscombroid fish and, more rarely, with cheese.
5. Clusters of patients presenting from the ingestion of the same meal increase the likelihood that scombroid poisoning.
6. The onset of symptoms is usually within an hour after ingestion.
7. Most cases are mild and self-limiting, resolving within 2–3 h if antihistamines are given or within 24 h if untreated.

(continued)

8. Signs and symptoms vary; however, common symptoms include flushing, itching, hives, throbbing headache, dizziness, nausea, vomiting, and diarrhea.
9. Respiratory distress or cardiac complications are rare and usually occur in patients with preexisting pulmonary or cardiac disease.
10. Severe symptoms such as shock and acute coronary syndrome have been reported in otherwise young and healthy individuals and generally occur within a few hours of symptom onset.
11. Fatalities are reported.

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Tetrodotoxin (TTX) with a toxicity more than 1000 times greater than sodium cyanide (median lethal dose approximately 10 µg/kg versus 10 mg/kg for sodium cyanide) is one of the most potent marine poisons known [1–3]. It also may be the best known marine toxin, because it is responsible for puffer fish poisoning (fugu or *Tetraodon* poisoning), which has caused many fatalities, particularly in Japan. Although puffer fish poisoning has been associated with a high fatality rate in Japan for centuries, the danger of puffer fish consumption has long been recognized in other countries, including China and Egypt [3, 4]. The first Chinese pharmacopoeia, the *Book of Herbs* (*Pen-T'so Chin*), usually attributed to the legendary Emperor Shun Nung (2838–2698 BC), listed puffer eggs as one of the 120 medium drugs that were believed to have tonic effects but could also be toxic, depending on the dose [3]. A detailed description of the appearance and general toxic properties of a puffer fish (known as “piglet of the river” in Chinese, likely representing *Tetraodon oscellatus*) was given in the most authoritative pharmacopoeia of traditional Chinese medicine, *The Great Herbal* (*Pen-T'so Kang Mu*), by Li Shih-Chen in 1596 AD [3]. A puffer fish identified as *Tetraodon lineatus* is shown on an Egyptian tomb from 2500 BC, and there is evidence that the Egyptians knew the poisonous nature of this fish [4].

Despite biblical admonitions prohibiting the consumption of scaleless fishes [5, 6], Europeans probably were unaware of puffer fish poisoning

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until they began to visit the Orient in the seventeenth century. In his classic work *History of Japan*, published in 1727, Engelbert Kaempfer, a physician to the Dutch embassy in Japan, described the lethality of puffer fish and its use in suicide attempts [3]. Direct and well-documented European experiences of puffer fish poisoning first occurred during the second voyage of Pacific explorer Captain James Cook [1, 3]. In 1774, he and two naturalists, J.R. and G. Forster, on the *Resolution*, experienced various neurologic manifestations after eating a fish traded with a native in New Caledonia. According to his journal record and the Forsters' description of the fish, it is believed that they had been served puffer fish.

Puffer fish are also known as *blowfish*, *swellfish*, *globefish*, *porcupine fish*, *balloonfish*, and *toadfish* because they can take large quantities of water into the stomach when they are frightened or injured and assume an enlarged, globular shape. The skin of puffer fish is distinct because it is smooth or prickly and is covered partially by bristly or hairlike spines. Most puffer fish live in shallow warm waters. Puffer fish belong to the order *Tetraodontiformes*, which includes the families Tetraodontidae, the puffer fish; Diodontidae, the porcupine fish; Canthigasteridae, the sharp-nosed puffer fish; Molidae, the mola or ocean sunfish; Triodontidae, the three-toothed puffer fish; and others. Currently, there are at least 40 species of puffer fish that have been shown to be poisonous, most belonging to the family Tetraodontidae [1, 5]. The term *puffer fish poisoning* has been reserved largely for poisonings caused by ingestions of members of the family Tetraodontidae or, on some occasions, of other aforementioned families. In puffer fish, TTX is found mainly in the liver, ovaries, intestines, and skin [4, 5]. The musculature is usually safer to eat than other parts of the fish (especially when it is prepared by a licensed chef), but for some species (e.g., *Lagocephalus lunaris*), it can also be toxic [7]. The testes almost always are safe to eat, although they can be weakly toxic in certain puffer fish (e.g., *Spheroides niphobles*) [3]. Female puffer fish generally are more toxic than males, and the level of toxicity seems to be related to the reproductive cycle, with the toxicity

increasing from the beginning of the puffer fish season (usually, October through March) and reaching its peak during the spawning season (May and June, for most puffer fish) [3, 5].

In Japan, puffer fish have long been considered an epicurean delight, and it is believed that eating *sashimi*, thin slices of raw puffer fish meat, can give a peculiar tingling oral sensation, sensation of warmth, and euphoria induced by minute amounts of TTX contained in the flesh [5, 6]. For this reason, many Japanese regard eating fugu as a "must-have" experience despite the potentially severe toxicity of the fish. Some Japanese also believe that drinking a mixture of hot sake and fugu testes can contribute to virility and that adding a small amount of puffer fish liver can impart a particularly piquant flavor to certain dishes [1]. All of these eating behaviors may incur various risks of TTX poisoning.

Compared with the frequency of other food poisonings or the amount of fish consumed annually in Japan, the incidence of puffer fish poisoning is small; it is not considered a major public health hazard [3, 8]. Puffer fish poisoning is remarkable, however, for its dramatically severe course and for the multiple deaths that may occur in the same household [3]. Data obtained from the Ministry of Health and Welfare of Japan indicate that the overall case fatality rate of puffer fish poisoning, excluding the 6-year period of 1943–1948, was 59.4% in the period 1886–1963 [5] and was 36.7% in the period 1967–1976 [8]. Puffer fish poisoning accounted for more deaths than all other types of food poisoning combined in Japan [8]. Because of the popularity of eating fugu and the high case fatality rate, legislative controls, such as licensing of chefs in special restaurants requiring them to be knowledgeable regarding the species and seasonal variations in toxicity and education of the public, have been implemented in Japan to prevent puffer fish poisoning. As a result of these efforts and better therapeutic measures, the number of deaths caused by puffer fish poisoning per year declined from more than 100 persons in the late nineteenth and early twentieth centuries to approximately 20 during the period from 1974 to 1979 [3, 4]. Nevertheless, because the cost of the fugu

delicacy is usually high in Japan, people of low socioeconomic status continue to eat puffer fish that is prepared or sold privately by unlicensed peddlers, a behavior that increases the likelihood of poisoning [3, 5]. The statistics in 1957 showed that there were 119 incidents of puffer fish poisoning involving 176 persons [3]. Of these, only two incidents occurred after the eating of fugu in a licensed restaurant, neither of which had a fatal outcome. Of the remaining 174 persons, 90 died. Similar statistics also have been noted in other countries. In an analysis of Taiwan Poison Control Center data over the period 1988–1995, Yang and colleagues [9] found that among 18 incidents of puffer fish poisoning that involved 36 persons, only one victim purchased the fish from a restaurant, whereas the others collected the fish directly from the offshore waters by themselves or purchased them from fishmongers.

Puffer fish have a worldwide distribution and may extend from latitudes 63°N to 47°S. Although many cases have been reported from Japan, poisonings may be encountered wherever these fish are consumed [5]. Poisonings have been reported in many countries other than Japan, including the United States [10–12], Mexico [13], Brazil [14], Australia [15, 16], Europe [17], Papua New Guinea [18], China [5, 19], Taiwan [9, 20], Bangladesh [21], and several other Southeast Asian countries [5, 22–27]. Accidental poisoning due to consumption of mislabeled or improperly processed puffer fish also has occurred in Italy [6] and the United States [11]. Outside of Japan, accurate statistics of puffer fish poisonings generally are not available because reporting this poisoning is not a regulatory requirement [5]. Currently available, albeit incomplete, statistics from Taiwan revealed a case fatality rate of 16.7% for puffer fish poisoning in that country during the period from 1988 to 1995 [8], with an average of 1–2 deaths yearly [9, 20]. In a large outbreak of puffer fish poisoning that involved 141 Bangladesh victims in 2008, the case fatality rate was found to be 12% (17/141) [21].

Although TTX poisoning previously was thought to occur almost exclusively from puffer fish poisoning, more recent evidence has shown that the toxin can also be found in a wide variety

of seemingly unrelated aquatic organisms and amphibians, including the Australian blue-ringed octopus (*Hapalochlaena maculosa*) [28], other blue-ringed octopuses (*Hapalochlaena fasciata*, *Hapalochlaena lunulata*) [29, 30], other gastropod mollusks (Japanese ivory shell [*Babylonia japonica*], trumpet shell [*Charonia sauliae* and *Charonia lampas lampas*], and several species of *Nassariidae*) [5, 17, 31, 32], Indo-Pacific goby (*Gobius criniger*) [33], starfish (*Astropecten latespinosus* and *Astropecten scoparius*) [5, 34], crabs (xanthid crabs [*Atergatis floridus*], *Zoysymus aeneus*, and horseshoe crab [*Carcinoscorpius rotundicauda*]) [5, 35–38], ribbon worms (*Lineus fuscoviridis* and *Tubulanus punctatus*) [39], frogs (*Atelopus chiriquiensis* and *Atelopus varius*) [40], and salamanders and newts (Salamandridae family [true newts], e.g., true salamander [*Cynops ensicauda*], Oregon newt [*Taricha granulosa*], and California newt [*Taricha torosa*]) [5, 41–43]. Human cases of TTX poisoning have also been reported after the ingestion of goby fish [5, 9, 44, 45], gastropod mollusks [32], trumpet shell [17], blue-ringed octopus [29], and salamanders [46, 47] and after being bitten by a blue-ringed octopus [48–50]. Among these species, the finding of TTX in salamanders and blue-ringed octopuses merits further discussion.

In 1932, Twitty serendipitously found that the larvae of striped salamanders (*Ambystoma tigrinum*) became paralyzed after receiving grafted eye and limb buds from embryos of the California newt (*T. torosa*) [1]. No further extensive studies of the compound were carried out until the 1960s. In 1962, a potent nonprotein toxin, of which 1 mg was capable of killing 7000 mice, was crystallized and was named *tarichatoxin*. To the investigators' astonishment, it was found later that tarichatoxin and TTX were identical in their infrared and nuclear magnetic resonance spectra and in their characteristics in various chromatographic systems. Newts did not become intoxicated after exposure to TTX. It is apparent that the two biologically different species – puffer fish and newts – contain the same toxin.

The isolation of TTX from the posterior salivary gland of the blue-ringed octopus

Hapalochlaena maculosa was the first instance that TTX was found in extracts of the venom glands, in contrast to the identification of toxin in the skin, muscle, liver, ovaries, or eggs in other species [28]. The chemistry and pharmacology of extracts of *Hapalochlaena maculosa* were investigated after the occurrence of several human envenoming cases, including two fatalities, in Australia [47, 48]. The principal toxin present in the venom glands was found to be a neurotoxin, which initially was named *maculotoxin*. Although it is now believed that toxic components other than maculotoxin are also present in octopus venom (e.g., haplo toxin, histamine) [5, 50], there is little doubt that maculotoxin is TTX [28, 50]. Recently, TTX was found to be present in all body parts of *Hapalochlaena maculosa*, including high concentrations of TTX in the arms [51].

In addition to *Hapalochlaena maculosa*, a blue-ringed octopus-related TTX food poisoning incident occurred in Taiwan in 2010. After detailed toxin analysis and gene sequencing, the culprit octopus was identified as *Hapalochlaena fasciata* [29]. The authors did not report which body parts of *Hapalochlaena fasciata* contained TTX. However, TTX had previously been found in many body parts of *Hapalochlaena fasciata*, including the posterior salivary gland, arms, mantle, anterior salivary gland, digestive gland, testes contents, oviducal gland, and nephridia [30].

The origin of TTX remains a mystery. The erratic distribution of TTX in widely different species suggests that the toxin is acquired through the food chain as a consequence of consuming toxic marine algae. Evidence supporting this hypothesis has come from the discovery of a TTX-producing *Pseudomonas* species isolated from a red alga *Jania* [5, 52] and the skin of puffer fish [53], the observed difference in toxicity between cultured and wild puffer fish [8, 54], the documented transmission of TTX from one fish to the next in a feeding experiment [5], and the regional variation in toxicity of puffer fish [5]. Some investigators proposed, however, that the ability to synthesize TTX in various marine organisms and amphibians may be simply a coincidental genetic development because of its

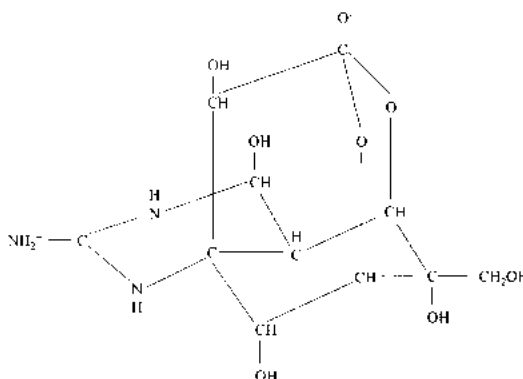


Fig. 1 Chemical structure of tetrodotoxin

survival value [40]. The finding of unique exocrine glands for the secretion of TTX in puffer fish supports the possibility that puffer fish may actively produce the toxin [55].

Biochemistry and Pharmacology

In the 1950s, Yokoo and Tsuda independently crystallized TTX in a relatively pure form [1, 5]. TTX is an amino perhydroquinazoline compound with an empirical formula of $C_{11}H_{17}N_3O_8$ (Fig. 1) and a molecular weight of 319 g/mol [1, 3, 5]. It forms a colorless crystal and is a monoacidic base with a pK_a of 8.5 in aqueous solution [3]. It is soluble in water if a trace of acid is added but readily decomposes in strongly acidic or alkaline conditions [1, 3, 5, 56, 57]. The toxicity of TTX reportedly has been destroyed by the action of 2% sodium hydroxide treatment for 90 min [5]. Because TTX is a nonprotein toxin, it is relatively heat stable; frying, stewing, baking, or boiling for hours does not destroy the toxin [5]. Storage at -15°C for 12 h or exposure to sunlight for 20 days also does not change its activity [5]. Commercial canning processes do not significantly reduce the lethality of the toxin. In contrast to its heat stability, TTX is found to lose its activity markedly even after minor alterations of its chemical structure [2].

Although TTX is one of the most potent marine toxins, little is known about its mode of action. Current evidence indicates that TTX abolishes

propagated action potentials through its selective blockade of voltage-gated neuronal sodium channels [1–3, 5]. In some animal experiments, TTX has also been shown to reduce the production of acetylcholine [58, 59] and to depress cytochrome oxidase and acetylcholinesterase at high concentrations [5]. There is no universal agreement, however, on whether the toxin acts on cytochrome oxidase [3]; in most experiments, the toxin does not inhibit, or only slightly affects, acetylcholinesterase, even in high concentrations [59–62].

Pharmacokinetics of Tetrodotoxin Poisoning

Volume of distribution: widely distributed; more specific data not available

Protein binding: low; specific data not available

Mechanism of clearance: renal

Active metabolites: none

Methods to enhance clearance: none

Pathophysiology

The main pharmacologic effect of TTX appears to be blockade of the propagation of nerve and muscle action potentials by a nondepolarizing blockade of sodium channels [2, 3, 5, 57]. As a consequence, the neuromuscular effects are prominent, and rapidly progressive skeletal muscle paralysis, including muscles associated with respiratory function, is characteristic of TTX poisoning. Although TTX primarily inhibits the transmission of nerve impulses, it also has a direct action on skeletal muscle. This blockade of neuromuscular transmission generally is believed to occur on motor nerve axons and on muscle fiber membranes, rather than at the motor end plates [3, 60, 63]. After administration, the time required to inhibit muscle fiber function is usually longer than that for nerve block, except in the case of diaphragmatic muscle involvement [3, 63]. Slow muscle fibers are more susceptible to TTX than are fast fibers. Because TTX generally does not act on the motor end plate, the administration of anticholinesterase drugs, such as neostigmine or

edrophonium, is not likely to antagonize TTX-induced neuromuscular blockade effectively [3]. The axonal blockade caused by TTX is not limited to somatic motor nerves, and disturbance of sensory nerve function is frequently seen in the early phases of poisoning [3, 5]. TTX is approximately 160,000 times more potent than cocaine in blocking axonal conduction in sensory neurons [5].

Respiratory depression is the most prominent and serious toxic effect of TTX poisoning and is usually the cause of death among TTX-poisoned patients [3, 5, 63, 64]. Despite considerable controversy over how TTX produces respiratory paralysis, and the belief of some investigators that depression of the medullary respiratory center is responsible for respiratory arrest [5, 64, 65], more recent work has shown conclusively that TTX causes respiratory depression predominantly through direct paralysis of the diaphragmatic muscles [3, 57, 63]. The respiratory musculature is extraordinarily sensitive to TTX, and low doses of TTX (4% of the lethal dose) can depress respiration markedly in experimental animals [3]. Respiratory muscles may be more vulnerable to TTX than other skeletal muscles, or the phrenic nerve, because of their greater blood supply, resulting in a more rapid and proportionately greater distribution of toxin to the diaphragm [63]. Although central depressant effects are unlikely to be important in most instances of TTX poisoning, their role in the terminal stage of severe TTX poisoning, or after rapid intravenous administration of the toxin, cannot be dismissed [3, 57, 63]. Besides the inhibition of the respiratory musculature, TTX also causes depression of the cough reflex and relaxes bronchial smooth muscles [3].

Profound hypotension is a characteristic manifestation of TTX poisoning, which may or may not be associated with bradycardia [3, 62]. Hypotension has been noted as a cause of death in certain animal TTX poisonings [50]. Although a central vasomotor depressant effect previously was thought by many Japanese investigators to be the mechanism of TTX-induced hypotension [3, 5], the experimental evidence supporting this view was weak and unconvincing [3, 57]. Kao [2, 3],

in a series of head-body cross-perfusion experiments, showed that hypotension did not develop in the recipient's body when TTX, in a dose large enough to cause hypotension in the donor, was administered to the recipient's head via the donor's circulation. In other studies, the decrease in blood pressure was not accompanied by slowed heart rate or decreased cardiac output, which suggests that hypotension is attributable to direct peripheral vasodilation by TTX, rather than to cardiac depression [60, 64]. Large doses of TTX cause prolonged cardiac depression [2, 3, 62, 66] or conduction disturbances (e.g., bradycardia) [60, 66]; however, hypotension occurs before the cardiac depression at such doses [57, 66].

Most investigators now agree that TTX-induced hypotension is caused primarily by decreased peripheral vascular resistance rather than affecting the heart or the vasomotor center [2, 3, 57, 66], but the exact mechanism for this vasodilation is unclear. Some investigators believe that TTX causes hypotension by blocking sympathetic vasomotor nerves, causing relaxation of vascular smooth muscles [3, 57, 66]; others propose that TTX also has a direct effect on arterial smooth muscles [2, 67]. Kao [2] showed that the systemic hypotension seems to be due to a combination of a direct relaxant effect of TTX on vascular smooth muscle at low doses and blockade of vasomotor nerve conduction at high doses. Li [64] found that the TTX-related vasodilatory action had a histamine-like component because pretreatment with an antihistamine prevented the decrease in blood pressure caused by a sublethal dose of the toxin.

The effect of TTX on blood pressure seems to be dose dependent. In dogs, Nomiyama [5] found that small doses of puffer fish toxin produced an initial increase in blood pressure and heart rate followed by a decrease in blood pressure, whereas large doses produced immediate hypotension followed by a gradual increase in heart rate. Duce and colleagues [68] noted that nonlethal doses of TTX (0.6–2.4 $\mu\text{g/kg}$) resulted in an increase in heart rate and mean arterial blood pressure in unanesthetized dogs; higher concentrations of TTX caused moderate hypotension, apnea, and death. These investigators also

reported that TTX produced persistent hypotension and bradycardia in all anesthetized dogs and suggested that the difference between unanesthetized and anesthetized animals may be attributable to an indirect effect of TTX on the activation of the sympathetic nervous system or on a reduction in vagal tone. Hypertension has been noted in some human cases of TTX poisoning; almost all of them were of mild severity [9, 11, 20, 32]. It seems likely that, in nonlethal TTX poisoning, hypertension can be caused by an exaggerated reaction to sympathetic stimuli.

The primary systemic action of TTX is to block nerve conduction. Although TTX acts primarily on peripheral nerves, it can also cause central nervous system effects in sufficient doses. As previously mentioned, TTX may exert effects on medullary respiratory and vasomotor centers. TTX is also known to induce vomiting, a frequent manifestation of TTX poisoning [3, 5]. Because surgical ablation of the medullary chemotrigger receptor zone in dogs and cats abolishes this emetic action, vomiting seems to represent a central action of TTX [3, 69]. Nicotinic antagonism by TTX also has been suggested to be responsible for vomiting because tetraethylammonium (a nicotinic agonist), but not chlorpromazine or hexamethonium (a nicotinic antagonist), prevented the emetic action [5, 69].

In experimental animals, TTX causes a sustained decrease in rectal temperature [3, 65, 68], but little is known about the mechanism of this action. Anecdotal reports also suggested that TTX might have a central narcotic or sedative effect; and TTX subsequently has been used as a sedative in the treatment of opioid addiction [5]. Nevertheless, currently available data about the efficacy of TTX in the treatment of this addiction are inconclusive. Paralysis of the motor and sensory components of the spinal cord and indirect central actions of TTX, such as hypoxia-related convulsions, are among the other central nervous system manifestations that have been reported in TTX poisonings [5].

TTX blocks the neurally elicited responses of the autonomic nervous system [3, 5, 60] and may cause a decrease in gastric secretory volume, mydriasis, salivation, and hyperglycemia [5]. It

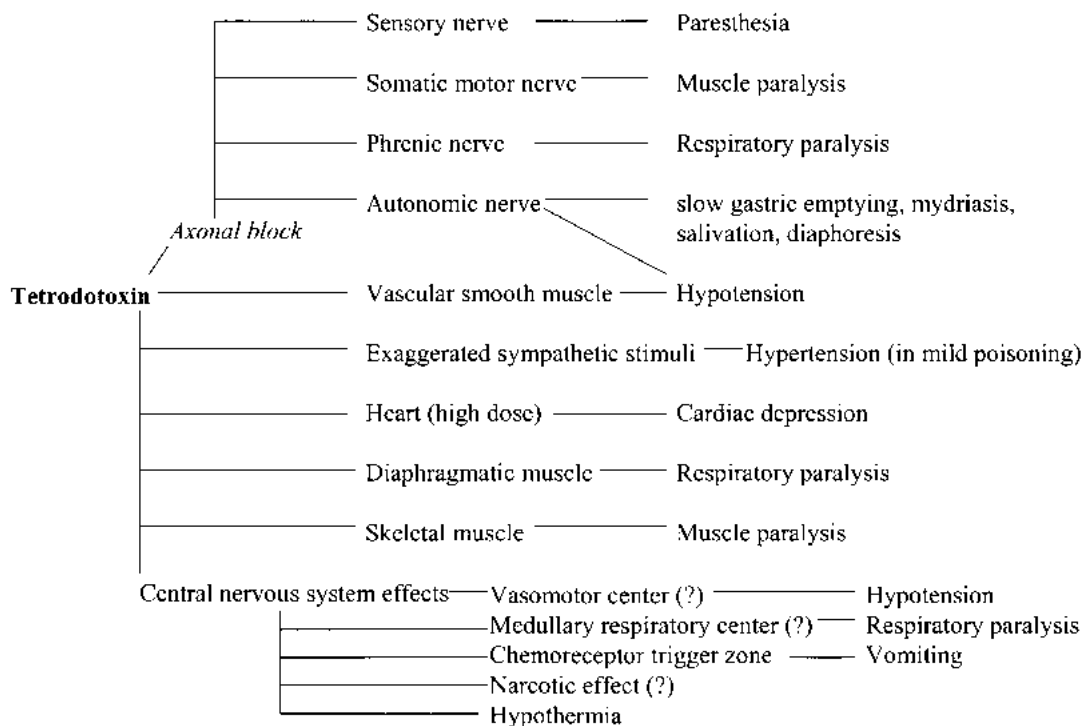


Fig. 2 Pathophysiology of tetrodotoxin poisoning

has been suggested that TTX may cause a pathologic state that is similar to the pathologic states of organophosphate or carbamate insecticide poisonings [70]. These toxic effects are not consistently observed, however, in animal or human TTX poisonings. Moreover, the autonomic nerves seem to be more resistant to the effects of the toxin than are the somatic nerves [5]. It also has been suggested that parasympathetic nerves are blocked by TTX before the sympathetic nerves [5] and that the postganglionic nerves are affected less severely than are the preganglionic cholinergic nerves [60]. Although TTX does affect autonomic nerves and probably vascular smooth muscle as well, it is unclear whether it has any direct effects on other smooth muscle or autonomic effector cells.

Few data regarding the pathology of human TTX poisoning are available. In reported cases [5, 8, 12, 20, 46], fatalities caused by TTX poisoning have been characterized by pulmonary edema and generalized congestion of the viscera. Localized changes in the gastric mucosa also have

been noted occasionally. There are no reported human neuropathologic alterations based on autopsy findings, although significant changes have been observed in experimental animals [5]. Figure 2 summarizes the pathophysiology of TTX poisoning.

Impure TTX was used widely as an analgesic in Japan in the early twentieth century [1]. Currently, there is no clinical utility for TTX in any practice because its anesthetic properties are generally attained only with near-lethal doses [5].

Clinical Presentation

There have been numerous reports of human TTX poisoning [5, 8–12, 14–27, 29, 30, 37, 44–49, 71, 72], and most humans were poisoned by ingesting puffer fish. Typically, symptoms begin within 10–45 min of ingestion, because TTX is absorbed rapidly from the gastrointestinal tract; [3] however, this may be delayed for 3 or more hours [5,

10, 15]. TTX poisoning usually manifests first with a tingling sensation involving the tongue and inner surface of the mouth and throat [5, 7, 9, 11, 12]. General malaise, pallor, dizziness, headache, ataxia, constricted pupils, nausea, vomiting, and sweating are also likely to be present early [5, 9, 11, 15]. Paresthesias subsequently may involve the fingers and toes and spread to other parts of the limbs [5]. In more severe poisonings, marked limb numbness, hypotension, cardiac dysrhythmias, dyspnea, and generalized weakness may develop, followed by respiratory paralysis, fixed and dilated pupils, and convulsions over the ensuing 4–24 h [5, 7, 9, 11]. Patients with severe TTX poisoning may become or look comatose, yet in most instances, their sensorium is intact [5, 15, 18]. Death in TTX poisoning generally occurs within the first 6–24 h [5, 7, 11, 15] and is usually the result of progressive respiratory paralysis [1, 5, 7, 9, 12, 21]. Less frequently, death may result from profound hypotension [1, 5] or other complications, such as hypertensive congestive heart failure among hypertensive patients [20] or aspiration pneumonia [30]. Death occurring as quickly as 17 min after TTX poisoning has been reported [3].

The onset and types of signs and symptoms of TTX poisoning can be diverse because they depend on the individual and the amount of toxin consumed [5, 7, 9]. Toxic features that have been reported are as follows:

1. *Neuromuscular*: [5, 9–12, 14–16, 18–21, 23, 25, 29, 32, 37, 44–46, 48, 71–73] circumoral numbness, paresthesia of phalanges and extremities, constrictive sensation of throat, dry mouth, floating sensation, generalized paresthesia, extreme weakness with walking difficulty, muscle twitching, tremor, incoordination, extensive limb paralysis, aphonia, dysarthria, dysphagia, backache
2. *Cardiovascular/pulmonary*: [5, 9–12, 14–16, 18–23, 25, 29, 32, 37, 44, 48, 71–73] hypotension, rapid and weak pulse, hypertension, cardiac dysrhythmias (sinus bradycardia, tachycardia, conduction block, asystole), chest tightness/pain, cyanosis, pallor, chilliness, facial flush, dyspnea, tachypnea, shallow respiration, aspiration pneumonia, acute pulmonary edema, acute respiratory failure, sudden death
3. *Central nervous system (direct or indirect effects)*: [5, 8–11, 14–16, 18–23, 25, 29, 32, 37, 44–46, 71–74] dizziness, vertigo, headache, drowsiness, lethargy, anxiety, transient/prolonged ataxia, blurred vision, hyporeflexia/areflexia, muscle fasciculation, convulsion, peculiar taste sensation, cranial nerve palsy, hypothermia, diabetes insipidus, reversible locked-in syndrome, coma
4. *Autonomic*: [5, 9, 10, 12, 14–16, 18, 19, 21, 32, 37, 44, 71–73] diaphoresis, initial miosis followed by mydriasis (or, rarely, prolonged constricted pupils), irregular pupils, reflex change of pupils, hypersalivation, urinary incontinence, bronchorrhea
5. *Peripheral sensorimotor nerve functions*: [5, 9, 16, 18, 71] diffuse reduction of conduction velocities and amplitudes of sensory and motor nerve action potentials in nerve conduction studies
6. *Gastrointestinal*: [5, 8–12, 14, 15, 19, 21–23, 29, 32, 37, 44, 46, 48, 71–73] nausea, vomiting, retching, hyperemesis, hematemesis, increased/decreased gastrointestinal motility, diarrhea, epigastric/abdominal pain
7. *Dermatologic (rare)*: [5, 73] exfoliative dermatitis, petechiae, blister, itching
8. *Miscellaneous*: [5, 9, 10, 16, 17, 19, 25, 44, 73] delayed coagulation of blood, hypokalemia, hypocalcemia, elevated hepatic transaminase levels, hyperglycemia, leukocytosis

Anecdotal reports also suggested that TTX might cause a “living dead” phenomenon; two patients recovered hours or days after they were pronounced dead in the late nineteenth century [5]. It is unclear, however, how the “death” diagnoses in these two patients were made and whether they were confirmed by any objective tests. TTX has been found in some voodoo potions used to transform a person into a creature of living death (zombie) of Haitian folklore

Table 1 Severity classification of tetrodotoxin poisoning

Degree of poisoning	Clinical manifestations
First degree	Oral paresthesia with or without gastrointestinal symptoms (e.g., vomiting)
Second degree	Advanced paresthesia and limb paralysis with intact reflexes
Third degree	Presence of gross muscular incoordination, dysphonia, dysphagia, respiratory depression, chest pain, cyanosis, and hypotension, with clear consciousness
Fourth degree	Coma, respiratory paralysis, and severe hypotension, followed by cardiac arrest in the absence of prompt treatment

Data from Fukuda and Tani (1941) [88]

[75, 76]; however, its role in zombification is questionable [77].

In 1941, Fukuda and Tani proposed a severity measure of TTX poisoning (Table 1) [5]. This scoring system is still used today.

Diagnosis

The diagnosis of TTX poisoning is based largely on clinical manifestations (i.e., the presence of typical neurologic manifestations, such as paresthesia and motor paralysis) and a history of exposure to puffer fish or other TTX-containing organisms. An accurate exposure history may not be available, however, and the clinical presentations of TTX poisoning may be atypical.

Some TTX-containing organisms also possess toxins other than TTX (e.g., saxitoxin) [5, 31, 36, 38, 49, 73, 78–80]. It is important to formulate a careful differential diagnosis that includes other neurotoxic exposures and nontoxic acute paralytic disorders. Among various marine poisonings, paralytic shellfish poisoning (saxitoxin) and ciguatera poisoning (ciguatoxin) are least likely to be distinguished from TTX poisoning based on clinical manifestations [6]. An accurate and detailed history is crucial because the species harboring these other neurotoxins are usually different from TTX-containing organisms [73]. A complete

physical examination, including a thorough neurologic examination, and electrophysiologic studies are helpful in making the final diagnosis of TTX poisoning; routine laboratory tests are not useful. TTX poisoning should be differentiated from anticholinesterase poisonings, such as those caused by organophosphate or carbamate pesticides or nerve agents. The differential diagnosis is unlikely to be difficult because TTX does not significantly affect cholinesterases [59–62], and cholinergic features are usually minor and transient in TTX poisoning.

The definitive diagnosis of TTX poisoning relies on the detection of TTX in poisoned patients or in the incriminating poisoning source. Specific methods for detecting TTX (e.g., gas chromatography–mass spectrometry, liquid chromatography coupled with tandem mass spectrometry) have been developed [8, 71, 78, 81]. The procedures are usually complicated, however, and the assay is not routinely available in most healthcare facilities. The clinical utility of these assays is therefore limited. More commonly, bioassay methods can be used to determine the toxicity of a suspected TTX source. These methods are reasonably specific when properly performed [3]. A commonly employed method involves the injection of dilute crude toxin intraperitoneally into mice. The toxicity is expressed semiquantitatively in mouse units (MU) per gram of specimen [3, 8, 9], and 1 MU (1 MU = 0.178 µg TTX) [29] is defined as the amount of toxin that kills a 20-g mouse in a standard period of time. It has been said that 200,000 MU of toxicity is the minimal lethal dose for humans [8, 20, 32], yet deaths after ingestion of lower doses of TTX have been reported [20, 32]. Although these bioassay methods can be performed easily, they are unlikely to be helpful in the early management of TTX-poisoned patients because they are generally unavailable in acute-care settings. Nevertheless, these methods can serve as a useful tool in confirming the diagnosis, especially when the exposure history is unclear or there is uncertainty about the incriminating source (e.g., in cases of mixed ingestion of various seafoods). Repeated exposure to TTX does not produce immunity.

Treatment

Indications for ICU Admission in Tetrodotoxin Poisoning

Respiratory paralysis or marked respiratory depression (i.e., difficulty in dealing with saliva or bronchial secretions, increasing dyspnea, rising respiratory rate, or worsening arterial blood gases)

Hypotension with impaired perfusion (e.g., oliguria, abnormal renal function, shock)

Symptomatic or significant cardiac dysrhythmia or conductive disturbance

Extensive neurologic dysfunction (e.g., coma, areflexia, fixed and dilated pupils)

Seizures

Other life-threatening complications (e.g., congestive heart failure, severe aspiration pneumonia)

There is no specific antidote for TTX poisoning [5, 57]. Treatment is mainly symptomatic and supportive. After exposure to TTX, rapid removal of unabsorbed toxin is theoretically important. If spontaneous vomiting does not occur, an emetic (often apomorphine) [5, 10] frequently is given, provided that there is no risk of aspiration [5, 6, 15]. This practice has not been shown to improve outcome, however, or alter the clinical course. Induction of emesis should be considered to be contraindicated because of an increased risk of aspiration. Gastric lavage may be used shortly after TTX poisoning (1–3 h; Level III evidence) [5, 10, 14, 15] in an attempt to remove toxin still in the stomach. This technique also has not been shown to improve outcome or affect the patient's clinical course. Although it is uncertain whether gastric lavage would be effective, theoretically it may remove some toxin even more than 3 h after ingestion because TTX can slow gastric emptying [5]. Therefore, the benefits of gastric lavage probably outweigh its risks among patients with TTX poisoning who present to the emergency department within one to three hours postexposure provided that airway protection is secured. Because

TTX is less stable in an alkaline environment, Sims and Ostman [10] suggested the use of 2% sodium bicarbonate solution (Level III evidence) in gastric lavage. The efficacy of this intervention is unproven, however. Activated charcoal is reportedly effective in early TTX poisoning (Level III evidence) [9, 10]. Some investigators even recommend endoscopy as a measure to remove the ingested toxin (Level III evidence) [44, 82].

After the occurrence of systemic manifestations, treatment should be aimed at the maintenance of adequate ventilation and circulation because respiratory arrest and profound hypotension are the two major causes of death [5, 15]. Supplemental oxygen is indicated in patients with hypoxia, hypoventilation, or respiratory distress (Level III evidence). Early endotracheal intubation and mechanical ventilation, which are potentially lifesaving interventions (Level III evidence) [9, 25], are indicated in patients with difficulty handling saliva or respiratory secretions, increasing dyspnea, hypoventilation or hyperventilation, or worsening arterial blood gases [5, 15]. Because patients usually are conscious, a full explanation of all procedures and sedation should be provided if intubation is necessary [15]. Tracheostomy is not necessary because recovery from TTX poisoning is usually rapid and complete within 24 h [5]. Antibiotics may be required in patients whose clinical courses are complicated by aspiration pneumonia [9, 23].

In patients with hypotension, fluid resuscitation should be given as indicated based on arterial blood pressure, urinary output, cardiac output, systemic vascular resistance, or central venous pressure [5, 15]. Vasopressor agents, inotropic agents, or both also may be required to alleviate hypotension if cardiac output, systemic vascular resistance, or both decrease or if central venous pressure increases without restoration of urine output. A target urine output of equal to or greater than 40 mL/h has been suggested (Level III evidence) [5]. Maintenance of a brisk production of urine is theoretically important in speeding recovery because TTX is eliminated mainly unchanged by the kidney within a few hours of ingestion [3, 57].

Among various inotropic agents, it has been shown in experimental animals that amphetamine, phenylephrine, and norepinephrine are the most effective in treating hypotensive effects of TTX, possibly due to their ability to stimulate directly or indirectly postsynaptic α -adrenergic receptors [51]. Epinephrine, probably because of its predominantly β -adrenergic effects, is less effective or in some instances detrimental [5, 51]. It is unclear whether these observations can be applied to human TTX poisonings. Some investigators have suggested the use of dopamine as the first-line inotropic agent (Level III evidence) [10]. Atropine can be given to patients with bradycardia, but its efficacy is controversial [10, 15, 16, 62]. Because bradycardia is rarely a serious problem in TTX poisoning, atropine is not routinely necessary. The electrocardiogram should be monitored continuously for cardiac dysrhythmias, however, and a temporary pacemaker may have to be inserted in cases of severe conduction disturbance (Level III evidence) [5, 15].

Hypertension in TTX poisoning is usually mild and transient [9] but may require treatment with antihypertensive medications in severe cases or in patients with preexisting hypertension [20]. Because of the possibility of the patient's progression from hypertension to hypotension, only short-acting antihypertensive agents, such as sodium nitroprusside, should be used (Level III evidence).

Several experimental therapeutic modalities have been suggested in the management of human TTX poisoning but their roles are controversial, and none has been scrutinized by large-scale prospective clinical studies [10, 19]. Anticholinesterase drugs (e.g., edrophonium and neostigmine), which can increase the concentration of acetylcholine at the neuromuscular junction, have been shown to be promising in some reports [15, 25] but not in others [3, 5, 9, 16]. Because TTX probably does not act on the motor end plate until its concentration reaches a high level [83], anticholinesterase drugs are not likely to be useful treatments [3]. In a recent systematic review of 23 case series and 14 case reports that provided some information

regarding the use of neostigmine in severe pufferfish-associated TTX poisoning, Liu and colleagues also concluded that the current literature was insufficient to provide an evidence base for or against the use of neostigmine in adults with TTX-associated respiratory failure (Level III evidence) [84].

Cysteine has been claimed to be potentially effective in the management of TTX poisoning [5, 10], and several possible mechanisms have been proposed [19]. Nevertheless, its benefit in human poisonings has not been documented. Other possible, yet unproven, therapeutic strategies for TTX poisoning are antihistamines, steroids, naloxone, veratrine-like agents, calcium, and hyperbaric oxygenation [5, 6, 19, 26, 73]. Antiserum and monoclonal antibodies against TTX have been developed and tested successfully in experimental animals [85–87], but their role in human TTX poisoning needs further research.

Hemodialysis instituted 21 h after TTX poisoning was reported to be effective in a uremic patient with profound neurologic dysfunction [45]. It is not clear, however, whether the relationship of this intervention to clinical outcome was more than a coincidence. TTX is only slightly water soluble under normal circumstances [3, 5, 57], and hemodialysis may not be an effective treatment. TTX has a low molecular weight and is minimally protein bound, however, which are properties often found in toxins amenable to hemodialysis. Despite these considerations, the short course of TTX poisoning and the effectiveness of mechanical ventilation and supportive measures undermine the potential benefits of hemodialysis.

The prognosis of TTX poisoning is usually favorable if adequate supportive measures can be instituted before cardiopulmonary arrest occurs. Because TTX can cause coma, areflexia, dilated pupils, or other signs of extensive brain damage early in the course of poisoning, resuscitation should not be abandoned prematurely even in the presence of the above-noted signs [16, 22]. If a patient survives beyond 24 h, the recovery is likely to be complete unless complicated by other life-threatening conditions [5, 6, 9, 15, 19].

Criteria for ICU Discharge in Tetrodotoxin Poisoning

Successful weaning from ventilatory support
 Normal blood pressure in the absence of inotropic agents
 Adequate control of life-threatening complications

Common Misconceptions About Tetrodotoxin Poisoning

1. Tetrodotoxin is found only in puffer fish.
2. The musculature of puffer fish is always safe to eat.
3. It is not difficult to differentiate between poisonous and edible puffer fish.
4. A puffer fish that was previously safe to eat is always nontoxic.
5. Puffer fish or other tetrodotoxin-containing organisms contain only tetrodotoxin.
6. Tetrodotoxin has a major effect on the acetylcholine-cholinesterase system.
7. Tetrodotoxin causes respiratory depression and hypotension mainly through its central depressant effects.
8. Tetrodotoxin poisoning always manifests hypotension.
9. The presence of extensive neurologic dysfunction in a patient with tetrodotoxin poisoning often indicates severe hypoxic brain damage, and aggressive resuscitation is unnecessary.

5. In puffer fish, tetrodotoxin is found mainly in the liver, ovaries, intestines, and skin.
6. The toxicity of puffer fish varies according to sex, species, season of the year, geographic locality, and organ of the animals.
7. The main pharmacologic mechanism of tetrodotoxin is to block the propagation of nerve action potentials by nondepolarizing blockade through its selective inhibition on the sodium channel.
8. Tetrodotoxin mainly affects the neuromuscular system, especially respiratory muscles.
9. Respiratory depression and hypotension are the two characteristic manifestations and the leading causes of death from tetrodotoxin poisoning.
10. Tetrodotoxin poisoning is not common; however, it has high mortality if proper treatment is not instituted promptly.
11. The treatment of tetrodotoxin poisoning is largely symptomatic and supportive. Treatment should be aimed primarily at the maintenance of adequate ventilation and circulation.
12. If a patient survives the first 24 h, a complete recovery should be anticipated unless complicated by other life-threatening conditions.

Key Points in Tetrodotoxin Poisoning

1. Tetrodotoxin is a heat-stable nonprotein toxin.
2. Tetrodotoxin can be found in a wide variety of totally unrelated aquatic organisms and amphibians.
3. Tetrodotoxin poisoning most commonly is caused by consumption of puffer fish, which has a worldwide distribution.
4. Puffer fish poisoning usually is the result of improper handling of the fish (e.g., private sale and preparation by fishmongers or vagabonds).

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Part XX

Natural Toxins: Mushrooms

Michael C. Beuhler

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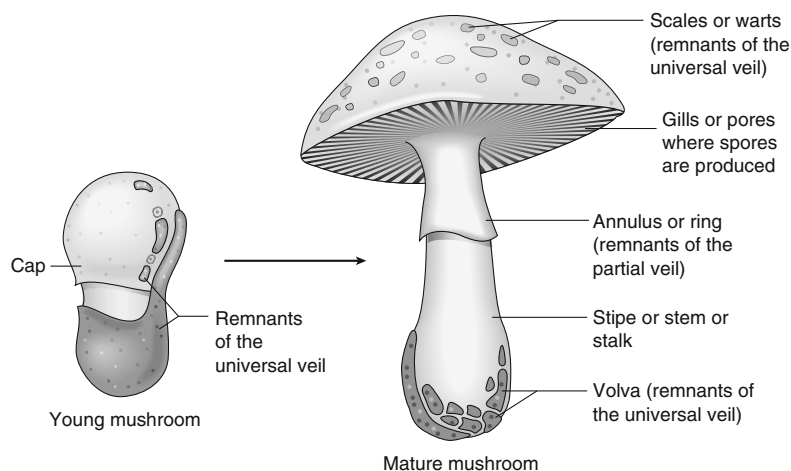
Mushrooms are the visible fruiting body of a fungus with the bulk of the organism usually below the ground and/or growing in substrate. Worldwide, mushrooms have important use as food, medicines, religious observance and dyes and are found almost everywhere on earth. Unfortunately, some mushrooms are toxic, and the number of mushroom species recognized as poisonous has grown in recent years. Additionally, because of world commerce and changing environments, some mushroom species are “migrating” and occasionally are found in places never before seen. Finally, when certain ethnic groups who are familiar with their traditional edible mushroom species move to a new area they occasionally suffer grave poisoning due to mistaken identification.

Mushroom ingestions are often associated with uncertainty because of the lethality of some species and the difficulty differentiating between types of mushrooms. Some basic understanding of the anatomy of a mushroom can be important for genus/species determination [1] (Fig. 1). When mushroom samples are collected, it is important that the bulb or volva be dug up using an appropriate tool because if a mushroom is simply picked, important morphological characteristics will be left behind. The annulus or ring may be fragile and easily dislodged and so the stem should be examined closely for remnants. Apparent puffballs should be cut open vertically and inspected carefully as young mushrooms that

are not fully developed have been mistaken for them. A spore print can be produced from a reasonably fresh mushroom cap; spore color and microscopic morphology can be extremely helpful for definitive identification. Spore prints are made by placing the mushroom cap spore-bearing surface down on a piece of white paper and covering the cap with a cup; if the mushroom cap is somewhat old and slightly dry, a single drop of water can be placed on the top of the cap before covering. The spore print generally takes at least 4 h to develop. Some mushrooms have distinctive morphological characteristics that can guide even the mycologically naive clinician in their diagnostic dilemma. These are described later in this chapter and in ► [Chaps. 108, “Cyclopeptide-Containing Mushrooms: The Deadly *Amanitas*,”](#) and ► [109, “*Gyromitra* Mushrooms.”](#) The assistance of a mycologist is often needed if there is a question of ingestion of a possibly poisonous mushroom. A poison control center, mushroom club, or botanical garden may be of assistance in identifying a local mycologist.

In many cases, management is not reliant on the exact species; even if the allegedly culpable mushroom is brought to the emergency department along with the patient, it may not be the actual mushroom species consumed. Multiple species often grow together, and some mushrooms contain multiple pharmacologically active compounds, further complicating the clinical picture. Laboratory tests to identify mushroom

Fig. 1 Anatomy of a mushroom



toxins are usually unavailable, and when they are, results may not be available for days to weeks. It is important to focus initially on the patient examination, clinical presentation in relation to the time of consumption, and emergent supportive treatment.

With the recent recognition of new mushroom poisoning syndromes, and the realization that some of the older clinical management “rules” are not always holding true, alternative categorization systems for the toxic mushrooms have been proposed. The categorization system proposed by White et al. [2] will be used in this chapter. However, due to the rarity and lack of critical illness for some of these mushroom poisoning syndromes, not every toxic mushroom will be included. Table 1 is a summary of the six groups of mushrooms known to cause human poisoning along with their toxin (when known) or species, its signature clinical effect, and a summary of commonly associated clinical effects.

Because of the overall paucity of information on mushroom toxicity, it is difficult to give evidence-based recommendations. In general, cases of mistaken identity of mushroom ingestions when cooked for food tend to be associated with greater toxicity than other scenarios. Conversely, unintentional exploratory ingestions of raw mushrooms by children are unlikely (but not impossible) to cause significant injury, with one series of almost 60,000 pediatric cases showing significant illness in less than 0.7% cases, with no deaths [3]. However, the toxicity of some mushrooms, is so great that a single mushroom ingestion can be lethal, emphasizing the need for caution.

Universal treatment recommendations for mushroom ingestions do not exist. Gastric lavage is not indicted following mushroom ingestion. It is not risk-free and has not been shown to alter outcome. Additionally, lavage tubes often have become blocked by mushroom fragments [4]. Activated charcoal may be used for gastrointestinal decontamination if there is a concern for amatoxins, but caution should be used because of the risk of aspiration, especially in the presence of altered mental status. Global treatment of any mushroom ingestion that causes gastrointestinal

distress with atropine is no longer recommended because it could exacerbate the toxicity of some types of mushroom ingestions.

Indications for ICU Admission in Mushroom Poisoning

- Evidence of significant end-organ toxicity (e.g., renal insufficiency or failure, elevated hepatic transaminases, rhabdomyolysis)
- Persistent altered mental status or status epilepticus
- Unstable or significantly abnormal vital signs
- Persistent hypovolemia with or without electrolyte abnormalities

Common Misconceptions About Mushroom Poisoning

- Gastric lavage has been shown to alter outcome after mushroom ingestion
- If a patient is ill early (<4 h) after mushroom ingestion, the patient will not become critically ill later

Key Points in Mushroom Poisoning

- Identification of mushrooms and their toxins is generally not readily available
- Occasionally, distinctive characteristics of the mushroom, knowledge of the species that grows locally, and clinical picture may be used together to include/exclude certain diagnoses
- Focus should be on the clinical course and supportive care of patients

Cytotoxic Mushroom Poisoning (Group 1)

This group contains mushrooms that cause toxicity by cellular injury and death, with the liver and kidneys being the primary target organs. Nearly all mushroom fatalities are due to the amatoxins, but there are some notable exceptions [5].

Table 1 Overview of selected mushroom poisoning groups (based on ref [2])

Group	Principal mushroom, toxin or syndrome	Primary clinical effect	Other clinical effects	Onset within 6 h?
Cytotoxic mushroom poisoning				
1A-Primary hepatotoxicity	Amatoxins	Hepatic failure	Nausea, vomiting, diarrhea, renal injury	No
1B-Primary nephrotoxicity	Aminohexadienoic acid	Renal failure	Nausea, vomiting, diarrhea, headache, fatigue, ±rash	Yes ^a
1C-Delayed Primary nephrotoxicity	Orellanines	Renal Failure	Headache, drowsiness, sweating, nausea/vomiting, malaise	No
Neurologic mushroom poisoning				
2A-Hallucinogenic	Psilocybin	Reality distortions	Nausea, vomiting, yawning, mydriasis. Not delirious; usually oriented	Yes
2B-Cholinergic mushroom toxicity	Muscarines	Cholinergic	Nausea, vomiting, diarrhea, fatigue, salivation, lacrimation, miosis, bradycardia	Yes
2C-Central nervous system toxicity	Ibotenic acid/muscimol	Altered mental status	Nausea, vomiting, flushing, wax/wane between mania and drowsiness, seizures, headache	Yes
2D-Morel neurologic syndrome	Morels	Vision changes, Headache	Nausea, vomiting, diarrhea, abdominal pain, asthenia, ataxia, sweating	Sometimes
Myotoxic mushroom poisoning				
3A-Rapid onset myotoxicity	<i>Russula subnigrans</i>	Rhabdomyolysis	Nausea, vomiting, diarrhea	Yes
3B-Delayed onset myotoxicity	<i>Tricholoma</i>	Rhabdomyolysis	Fatigue, myalgias	No
Metabolic pathway mushroom poisoning				
4A-GABA decreasing	Gyromitrins	Seizures	Nausea, vomiting, diarrhea, headache, hepatic injury	No
4B-Disulfuram like	Coprines	Flushing	Rash, headache, nausea, vomiting, diarrhea	Yes ^b
5-Gastrointestinal irritant mushroom poisoning				
6-Miscellaneous adverse reactions				
6A-Shiitake dermatitis	Lentinan (Shiitake)	Dermatitis	Linear rash/whiplike lesions, photosensitivity	Mostly No
6B-Erythromelalgic	Acromelic acid	Erythromelalgia	Swollen, red, painful hands/feet	No
6C-Paxillus	Paxillus syndrome	Hypotension	Nausea, vomiting, diarrhea, hemolysis, shock, AKI	Yes ^c

^aAlthough the GI disturbance begins within a few hours, the renal failure takes longer to develop

^bTiming dependent upon consumption of alcohol as well

^cSyndrome believed to require sensitization, so the initial exposure will only have minor symptoms

► **Chap. 108, “Cyclopeptide-Containing Mushrooms: The Deadly *Amanitas*”** covers group 1A. These are mushrooms containing amatoxins, which primarily cause hepatotoxicity. This chapter will discuss primarily nephrotoxic mushrooms

that do not cause significant hepatic injury. This group is interesting because in some cases the mushroom may have been ingested days earlier and thus that history element may be overlooked due to the delayed onset of symptoms. Of note,

other mushroom classes can result in renal injury through secondary mechanisms such as rhabdomyolysis (myotoxic mushrooms) and hypovolemia (metabolically toxic mushrooms and gastrointestinal irritant mushrooms).

Early Nephrotoxicity (Group 1B)

The primary clinical toxicity of this group of mushrooms is renal failure with onset somewhat earlier than the group causing delayed nephrotoxicity. The principal member of the early toxicity group is *Amanita smithiana*, but *A. boudieri*, *A. proxima*, *A. pseudoporphyria* and *A. echinocephala* have also been implicated [6–9]. *Amanita smithiana* is found in the Pacific Northwest of the USA and is commonly mistaken for the pine mushroom *Tricholoma magnivelare*; there are now members of this nephrotoxic group that have been identified in Europe [6, 8, 10]. *Amanita smithiana* usually is found growing under conifers. It is a light-colored mushroom that changes from a light brown to yellow-brown with age and handling. It has a large (5–12 cm) cap with white gills and spores and a long white, rough, bulbous (10–20 cm) stem with a ring; the *Amanita* stem characteristics will be lost if the mushroom is picked instead of being dug up [6, 10]. Older specimens of *A. smithiana* may have a strong unpleasant, putrid odor [7, 11].

Biochemistry

The compound responsible for the toxicity of *A. smithiana* has been proposed to be aminohexadienoic acid (2-amino-4,5-hexadienoic acid) [6, 12, 13]. The renal injury from aminohexadienoic acid observed in cell culture and animal models is similar to that seen after ingestion of *A. smithiana* and tends to occur after a latency period of up to 12 h [7, 13, 14]. However, there is uncertainty to this conclusion due to the relatively low concentration of aminohexadienoic acid compared to its LD₅₀ in animal models as well as its presence in non-nephrotoxic mushrooms. Based on thin-layer chromatography studies, it has been proposed for some (not *A. proxima*) of these mushrooms that the toxicity is due to an

“*A. smithiana* toxin” whose nature has yet to be determined [8]. Ingestion of one fruiting body of *A. smithiana* has been reported to cause renal injury in otherwise healthy individuals [7].

Clinical Presentation

Patients ingesting early nephrotoxic mushrooms usually have a short, but variable, asymptomatic period, ranging from 30 min to 12 h (average 5–6 h), although the reported very short onset times may have been due to a concomitant gastrointestinal mushroom ingestion [11]. Ingestions of *A. proxima* seem to have a longer onset of GI symptoms (average 13 h) compared to other members of this group [11]. This pattern of symptom onset in this group occurs more rapidly than that seen with orellanine-containing mushrooms (Group 1C) [11]. This pattern can be important in distinguishing these ingestions. Symptoms of nausea, vomiting, diarrhea, abdominal cramps, rash, myalgias, fatigue, headache, and weakness are characteristic and can last for days but may improve before the onset of renal failure. Patients intoxicated with *A. smithiana* tend to develop renal failure 2–5 days after ingestion. Occasionally, clinically insignificant hepatic transaminase elevations occur and LDH elevations have also been noted in patients who develop significant renal toxicity [6, 7, 11].

Diagnosis

The diagnosis of nephrotoxicity in this group of mushrooms is usually made based on the description of the ingested mushrooms and the clinical presentation, with many cases due to mistaken identity for the pine mushroom, *Tricholoma magnivelare*.

Treatment

No specific treatment for *A. smithiana* has been proposed. Approximately 90%+ recover renal function after about 4 weeks, but they may need hemodialysis in the interim [11]. The more rapid onset of injury that occurs with this group suggests that early dialysis is unlikely to be beneficial. A greater percentage of patients poisoned by *A. smithiana* recover renal function than do patients poisoned by *C. orellanus* [8]. Chronic

renal injury is not usually seen [11]. It is believed that patients with preexisting renal insufficiency are at greater risk for developing renal failure from *A. smithiana*. Elderly and diabetic patients intoxicated with *A. smithiana* tend to develop renal failure more rapidly than other patients [7].

Delayed Nephrotoxicity (Group 1C)

The primary nephrotoxicity of group 1C is similar to 1B but is more delayed. The mushrooms responsible are members of the genus *Cortinarius* which grows in semi-mountainous forests and is usually found from the end of summer through early autumn [15]. Nephrotoxic species include *Cortinarius orellanus*, *C. gentilis*, *C. speciosissimus*, and *C. splendens* [16, 17]. They are found mostly in Europe but occasionally in Australia and, less commonly, in North America [18, 19]. *Cortinarius orellanus* is difficult to identify because of a lack of distinctive morphologic characteristics. The caps are medium sized (2–5 cm) with orange or orange-brown to dark gray-yellow coloration with fine scales. The gills are rusty orange to dark orange-yellow, the stalk is thick with a yellow-to-orange color, and the spores are rust brown [1, 15].

Biochemistry

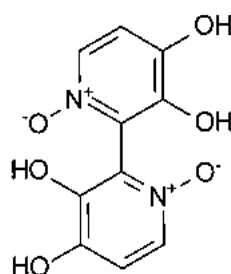
The nephrotoxicity of *C. orellanus* was first described in Poland in 1956; this relatively recent recognition was because of the long delay between ingestion and the development of renal failure [20]. The toxic compound in *Cortinarius* mushrooms is orellanine, a cationic bipyridine similar to paraquat, present in amounts up to 1.4% by weight (Fig. 2)

[21, 22]. It is a resilient toxin, resistant to heat, freezing, and drying, although it is light sensitive [21, 23, 24]. Orellanine is concentrated in renal tissue, possibly due to active cellular uptake. The exact mechanism of toxicity of orellanine is unknown, but evidence suggests that it causes a disruption of cellular cytoskeleton actin filaments and inhibits protein synthesis [23, 25, 26]. Orellanine requires activation by mitochondria (or possibly light) before becoming cytotoxic [16, 26]. *Cortinarius* spp. also contain cortinarin A and B which are cyclopeptides that may contribute to nephrotoxicity [16, 17, 22]. Ingestion of one fruiting body of *C. orellanus* has been reported to cause renal injury in otherwise healthy individuals; however, a dose of approximately 100 g usually is required [20, 27].

Clinical Presentation

Acute renal failure has been reported to develop in approximately 60% of orellanine-poisoned patients, but this percentage has been found to depend on the amount eaten, the age of the mushrooms, and the environmental conditions [28, 29]. The onset of *C. orellanus* toxicity is delayed, with no early symptoms. Patients who ingest *C. orellanus* are typically asymptomatic for 2–14 days (median 3 days and maximum 17 days) [7, 18, 24, 27]. Symptoms consist of nausea, vomiting, abdominal pain, chills, lumbar pain, malaise, dizziness, paresthesias, myalgias, headache, polydipsia, and polyuria followed by oliguria or anuria [20, 24, 28]. Renal insufficiency (median onset 8.5 days) has been reported to occur in approximately 70% of all ingestions [24]. Severely poisoned patients tend to present earlier. The onset of symptoms coincides with the clinical manifestations of renal failure rather than occurring as a separate prodrome as with *A. smithiana* (group 1B) [30, 31]. Recovery of renal function after poisoning (if it occurs) may take several weeks. Of patients poisoned with *C. orellanus*, about half develop chronic renal insufficiency or failure and hypertension [15, 16, 18, 25, 28, 29]. Elderly patients tend to have less renal improvement after poisoning by *C. orellanus* and require dialysis longer than younger patients [18].

Fig. 2 Chemical structure of orellanine



Diagnosis

The diagnosis of nephrotoxicity from group 1C is usually made retrospectively based on descriptions of the ingested mushrooms and the clinical presentation, realizing that there may be a delay of days between ingestion and symptom onset. After ingestion of *C. orellanus*, leukocyturia, proteinuria, and hematuria are typically observed early in the clinical course [16, 32]. Orellanine may be found in urine for 24 h after ingestion but cannot be found in urine, plasma, or dialysis fluid after onset of symptoms [27, 33, 34]. Orellanine may be assayed by high-performance liquid chromatography or thin-layer chromatography, but these tests are not routinely available [34, 35]. A qualitative test for orellanine in a mushroom sample can be done using ferric chloride. This test is accomplished by crushing fresh or dried mushrooms in five parts of water, let stand for 10 min at room temperature and filter. The filtrate is mixed with an equal amount of 3% ferric chloride hexahydrate dissolved in 0.5 M hydrochloric acid. The presence of orellanine is suspected if a dark gray-blue color appears [30].

Renal biopsy findings of patients with *C. orellanus* poisoning have shown acute tubular necrosis, interstitial edema, initial interstitial fibrosis, and inflammatory edema; tubulointerstitial nephritis is the most common biopsy finding [18, 24–26, 32, 33, 36]. Rat studies show interstitial and tubular epithelial pathology beginning within 12 h of poisoning; however, rats exhibit great variability in sensitivity to orellanine-induced renal injury [27]. Orellanine has possibly been detected in small quantities in renal tissue biopsies weeks after ingestion, but this has not been well studied and there are concerns of analytical limitations [24, 34].

Treatment

Treatment options for orellanine poisoning are limited because the patient is unlikely to present during the asymptomatic period early after the ingestion. Patients in renal failure should be admitted for monitoring and possible hemodialysis. Although some advocate early, aggressive dialysis, the benefit of this intervention is questionable because the toxin seems to be dialyzable

only within the first 24 h. The injury occurs subclinically as early as 12 h, and clinical presentation is typically delayed [27, 31, 32]. Orellanine crosses the dialysis membrane and has been shown to adsorb onto hemoperfusion resin [31, 33]. There is extremely limited clinical experience using hemoperfusion, but anecdotal data suggest improved outcome; plasmapheresis has also been used [33, 37] (grade III evidence). Other treatments have been tried on an individual basis, including corticosteroids, acetylsalicylic acid, diltiazem, and dopamine, but none have demonstrated any effect on clinical outcome [29]. Furosemide worsened outcome in animals [33, 38]. Some patients have received renal transplantation [30, 31].

Nephrotoxic Mushrooms

- Include *Cortinarius* spp. and *Amanita smithiana*
- *Cortinarius* spp. ingestion associated with delay of days before symptom onset
- May need hemodialysis for renal failure

Neurotoxic Mushroom Poisoning (Group 2)

This group contains mushrooms that primarily cause neurotoxicity, including both peripheral and central effects. This chapter will discuss the mushroom subgroups hallucinogenic, cholinergic, central nervous system toxic and the more neurologic syndrome.

Hallucinogenic Neurotoxic Mushroom Poisoning (Group 2A)

The mushrooms in this category are sometimes referred to as “magic mushrooms” due to their hallucinogenic properties. The toxicity from this group of mushrooms is from the active compound(s) psilocybin and psilocin, which are present in many different genera and species of mushroom, with the genus *Psilocybe* being the most frequently encountered. *Psilocybe semilanceata*

(“liberty cap”), *P. stuntzii*, *P. cubensis*, *P. cyanescens*, and *P. baeocystis* are some of the more commonly encountered species [39]. Other genera containing psilocybin include *Panaeolus*, *Stropharia*, *Conocybe*, *Gymnopilus*, *Inocybe*, and *Pluteus* [39, 40]. Psilocybin-containing mushrooms are found worldwide. For example, in the USA, they are more common near the Gulf of Mexico and in the Pacific Northwest.

The morphology of psilocybin-containing mushrooms is varied; generally they have smooth, light-colored caps, elongated stalks, dark gills, and dark spores which are occasionally purple/black in color. A characteristic of some psilocybin-containing mushrooms is that the flesh stains a bluish-green color when bruised [1]. This color change is found consistently only in some of the *Psilocybe* and *Panaeolus* spp.; it is absent in others. The reaction is thought to be related to the conversion of psilocin to a bluish pigment [41, 42]. However, blue staining with bruising is not limited to only psilocybin-containing mushrooms.

The major danger inherent in consumption of these mushrooms is misidentification and consumption of other toxic species. This danger is especially worrisome in areas where the prevalent hallucinogenic mushroom has a relatively low concentration of psilocybin, prompting consumption of many mushrooms. Examples of mushrooms similar in appearance to some *Psilocybe* spp. that have been inadvertently ingested include *Galerina autumnalis* (contains amatoxin) [39], *Cortinarius* spp. (contain orellanine) [43], *Inocybe geophylla* (contains muscarine) [44], and *Chlorophyllum molybdites* (produces gastroenteritis) [45].

Biochemistry

The pharmacologically active compounds present in these mushrooms are psilocybin (Fig. 3), a serotonin-like indole compound with similarities to LSD (lysergic acid diethylamide) and its dephosphorylated metabolite, psilocin. Both are 4-substituted tryptamine compounds; Psilocin is never found without psilocybin. Other biologic amines such as baeocystin and norbaeocystin are

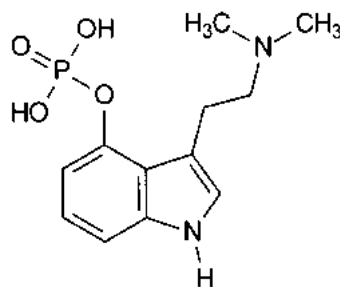


Fig. 3 Chemical structure of psilocybin

also present, but their exact physiologic effects are unknown [46, 47]. Phenylethylamine, found in *P. semilanceata*, has been suggested as a cause of tachycardia and flushing; others believe that phenylethylamine is essentially inactive in humans [48, 49]. There is great variability in the interspecies concentration of psilocybin, with an average of approximately 2 mg/g of dry flesh. *Psilocybe semilanceata* often contain large amounts of psilocybin, usually greater than 10 mg/g of dried tissue [39], whereas other species may have only 0.1 mg/g. There is even a substantial difference in the content between subsequent growths (flushes) on the same culture media, a fact worth appreciating due to the common practice of *Psilocybe* cultivation [50]. Because of the great variation in psilocybin concentrations, ingestion of collected wild mushrooms may result in overdose since 20–100 mushrooms are usually eaten at one time; any one of which may have an unexpectedly large amount of psilocybin [51–53].

Psilocybin is approximately 50% absorbed orally and is rapidly dephosphorylated to psilocin [54]. Psilocin is responsible for the central nervous system effects because it is more lipid soluble and crosses the blood–brain barrier. It has an elimination half-life of about 50 min [55]. Approximately 65% of a psilocybin dose is excreted in the urine, 25% is as psilocin, and the rest as 4-hydroxyindolacetic acid and conjugated derivatives [56]. Tolerance to the hallucinogenic effects of psilocybin develops rapidly and is hypothesized to occur even during its continued absorption [52].

Psilocin is an agonist at 5HT_{2A} and 5HT_{1A} serotonin receptors in the raphe nuclei of the reticular formation, among other areas [55, 57]. This stimulation is thought to decrease negative feedback on sensory input (i.e., disinhibit), causing increased stimulation of cognitive, emotional, and visual areas [46]. The reduction in negative feedback also may contribute to (the very rarely reported) seizures and hyperthermia. The threshold dose of psilocybin is around 3–6 mg, and a dose of 8–25 mg results in the full range of clinical effects [55, 56].

Clinical Presentation

Euphoria is common, and “bad trips” (dysphoria) are the exception after the ingestion of these mushrooms; however, the latter are more common when an individual ingests psilocybin-containing mushrooms without intending to do so. Most people ingesting psilocybin-containing mushrooms never seek medical attention. The onset of effects generally occurs approximately 15–45 min after ingestion, depending on the preparation. A full stomach may delay onset. The peak hallucinogenic activity lasts approximately 1 h and usually resolves after 4–12 h [56, 58, 59]. Symptoms persisting greater than 12 h are atypical and should prompt a search for alternative explanations, although some clinical manifestations (including pupillary dilation) may persist beyond this time frame [52, 60].

Central nervous system effects of psilocybin-containing mushrooms include optical (especially faces), auditory (distortions and hallucinations), and tactile illusions, with true hallucinations occurring much less commonly [52]. Most patients remain aware that they are having altered perceptions or are hallucinating and usually remain able to engage in limited conversation [51]. The degree of perceptual alteration seems to be dose related. Depersonalization or body image distortion occurs infrequently. Racing thoughts, laughter, difficulty concentrating, and the experience of time distortions have been reported [56]. Occasional suicidal thoughts or self-harm attempts are made while suffering from psilocybin toxicity [52]. Other effects

include nausea, vomiting, abdominal pain, mydriasis, yawning, anxiety, upper trunk flushing, tachycardia, hypertension, hyperreflexia, and paresthesias, which can be unilateral and transient, involving the face and occasionally the extremities [46, 52, 53, 56, 59, 60]. Tachycardia and hypertension are probably due to agitation rather than a direct physiologic effect of psilocybin or psilocin [52, 56].

As symptoms resolve, exhaustion and depression may ensue. Mild cognitive alteration may persist for days. Persistent psychotic symptoms have been reported with repeated large ingestions, though the incidence of this is unknown. Hallucinogen-persisting perception disorder (flashbacks) has been reported [60–62]. Rare reported effects have included cerebral demyelination resulting in focal weakness, visual changes, and deafness 2 weeks after ingestion of *Psilocybe* mushrooms; rechallenge caused recurrence of symptoms and clinical findings [63].

The tachycardia and hypertension induced by psilocybin has caused paroxysmal supraventricular tachycardia and cardiac arrest in a patient with Wolff–Parkinson–White syndrome [64]. Patients with preexisting heart disease may be more likely to have ischemic injury or dysrhythmias as a consequence of ingestion of these mushrooms.

Intravenous injection of mushroom material was not reported to cause hallucinations but instead produced hyperpyrexia, rigors, hypoxemia, facial paresthesias, headache, vomiting, and myalgias. These effects are likely secondary to contaminants as these effects are not observed after injection of pure psilocybin [56, 65, 66].

Psilocybin-containing mushrooms are not hepatotoxic; however, two cases of transient elevation of aspartate transaminase, lactate dehydrogenase, and alkaline phosphatase after ingestion of *Psilocybe* and *Conocybe* mushrooms have been described; seizures were described in the same report [67]. Another case series detailed seizures in several children, with a 6-year-old developing status epilepticus and hyperthermia resulting in death. This is one of the few reported deaths directly due to psilocybin toxicity (and not secondary trauma) [68].

Diagnosis

The diagnosis of hallucinogenic mushroom poisoning is clinical and is often reasonably straightforward given the history, rapid onset of action, and physical examination findings, although other hallucinogens are occasionally substituted on purchased mushrooms. Urine assay for psilocin is not routinely available. Psilocin may be detected in urine, blood, or the mushroom itself after derivatization using gas chromatography–mass spectrometry [69, 70]. Small amounts of psilocin are excreted in the urine for days after mushroom ingestion. The presence of phenylethylamine has caused false-positive amphetamine screens using polyclonal antibodies [48]. The Meixner test, which is performed by squashing mushroom tissue against a piece of newsprint, allowing it to dry, and adding one or two drops of concentrated hydrochloric acid to the residue, will give a bluish color change for mushrooms in this class. However, this is a nonspecific test, producing indistinguishably positive results for amatoxin-containing mushrooms [71]. Identification of the mushroom through morphologic and microscopic characteristics is possible [44] but rarely clinically necessary.

Treatment

Agitated patients should be observed in a quiet, safe environment; if agitation persists, benzodiazepines are often the only further intervention required. Administration of activated charcoal has not been shown to alter outcome and is not indicated. Additionally, some patients will have vomited before presentation [58, 72]. The author recommends that neuroleptic agents should be initially avoided for theoretical reasons because their side effects may confuse the clinical picture, worsen hyperthermia, possibly potentiate the risk for hallucinogen-persisting perception disorder, and possibly increase the risk of seizures (grade III). Seizures induced by psilocybin should respond to benzodiazepines or barbiturates with careful monitoring of body temperature. If the hallucinations are causing distress for the adult patient, an oral dose of cyproheptadine could possibly diminish their intensity based on the theoretical reason that cyproheptadine, a treatment used

occasionally for serotonin toxicity, is an antagonist at serotonin 5HT_{2a} receptors, and a similar 5HT_{2a} antagonist compound, ketanserin, has been shown to limit some of the distortions and hallucinations [73, 74]. It is important to evaluate patients for injuries that may have been sustained as a result of their altered perceptual state and to monitor for evidence of hyperthermia and/or rhabdomyolysis.

Because of the short duration of effect, admission to the hospital usually is not required. Most patients are improving by the time they reach medical attention, and a short observation period in the emergency department is usually sufficient. Admission to the intensive care unit is recommended for patients who present with rhabdomyolysis, prolonged agitation, hyperthermia, seizures, or traumatic injuries. Recovery generally occurs within 12 h of presentation if psilocybin was the sole ingested toxicant. Younger children rarely may develop seizures after psilocybin ingestion and should be carefully observed [68]. Seizures are extremely rare in adults.

Hallucinogenic Mushroom Poisoning

- Includes *Psilocybe* spp. and *Panaeolus* spp.
- Toxins have similar structure to serotonin and LSD
- Meixner test may be positive but is nonspecific and will also be positive with amatoxins
- Rare seizures may be treated primarily with benzodiazepines.

Cholinergic Neurotoxic Mushroom Toxicity (Group 2B)

The muscarinic receptor agonist muscarine is found in a broad range of mushroom species, but the two genera of greatest importance are *Clitocybe* and *Inocybe*. The mushroom *Rhodophyllus rhodopolius*, found in Japan, has also been shown to contain muscarine in quantities sufficient to produce human illness [75]. Multiple other species, including *Amanita muscaria*, contain small amounts of muscarine but not enough to produce muscarine poisoning [76].

The genus *Clitocybe* includes edible species and multiple inedible muscarine-containing species, including *Clitocybe dealbata*, *C. cerrusata*, *C. rivulosa*, and *C. candicans* [1, 77, 78]. These mushrooms are found worldwide, usually growing in forests or grasslands, and may be found in fairy ring formations. The mushrooms often have white-to-brown, small, funnel-shaped caps with light-gray-, white-, or cream-colored gills. The spores are white to grayish yellow, pink, or violet. The flesh may have a pleasant/mealy smell, although this varies with the species [79]. No veil or ring is present. There are substantial differences in morphology among species [1].

The genus *Inocybe* includes many different species, and most contain muscarine [78, 80, 81]. These mushrooms are found worldwide and usually grow in soil under trees. The conical caps have a surface pattern similar to a bicycle wheel with streaks radiating from the center. Gills are light when young and become brown at maturity. The spores are brown to yellowish brown. The flesh has an earthy to unpleasant smell. The veil is fragile. There are minor differences in morphology among species [1].

Biochemistry

Muscarine is a quaternary ammonium compound (Fig. 4). Four stereoisomers are found in nature, but only L-(+)-muscarine has significant physiologic activity [46, 77]. Muscarine is not degraded by boiling or peptic digestion [82]. It is usually found in concentrations of 0.1–0.3% dry weight in

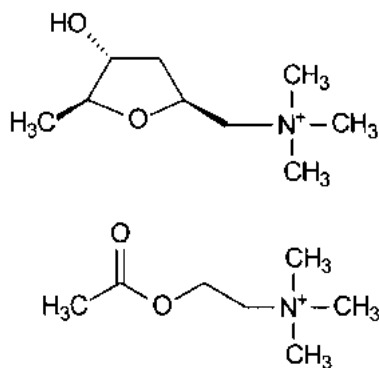


Fig. 4 Chemical structures showing homology between muscarine (top) and acetylcholine (bottom)

Inocybe and *Clitocybe* spp., but the amount may vary by up to three orders of magnitude among species [77, 80, 81]. Its gastrointestinal absorption appears to be limited and erratic. The median lethal dose in humans is unknown but has been suggested to be around 200 mg [82, 83]. Muscarine has specific agonist activity at acetylcholine muscarinic receptors, a property used experimentally to define these receptors. This agonism produces a cholinergic muscarinic syndrome. As a result of its positive charge, muscarine has limited ability to cross the blood–brain barrier, and its toxicity is limited to peripheral effects [76]. Muscarine has no affinity for, and is not metabolized by, acetylcholinesterase [76]. Some muscarine is renally excreted and may be detectable in urine [84].

Clinical Presentation

Symptoms from ingestion of muscarine-containing mushrooms are primarily cholinergic and typically begin 0.5–2.5 h after ingestion. Among the various mushroom poisonings, the constellation of signs that are characteristic of muscarine intoxication are lacrimation, perspiration, and salivation. Other commonly reported clinical manifestations are nausea and vomiting (seen in nearly all patients), abdominal pain, anxiety, wheezing, headache, fatigue, chills, perioral paresthesias, diplopia, urinary urgency, and diarrhea [85]. Muscarine-intoxicated patients occasionally are bradycardic and hypotensive and have miotic pupils. These effects usually last approximately 2 h; although untreated, they may persist for up to 24 h [78, 86].

The clinical presentation of muscarine poisoning is similar to that of some other mushroom ingestions, such as the gastrointestinal irritants; however, the triad of perspiration, salivation, and lacrimation also is seen. Central nervous system effects, such as confusion, vertigo, and hallucinations are not expected because muscarine does not cross the blood–brain barrier. If patients are confused, they may have ingested a mushroom with centrally active compounds, such as ibotenic acid from central nervous system toxicity group of neurotoxic mushrooms Group 2C, or alternatively are dehydrated from vomiting and diarrhea. It is

unproven, but suspected, that there are mushrooms containing muscarine and ibotenic acid that produce a mixed clinical picture of cholinergic and central nervous system effects [85].

Diagnosis

The diagnosis of muscarinic mushroom ingestion is clinical, based on the time course of the signs and symptoms and the description or identification of the ingested mushrooms. There is often difficulty differentiating gastrointestinal irritant mushroom poisoning from this group. With a mushroom sample, testing for muscarine can be performed with liquid chromatography [81], although this is not commonly done in a clinical setting. Gas chromatographic methods are technically difficult and are not commonly performed [87].

Treatment

Muscarine is one of the few toxins that has an almost perfect antidote. Atropine was recommended in the past to reverse muscarinic cholinergic effects based on both mechanistic reasons and case reports. Most references recommend sequential intravenous doses of 0.1 mg in adults and 0.02 mg/kg in children (minimum 0.1 mg per dose) (grade III evidence). The goal of treatment is symptom resolution; however, atropine is not an ideal antidote because it crosses the blood–brain barrier and may cause central anticholinergic effects. Although not studied, glycopyrrolate is a more selective antidote and may have an advantage over atropine. It antagonizes peripheral acetylcholine muscarinic receptors, but being a quaternary amine, it does not penetrate the blood–brain barrier. Sequential glycopyrrolate intravenous doses of 0.1 mg in adults and 0.005 mg/kg in children appear to be safe [88] (grade III evidence). When patients present with significant bronchospasm, inhaled ipratropium, an anticholinergic quaternary amine that has limited systemic absorption, could be utilized, based entirely on its mechanism of action (grade III evidence).

Intravenous volume replacement may be required if patients are significantly volume depleted from vomiting and diarrhea. Fluids may

help correct hypotension. An unclear diagnosis or significant clinical manifestations are indications for hospital admission. Mildly symptomatic or asymptomatic patients may be discharged from the emergency department after a period of observation and clinical recovery, provided that there is assurance that the patient has not ingested a more toxic mushroom. The possibility of a mixed-mushroom ingestion always should be considered, and close follow-up should be ensured.

Children and elderly individuals are at increased risk of dehydration from the cholinergic effects of muscarine. A more prolonged period of observation is warranted for these populations to ensure that there is no recurrence. It is unknown whether muscarine crosses the placenta. Data are limited regarding the safety of glycopyrrolate in pregnancy, but it has significantly less placental transfer than atropine and does not alter fetal hemodynamics [83].

Cholinergic Neurotoxic Mushroom Toxicity

- Muscarine-containing mushrooms
- Includes *Clitocybe* spp. and *Inocybe* spp.
- Agonists at acetylcholine muscarinic receptors
- Antidote is atropine or possibly glycopyrrolate

Central Nervous System Mushroom Toxicity (Group 2C)

Ibotenic acid and muscimol are structurally related isoxazole compounds present in certain *Amanita* spp. These substances are known for their sensorium-altering effects. Hundreds of years ago, Siberian and Eskimo tribes ingested these mushrooms for their intoxicating properties; the urine from intoxicated individuals was also consumed to cause inebriation [89]. The most important mushrooms containing ibotenic acid and muscimol are *A. muscaria* and *A. pantherina*; of note, subspecies of both with subtle morphological differences are known to exist [90–92].

Amanita muscaria (“fly agaric”) is found worldwide, except in the tropics, often growing under trees such as pine, beech, and aspen. It is the

classic mushroom often pictured in fairy tales (and video games), with a distinctive cap having a color ranging from red to orange, yellow, or white; the color may fade with age (Fig. 5). The cap, about 7–15 cm in diameter, is covered with pale yellow-to-white spots or warts. The stalk is white with a persistent membranous ring; the gills and spores are also white. The volva tissue is intergrown with



Fig. 5 *Amanita muscaria* (From Schneider S, Donnelly M: Mushroom toxicity. In Auerbach PS [ed]: Wilderness Medicine, 4th ed. Philadelphia, Mosby, 2001, p 1148, with permission)

the bulb, and there are characteristic rings along the volva from the universal veil [1].

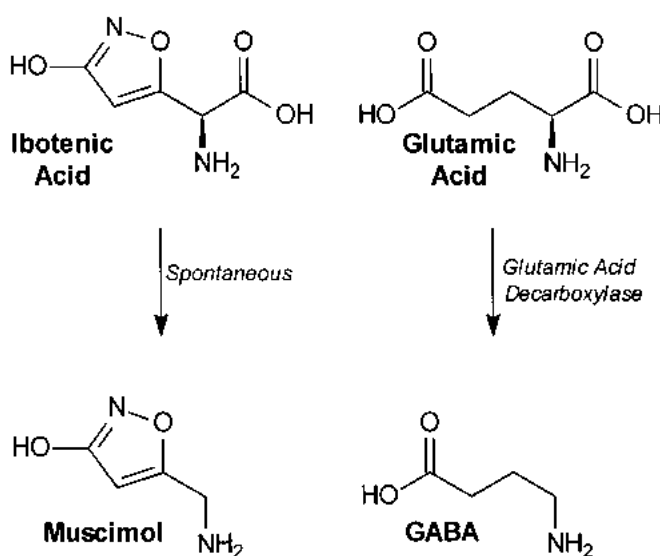
Amanita pantherina (“panther mushroom”) has a brown-to-dull yellow cap about 5–12 cm in diameter with white or yellow warts. It grows alone or in small groups and commonly is found under conifers. It has a white stalk with a white membranous ring, pale gills, and white spores [1]. Generally, *A. pantherina* has greater concentrations of ibotenic acid and muscimol toxins than does *A. muscaria* [90].

Biochemistry

Ibotenic acid and muscimol are false neurotransmitters; their structures are similar to the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter γ -aminobutyric acid (GABA) (Fig. 6), respectively. The major structural difference between the mushroom toxins and the true neurotransmitters is the presence of an isoxazole ring involving the terminal carboxylic acid residue on the former. In contrast to their true neurotransmitter counterparts, ibotenic acid and muscimol readily cross the blood–brain barrier, producing inebriation.

Muscimol is an agonist at GABA-A receptors [93]. This GABAergic activity is likely responsible for the somnolence and inebriation seen in poisoning by mushrooms in this group. Ibotenic acid is an

Fig. 6 Comparison of isoxazole toxins with endogenous neurotransmitter structures and metabolic pathways



agonist at N-methyl-D-aspartate–glutamate receptors, causing neuronal excitation. Ibotenic acid is decarboxylated to muscimol in a manner analogous to the enzymatic conversion of glutamate to GABA. The decarboxylation of ibotenic acid is spontaneous, whereas the conversion of glutamate to GABA requires glutamate decarboxylase (see Fig. 6).

Ibotenic acid and muscimol are not effectively removed from the neuronal synapse by the uptake systems that remove glutamate and GABA. About one third of the muscimol and almost all of the ibotenic acid absorbed after mushroom ingestion is excreted unchanged in the urine, with peak excretion of ibotenic acid occurring within 60 min. The remainder of muscimol is excreted as oxidative and conjugated metabolites [94].

Ibotenic acid and muscimol are present in roughly equal quantities at concentrations between 0.03% and 0.5% in relevant *Amanita* spp., [90, 94]. The total toxin content varies greatly even among mushrooms of the same species, collected at the same time, from the same area [95]. Their toxicity also depends on growth substrates, methods of preparation, and length of storage before use. Ibotenic acid is spontaneously converted to muscimol. Because ibotenic acid is much less potent than muscimol, drying the mushroom increases the muscimol content and, therefore, the potency. The yellow pigments of *A. muscaria* have been shown to possess a significantly larger amount of ibotenic acid than the rest of the mushroom. Although it is not recommended, people do eat *A. muscaria* after peeling off the skin and parboiling.

The median lethal dose of muscimol varies greatly in rats but is approximately 25 mg/kg. It is unusual for humans to ingest enough *A. muscaria* to cause death. Human toxicity usually occurs with ingestion of 6 mg of muscimol, or two to four mushrooms, but even a single mushroom has produced toxicity [95].

Clinical Presentation

Signs and symptoms begin 0.5–2 h after ingestion [95]. Experimentally, clinical manifestations begin within 1 h of ingestion of 10 mg of

muscimol or 75 mg of ibotenic acid. Symptoms consist of nausea and vomiting (in about half of the patients), diarrhea, cramps, increased reflexes, tremor, myoclonic jerking, fasciculations, ataxia, extremity paresthesias, incoordination, visual changes, and altered mental status [92, 95]. The pupillary response is variable. The skin has been described as flushed and diaphoretic. Respiratory depression, bradycardia, and hypotension are rarely reported. Seizures rarely occur but may be more common in children [95]. Deaths have been reported after large ingestions (>10 mushrooms) or in association with comorbidities [96].

The usual clinical presentation of toxicity by these mushrooms is an altered mental status or inebriation, without airway compromise. The clinical course is characterized by a waxing and waning sensorium, alternating between agitation and obtundation. This effect is especially pronounced in children. Patients often exhibit bizarre behavior – elation with disorientation, depersonalization, and increased motor activity [95]. Perceptual illusions are common [97]. As the effects resolve, lethargy usually develops followed by deep protracted sleep. Patients are often amnesic to events occurring during intoxication.

Occasionally, patients exhibit muscarinic-like symptoms, including salivation, bradycardia, perspiration, vomiting, and diarrhea [95]. It is not known whether these symptoms are due to the isoxazoles, to the presence of abnormally large amounts of muscarine [89], or to an unidentified compound [92]. Most patients have improvement of symptoms within 8 h, with major toxic effects lasting approximately 12 h [95]. Residual symptoms of headache, paresthesias, and fatigue occasionally are reported for as long as 48 h afterwards [97–99].

Diagnosis

No specific laboratory tests are required. Identification of the offending mushroom and its associated toxic syndrome is usually based on the description of the mushroom as it has distinctive morphological characteristics and the patient's clinical presentation. These mushrooms are not illegal and are occasionally ordered online, in

which case they will be dried and somewhat harder to identify.

Treatment

Treatment of central nervous system toxic mushroom poisoning is primarily supportive, with symptomatic patients requiring observation in a quiet environment. Most clinical toxicologists recommend that the patient be observed until the clinical manifestations resolve. Severely intoxicated patients may require admission to the intensive care unit (see the earlier box on “Indications for ICU Admission in Mushroom Poisoning”). Patients poisoned with these mushrooms require monitoring for seizures, central nervous system depression, and aspiration. Early administration of activated charcoal may decrease absorption, but the risk of aspiration may outweigh its theoretical benefits, especially if significant time has passed after ingestion (grade III evidence). Carefully titrated benzodiazepines are indicated to control agitation and seizures. The respiratory depressant effect of benzodiazepines is potentially increased with muscimol intoxication; small, incremental doses should be used to prevent apnea [97]. Volume replacement is indicated for patients with significant gastrointestinal losses or hypotension, with vasoactive agents reserved for hypotension refractory to fluid resuscitation.

Although these patients may manifest features similar to cholinergic or anticholinergic toxidromes, muscimol and ibotenic acid do not have significant activity at the muscarinic receptors, and therefore there is no role for either atropine or physostigmine. For a mixed ingestion that included a cholinergic mushroom, glycopyrrolate may be used instead of atropine because the former does not alter mental status; however, this has not been formally studied.

Seizures are much more likely to occur in children [95]. Mortality increases with age and the presence of significant comorbidities, including coronary artery disease and chronic obstructive pulmonary disease. There should be a reduced threshold for admission to the intensive care unit for these patients. There are no data relating to isoxazole-containing mushroom toxicity in pregnancy.

Central Nervous System Mushroom Toxicity

- Ibotenic acid/muscimol-containing mushrooms
- Includes *Amanita muscaria* and *Amanita pantherina*
- Inebriating mushrooms
- Toxins have similar structures to glutamate and γ -aminobutyric acid (GABA)
- Rare seizures may be treated with benzodiazepines

Morel Neurologic Syndrome (Group 2D)

Consumption of morels (*Morchella*) can rarely cause a syndrome of gastrointestinal and/or neurologic symptoms [100]. Illness usually occurs only when they are ingested raw or undercooked, but symptoms have also occurred after eating cooked morels. Gastrointestinal symptoms usually begin about 5 h (2–12 h being the usual range) after ingestion with longer delays possible. Reported gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal pain. Neurological symptoms usually begin about 12 h after ingestion, although delays up to 36 h have been reported. Symptoms include changes in vision, headache, paresthesia, ataxia, tremor, and drowsiness [101]. Other reported symptoms after consumption of morels include asthenia, sweating, and syncope. Treatment is supportive, and recovery occurs in nearly all patients within about a day [100, 101].

Myotoxic Mushroom Toxicity (Group 3)

Rhabdomyolysis induced by mushroom ingestion has only recently been reported, and human experience is somewhat limited.

Rapid onset myotoxicity (group 3A) is caused by the mushroom *Russula subnigricans*. It was reported to cause nausea, vomiting, and diarrhea

within 2 h of a single ingestion in nine patients. In most of these patients, symptoms were self-limited and resolved within 1 day, but two patients became progressively more ill. They developed muscle pain, weakness, dark urine, and rhabdomyolysis. One required dialysis; both survived, although one had an elevated creatinine on discharge (day 33) [102]. The toxin responsible in *R. subnigricans* is believed to be cycloprop-2-ene carboxylic acid [103].

Delayed onset myotoxicity (group 3B) has been caused by the mushroom *Tricholoma equestre* (or yellow-knight fungus). In one case series, this mushroom was ingested for at least three consecutive meals in 12 patients. They did not experience gastrointestinal symptoms but developed fatigue, myalgias, nausea, and dark urine associated with rhabdomyolysis 1–3 days after their last meal. Three of these patients developed increasing dyspnea at rest, myocarditis, acidosis, and renal failure and died despite aggressive intensive care unit support which included veno-venous hemofiltration in one case [104].

Treatment of toxicity from myotoxic mushrooms centers on recognition and early aggressive care. Decontamination will not have a role due to the unlikelihood of presentation early after ingestion. As rhabdomyolysis is a component of both, IV fluid hydration along with supportive critical care possibly including hemodialysis will be required.

Metabolic Pathway Toxicity (Group 4)

This group contains mushrooms with diverse effects on human physiology with the common thread being changes to various specific biochemical pathways. ► [Chapter 109, “Gyromitra mushrooms”](#) discusses the group causing GABA deficiency and seizures (group 4A). This chapter will discuss disulfiram-like metabolic mushroom toxicity in detail (group 4B), but there are a few other very rarely encountered syndromes in this group.

Polyporic mushroom toxicity is caused by ingestion of *Hapalopilus rutilans* (group 4C). Onset is several hours of ingestion, and clinical

effects include purple urine, nausea, vomiting, nystagmus, cerebral edema, and hepato-renal failure [105]. It is one of the very few specific (i.e. not just simple GI irritation) mushroom poisoning syndromes caused by a polypore (i.e., not a gilled mushroom). The addition of 3% potassium hydroxide to the mushroom will result in a deep violet color [106]. The treatment for this extremely rare syndrome is supportive.

Hypoglycemic mushroom poisoning (group 4E) is caused by a newly discovered Chinese mushroom *Trogia venenata* which has resulted in sudden death hours to days after ingesting meal-sized amounts [107, 108]; the mushroom is geographically restricted to one province in China (northern Yunnan).

Trichothecene mushroom poisoning (group 4D; *Podostroma cornu-damae*) is limited to Japan, Java, and Korea where the relatively rare mushroom is found. Ingestion of even small amounts of mushroom results in vomiting, diarrhea, dehydration, hypotension, acute renal injury, lethargy, hepatic necrosis, DIC, and death. With survival beyond a few days, hair loss, desquamation, pancytopenia, and cerebellar atrophy have been reported. Treatment is supportive [109, 110].

Other reported mushroom poisoning syndromes proposed to be included within this group are hyperprolactinemia mushroom poisoning (group 4F; *Boletus satanas* or *Rubroboletus satanas*) and pancytopenia mushroom poisoning (group 4G; *Ganoderma neojaponicum*) [2].

Disulfiram-Like Metabolic Mushroom Toxicity (Group 4B)

The disulfiram-like toxicity from *Coprinus* mushrooms occurs only with temporally proximate co-ingestion of ethanol [111–113]. *Coprinus atramentarius* is known as the “inky cap” because at maturity the cap and gills autodigest, or deliquesce, into a black, ink-like liquid. The mature mushroom has a gray-to-brown, bell-shaped cap 4–6 cm across, with small brown scales or fibrils located primarily in the center of the cap. The stalk, white above the ring and gray below, is

slender with a hollow center and false ring. The gills are crowded, and the spores are black to brown-black. The mushrooms are widely distributed in the fall and spring, usually growing in clumps at the base of trees or over buried wood [1].

Biochemistry and Pathophysiology

Coprinus atramentarius contains the nonessential amino acid coprine (N5-[1-hydroxycyclopropyl]-L-glutamine) (Fig. 7) [114, 115]. Coprine has been found in several other *Coprinus* spp. that are too tiny to be eaten in clinically significant amounts [116]. Other mushroom genera have been reported to produce similar symptoms when combined with ethanol, but none have been found to contain coprine; symptoms may be due to ethanol and a concomitantly ingested gastrointestinal irritant mushroom or other systemic illness [120]. Cooking does not generally change the concentration of coprine significantly [114, 116]. However, there are reports that cooking may increase toxicity [117].

Coprine is a protoxin that is metabolized to the active toxin, 1-aminocyclopropanol (ACP) after ingestion. 1-Aminocyclopropanol inhibits the activity of aldehyde dehydrogenase, the primary enzyme required for the metabolism of the ethanol metabolite acetaldehyde to acetate [112, 118, 119]. 1-Aminocyclopropanol irreversibly inactivates aldehyde dehydrogenase by forming a covalent bond with the active site, resulting in an accumulation of acetaldehyde, which is thought to contribute to the disulfiram-like syndrome [116, 118, 120, 121].

Although clinically similar to disulfiram, coprine does have some important differences. It is an alkylating agent and has been shown to be mutagenic and to cause bone marrow depression in dogs [122]. These actions are unlikely to be of clinical significance for the occasional human ingester of coprine-containing mushrooms. Coprine

appears to be a more potent inhibitor of aldehyde dehydrogenase than disulfiram. In contrast to disulfiram, coprine does not inhibit dopamine β -hydroxylase, the enzyme responsible for norepinephrine synthesis [121, 123].

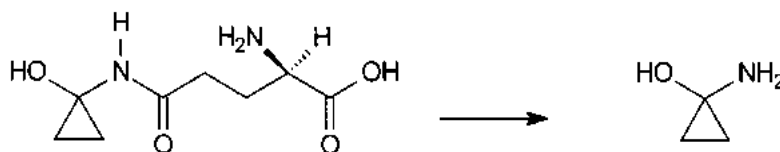
Clinical Presentation

The disulfiram-like reaction that occurs after coprine mushroom ingestion promptly occurs when ethanol is consumed within 24–48 h of eating the mushroom meal [116, 117, 124]. Symptoms can recur if alcohol is consumed again within 72 h after mushroom ingestion [116]. The intensity of the reaction is related to the timing and quantity of the mushrooms and the ethanol ingested. The reaction is more pronounced if ethanol is consumed several hours after the mushrooms are consumed rather than at the same time [125]. Typical symptoms occur within a few minutes of the ethanol ingestion. Facial flushing, a blotchy, erythematous rash extending over the arms and chest, dyspnea, headache, metallic taste, diaphoresis, nausea and vomiting, tachycardia, premature ventricular contractions, atrial fibrillation, hypotension, hypothermia, vertigo, confusion, and coma may occur [126–128]. Esophageal rupture is a reported complication of the forceful emesis that can occur [127]. Coprine/ethanol reactions typically cause more tachycardia than disulfiram/ethanol interactions [123]. Symptoms usually last 30 min to a few hours. Recovery usually occurs within 24 h even when reactions are severe [113, 116, 126].

Diagnosis

A history of mushroom and ethanol ingestion followed by a rapid onset of a disulfiram-like reaction described above is diagnostic. A careful history eliciting any other exposures capable of producing a disulfiram-like reaction should be obtained (e.g., metronidazole, trichloroethylene,

Fig. 7 Chemical structure of coprine (left) and conversion to the metabolite, 1-aminocyclopropanol



disulfiram). A serum ethanol assay may be obtained if confirmation of alcohol ingestion is warranted.

Treatment

Treatment is primarily symptomatic and supportive. There is no role for gastrointestinal decontamination. There is no evidence that antihistamines reduce the flushing associated with this poisoning. Propranolol has been proposed to treat the tachycardia; however, this has not been studied and may be risky in patients who are seriously ill [129]. Because the clinical effects are caused by acetaldehyde accumulation, an alcohol dehydrogenase inhibitor, such as fomepizole, administered while blood ethanol concentrations are elevated could theoretically reduce the severity of the symptoms by limiting acetaldehyde production; this, too, has not been studied. Hypotension occasionally occurs and usually responds to fluids but may require intravenous pressor agents. As noted above, in contrast to disulfiram, there is no inhibition of dopamine β -hydroxylase by coprine or its metabolites, and therefore dopamine could be effective based on mechanistic reasons [123]. However, other pressors, such as norepinephrine, may be preferable. The pressor of choice, to the extent that one is needed, has not been studied.

If the patient is critically ill, hemodialysis theoretically could be used to remove ethanol and acetaldehyde; however, this treatment would not be expected to limit the effects of coprine because at the time of dialysis the patient already would have undergone significant irreversible inhibition of aldehyde dehydrogenase; this has not been studied. The administration of any ethanol-containing preparation or product should be avoided for at least 72 h after ingestion of coprine-containing mushrooms.

The scenario of co-ingestion of mushrooms and ethanol is unlikely in children. Fomepizole has not been evaluated in pregnancy [130]. The elderly are more likely to have greater morbidity from a coprine-ethanol reaction, especially elderly individuals with cardiovascular disease or those who would have greater morbidity from the vomiting. Treatment for these groups is as outlined earlier.

Disulfuram-Like Mushroom Toxicity

- *Coprinus* mushrooms
- Contains a protoxin
- Produces a disulfiram-like reaction with concurrent or delayed ethanol consumption
- The Alcohol dehydrogenase inhibitor fomepizole could be beneficial in selected cases

Gastrointestinal Irritant Mushrooms (Group 5)

Gastrointestinal irritant mushrooms are the largest and least well-defined group of mushrooms; there are hundreds of species that produce primary gastrointestinal irritation. The toxins responsible for gastrointestinal irritation are varied and in many cases have not been identified. There is great individual variability in response to these toxins. Some people become very ill after ingestion; others do not become ill at all [131]. Clinical onset of nausea, vomiting, or diarrhea occurs within several hours after ingestion, an important distinguishing feature that can assist in differentiation from other more dangerous ingestions such as the hepatotoxic (amatoxin-containing) mushrooms, unless a co-ingestion of multiple mushroom types has occurred. With some very rare exceptions, toxicity arising from ingestion of a polypore (i.e., mushrooms that have pores and not gills) or puffball will be limited to gastrointestinal irritant toxicity.

Generally, only supportive care is required. There is no role for gastrointestinal decontamination; activated charcoal is unlikely to be of clinical benefit. Significant electrolyte disturbances and volume depletion with hypotension may occur. Children and the elderly are more likely to require medical treatment and admission to the hospital. Treatment consists of intravenous hydration, electrolyte supplementation, and antiemetic therapy. An antiemetic 5-HT₃ receptor agonist, such as ondansetron, is theoretically preferred to a phenothiazine, which may have side effects such as sedation that could be mistaken for a component of mushroom toxicity (grade III recommendation). The possibility of concomitant

ingestion of a cytotoxic mushroom should always be considered, and close follow-up is essential. Two mushroom species that will be discussed due to their prevalence and common misidentification are the jack-o-lantern mushroom and *Chlorophyllum molybdites*.

Jack-o-lantern Mushroom: *Omphalotus olearius/illudens*

The jack-o-lantern mushroom is an orange mushroom usually with bold color that grows in groups with non-forking faintly bioluminescent gills; it is occasionally mistaken for chanterelles. The toxin responsible for the gastrointestinal illness is believed to be the sesquiterpene illudin [132]. It has sometimes been incorrectly classified as a muscarine-containing mushroom [133]. The symptoms of abdominal pain, diarrhea, vomiting, rarely sweating, dry mouth or salivation, weakness, and visual changes may be similar to the cholinergic (muscarinic) toxicity mushrooms, but patients do not consistently report the cholinergic symptoms of salivation and lacrimation [134–136]. European reports of toxicity describe a more severe syndrome than that seen in North America including elevated transaminases, vertigo, salivation, diplopia, and fatigue with prolonged duration of illness (5–6 days) [135–137].

Green-Spored Parasol: *Chlorophyllum molybdites*

Chlorophyllum molybdites has worldwide distribution and is commonly found on lawns, occasionally growing in fairy rings; the reader is highly likely to already have seen this mushroom. The mature mushroom has a large white cap 7–30 cm in diameter that is covered with scales, frequently with a hint of pink-to-brown color at the center of the cap and scale tips. The stalk is smooth, tall (10–15 cm), and slender (2–2.5 cm at apex, 4–6 cm at base) with a thick ring. The flesh has a pleasant taste. The gills are pale yellow when young, turning green with age. The spore

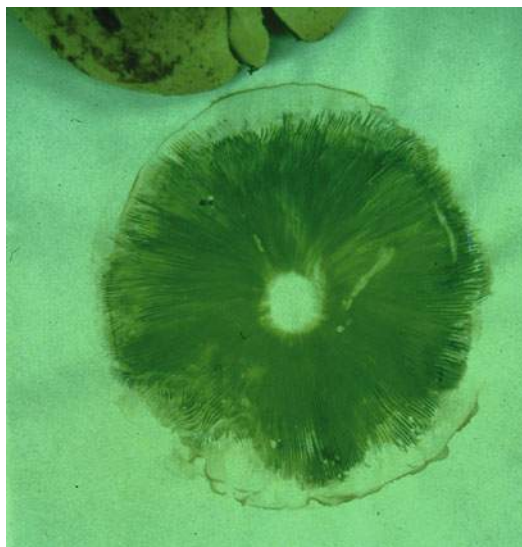


Fig. 8 *Chlorophyllum molybdites* spore print

print is a distinctive green color that can be helpful in identification (Fig. 8) [1].

The toxins have not been isolated. Cooking may reduce the potency of the toxins but does not render the mushroom edible.

A few people remain asymptomatic after ingesting *Chlorophyllum* mushrooms, an observation that is consistent with individual variation in response to the toxin. Ingestion of a portion of a single mushroom generally rapidly produces nausea and vomiting within 1–2 h of ingestion and rarely beyond that time limit. Vomiting is copious. Diarrhea also is common, and often explosive, and can be heme positive. Other symptoms commonly reported are diaphoresis, chills, dizziness, and abdominal pain [138–140]. Hypovolemia and electrolyte disturbances from the gastrointestinal losses may be severe and accompanied by other complications (e.g., seizures) if not treated. Gastrointestinal bleeding associated with disseminated intravascular coagulation has been rarely reported [141]. *Chlorophyllum molybdites* ingestion has not been reported to cause hepatic or renal injury.

Most patients improve within 4–6 h, but severely poisoned patients may not improve for 2–3 days. Patients with diarrhea and vomiting should be observed until symptoms subside.

Patients should be monitored closely for laboratory evidence of fluid or electrolyte depletion. Typing and screening for blood is recommended for patients with evidence of significant bleeding. Patients with refractory vomiting or bloody diarrhea should be admitted to the hospital. Fluid losses can be severe, necessitating several liters of intravenous fluid replacement in adults; vasopressors may be used if the patient continues to be hypotensive after adequate resuscitation. Invasive monitoring may be employed to guide treatment, if needed [140]. Deaths have occurred in pediatric patients, and intubation has been required [140]. Intensive care unit admission is warranted for children, elderly individuals, patients with significant fluid losses, and patients with significant comorbidities [140].

Analysis of the vomitus or stool may be done to determine the presence of *Chlorophyllum* spores [142]. The green spore print is nearly pathognomonic for *Chlorophyllum*.

Gastrointestinal Irritant Mushroom Poisoning

- Includes *Omphalotus olearius* and *Chlorophyllum molybdites* and many others
- Intravenous hydration may be necessary depending on the amount ingested and comorbidities

Miscellaneous Adverse Reactions (Group 6)

This group contains mushrooms that occasionally cause a variety of clinical effects which, excepting *Paxillus* syndrome, are not often life threatening or are extremely rare and geographically limited.

Shiitake Dermatitis (Group 6A)

The ingestion of raw or undercooked shiitake mushrooms can result in a distinctive dermatitis called shiitake dermatitis or “flagellate erythema” named after markings caused by self-flagellation [143]. The rash is pruritic, made of small (≈ 1 mm)

erythematous papules usually organized as linear streaks always found on the trunk but also potentially on the extremities, neck, face, and head. The rash is on areas the patient can reach and does not involve the mucosal surfaces; there is a photosensitivity component of the rash [144, 145]. It appears usually within 0.5–2 days of mushroom ingestion [145, 146]. The responsible toxin is believed to be the thermolabile polysaccharide lentinan [146, 147]. Histological changes are nonspecific, and diagnosis is by history and clinical presentation; there is no role for patch testing. Treatment recommendations are based on case level evidence (grade III); avoiding sun exposure combined with use of antihistamines provides some mild pruritus relief. Improvement is usually complete within 2 days to 2 weeks, with one outlier in a series having symptoms for 38 days [145, 146].

Erythromelalgic Syndrome (Group 6B)

The erythromelalgic syndrome (some have suggested acromelalgia syndrome) is usually reported in Japan but has been recently reported in Europe. The causative mushroom is *Clitocybe acromelalga* (known as “Dokugasako” in Japan; the mushroom is also found in Korea), but *C. amoenolens*, found in Europe, also likely causes this syndrome [148, 149]. The neuroexcitatory toxins responsible are acromelic acids, heat-stable potent analogues of the glutamate agonist, kainic acid [150–152]. The major symptom is pain in the extremities, beginning usually one to a few days after ingestion. The pain is described as a burning or electric shock-like pain which has an intermittent nature, lasting several hours with episodes occurring more at night. The pain can be made worse by even a simple light touch [153]. During episodes, there may be edema and erythema of the distal extremities. Other reported symptoms include paresthesias of the extremities and fatigue. This paroxysmal extremity pain may persist for weeks to months. Treatment is supportive, with some possible relief with short cold-water immersion, taking care to avoid injury from excessive

exposure (grade III evidence). Pharmaceutical treatment of the pain is often not effective, but acetylsalicylic acid, clomipramine, and morphine have been used with minimal success [149]. Treatment with IV (20 mg/day up to 100 mg/day for 7 days) and PO nicotinic acid (100 mg/day, slowly decreased and stopped after 3 months) has been used successfully in one case; the mechanism behind this might be due to vasodilatation or effects on metabolism [153] (grade III). As acromelic acids augment glutamate-induced depolarization, a possibility based entirely on mechanism of action might be seen with agents which inhibit glutaminergic transmission, such as topiramate [152, 154] (grade III).

Paxillus Syndrome (Group 6C)

Ingestion of *Paxillus involutus*, also known as “brown roll-rim,” can cause a severe immunologically based hemolytic illness known as *Paxillus* syndrome. This is a common mushroom illness reported in Europe [155]. Upon ingesting the mushroom (raw or cooked), an individual is exposed to the antigens; this first time they may or may not have mild symptoms (nausea, dizziness). The identity of these antigens is unknown. When ingested a second time, they absorb these antigens that form immune complexes which attach to the surface of erythrocytes. This results in agglutination and hemolysis [155, 156]. Some have suggested there may be another component of the illness caused by a direct cytotoxic compound [155]. Symptoms usually begin within 30 min to 2 h. Abdominal pain, back pain, dizziness, vomiting, and diarrhea are associated with hypotension, hemoglobinuria, oliguria/anuria, and mild jaundice [155, 157]. Patients can develop hemolysis, hyperkalemia, hypotension/shock, renal failure, and DIC. *Paxillus* syndrome has been fatal [156]. The diagnosis is clinical; a hemagglutination reaction against a *Paxillus* extract has been demonstrated in serum from some patients but this test is not commonly available. Treatment is supportive, with plasma exchange used in a few cases and hemodialysis required for those with renal injury [157].

Encephalopathy Syndrome (Group 6D)

The encephalopathy syndrome is from ingestion of the once believed edible mushroom, *Pleurocybella porrigens* (sugihiratake mushrooms). Cases of toxicity are extremely rare and limited to Japan where only a few cases have been reported. This syndrome appears to require that patients have some degree of preexisting renal insufficiency. The onset of the clinical syndrome occurs several days after ingestion of the mushroom and is marked by weakness, dysarthria, coma, seizures, and death; the mortality is around 30% [158, 159].

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In contrast to many of the man-made toxins found in the world today, the toxins present in amanitin-containing mushrooms probably have been afflicting humans for as long as they have been picking mushrooms from their varied habitats and consuming them as a readily available and tasty food source. Among all poisonous mushrooms, the widely distributed green death cap (Fig. 1), *Amanita phalloides*, may have played the leading role, having been recognized as poisonous mostly by trial and error.

Traditional treatments have been primarily based on anecdotal evidence. One of the treatments for amanitin poisoning that evolved in the 1800s and lasted until the 1930s was based on the observation that rabbits consumed these mushrooms with impunity. This led to the development of an antidote consisting of the stomachs of three rabbits and the brains of seven rabbits, with addition of sweeteners for palatability. The ingredients were finely chopped to mask their origins. Because many individuals who received this regimen survived – most probably those suffering from a less severe intoxication – the use of this remedy persisted for many years [1]. Another anecdotally touted antidote for amanitin poisoning was a cocktail proposed by Pierre Bastien, a practitioner from Alsace, which contained vitamin C, vitamin B, nifuroxazide, and neomycin. With this regime he survived several experiments on himself [2].

At the beginning of the last century, the mortality rate of amanitin poisoning was very high.

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Fig. 1 *Amanitas phalloides* (“Death cap”) (Image from Wikipedia under Creative Commons license)

Alder published a paper [3] in which he mentioned mortality rates at the beginning of the twentieth century. In 1905 and 1913, the rate was 63%/52% in France, 46% in Germany between 1914 and 1923, and 45% in France between 1921 and 1928. Nowadays the mortality rate is down to 5–10% most likely due to the improvement of intensive care and the introduction of a variety of antidotes as described below.

Mushrooms that contain amatoxins are largely from three genera: *Amanita*, *Galerina*, and *Lepiota* species. Amanitin-containing mushrooms are probably responsible for more than 95% of mushroom fatalities worldwide [4]. It can be confused with other green mushrooms such as *Russula cyanoxantha*, *Russula virescens*, and *Tricholoma flavovirens* [5]. Other *Amanita* spp. that contain amatoxins include *Amanita ocreata*, *Amanita verna*, *Amanita bisporigera* [6], and *Amanita virosa* (destroying angel). *Amanita virosa* and *Amanita verna* can be mistaken for *Agaricus campestris*, *Agaricus sylvaticus*, and

Agaricus abruptibulbus [5]. *Amanita* mushrooms are usually large in size and often fruit in sufficient numbers to invite picking. *A. phalloides* bears enough resemblance to a widely cultivated mushroom of southern Asia, *Volvariella volvacea* (paddy straw mushroom) that groups of immigrants in California, Oregon, and New York have mistakenly harvested and been poisoned by them. Nontoxic *Amanita* spp., including *Amanita caesarea*, *Amanita rubescens* (blusher), *Amanita calypttrata*, and *Amanita velosa*, are sought by knowledgeable collectors for their fine taste [6]. Two other *Amanita* spp., *Amanita pantherina* and *Amanita muscaria* (fly agaric), do not contain cyclopeptides but are toxic due to the presence of ibotenic acid, causing transient syndromes primarily involving the central nervous system.

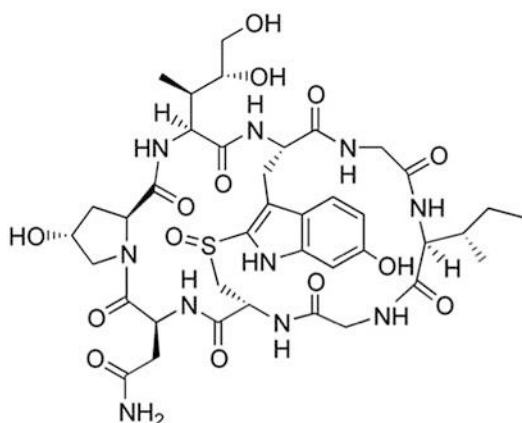
Galerina spp., another amatoxin-containing genus, are small brown mushrooms growing on decaying wood. Because *Galerina* mushrooms may be mistaken for hallucinogenic *Psilocybe* mushrooms, misidentification between these genera may lead to amatoxin poisoning. Especially *Galerina marginata* can be mistaken for *Kuehneromyces mutabilis* [7] or *Armillaria mellea* (honey-colored agaric). Further amatoxin-containing *Galerina* spp. include *Galerina autumnalis* and *Galerina venenata*. Some samples of *Conocybe filaris* also have been shown to contain the toxin [1]. Certain *Lepiota* spp. also contain amatoxins: *L. helveola*, *L. fulvella*, *L. josserandii*, and *L. brunneoincarnata*. *Lepiota* mushrooms are small and may be confused by the indiscriminate picker with larger *Lepiota* spp. as parasol mushroom (*L. procera*) and *L. rhacodes* [8] (Table 1).

Chemistry of Amanitin/Amatoxins

Alpha-Amanitin (Fig. 2) was first isolated from the mushroom *A. phalloides* in 1940 at the Ludwig Maximilian University in Munich by Heinrich Wieland and Hallermayer [12]. Its structure is an octapeptide and was elucidated in 1966 by Theodor Wieland and Gebert [13], the complete formula by Faulstich et al. 2 years later

Table 1 Concentrations of amatoxins (mg/g dry weight) in amatoxin-containing mushrooms. Assumed deadly dose: 0.1 mg/kg bw [9–11]

Mushroom	Amatoxins (mg/g dry weight)
<i>Amanita phalloides</i> A.var. <i>verna</i> and <i>Amanita</i>	1.4–6.8
<i>Amanita virosa</i>	1.9–2.6
<i>Lepiota brunneoincarnata</i>	1.3
<i>Lepiota josserandii</i>	3.5
<i>Galerina marginata</i>	0.6

**Fig. 2** Alpha-amanitin (Image from Wikipedia under Creative Commons license)

[14]. Today we know a group of nine thermostable cyclic peptides of this kind called the amatoxin family, with α - and β -amanitin constituting about 90% of all. Amatoxins are cyclic octapeptides. The molecule adopts a double-ring structure because of the sulfoxide bridge between the side chains of the two juxtaposed amino acids in the cyclic peptide, cysteine and hydroxytryptophan. Amatoxins vary in the extent of hydroxylation in one of the isoleucine side chains or in replacement of asparagine for aspartic acid. The lethal dose of amatoxins for man is assumed to be 0.1 mg/kg body weight and may be contained in a single mushroom [11].

Other cyclopeptides found in *Amanita* mushrooms include heptapeptides referred to as phallotoxins and virotoxins. Phalloidin, the main

component of the phallotoxins, was previously thought to be responsible for symptoms like the gastroenteritis that develops after cyclopeptide mushroom ingestion [15]. However, in beagle dogs, amanitin alone produced the same symptoms as amanitin mixed with phallotoxins rendering unlikely that phallotoxins contribute to human *Amanita* poisoning [16]. Similarly, the virotoxins [17], exhibiting the same toxic activity on the actin cytoskeleton of cells as phallotoxins, are unlikely to play a role in human *Amanita* poisoning.

Phallolysins [18, 19], a group of glycoproteins in amatoxin-containing mushrooms, exert strong hemolytic activity on mammalian red cells, are heat-labile, and break down in the presence of low gastric pH. Hence, they are not believed to contribute to toxicity.

Toxicokinetics of Amatoxins

Pharmacokinetics of Cyclopeptides

Volume of distribution: 0.2 L/kg

Protein binding: none

Mechanism of clearance: renal clearance
83–89%

Metabolism: none

Methods to enhance clearance: Multiple doses of activated charcoal (MDAC) pharmacological blockers of OATP interrupting enterohepatic recirculation

Toxicokinetic data of amatoxins were created in dogs using labeled amatoxins [20]. The volume of distribution is low with 0.2 L/kg body weight. There is no documented metabolism of amatoxin and no protein binding, nor are amatoxins cleaved by proteases. Amatoxins in severe poisonings can be detected in urine up to 4 days whereas detection in blood is only possible for a short time after ingestion [21–24] and may be negative at the patient's admission to the hospital. Amatoxins are rapidly excreted into the urine and bile. A bolus of (^{14}C) Methyl- γ -amanitin given into a beagle dog was excreted up to 85% into the

urine by 6 h [16], rendering extracorporeal purification procedures of blood of little utility. Experiments with perfused rat livers [25] suggested that amatoxins may undergo enterohepatic circulation, and that permanent reabsorption of the toxin by hepatocytes may be crucial for prognosis. This theory was confirmed in experiments with dogs showing that all animals having a bile fistula survived the lethal dosage of 0.1 mg/kg body weight amanitin, while all control animals died [16, 26].

Hepatotoxicity of Amatoxins

Hepatotoxicity of amatoxins is based on the presence of the “Organic Anion Transporting Protein 1B3” (OATP1B3) in sinusoidal membranes of hepatocytes [27]. When the transporting protein was transfected to MDCKII cells, these cells became about 80 times more susceptible to α -amanitin than the native cells, suggesting that OATP1B3 is the transporting protein on hepatocytes most responsible for the import of amatoxins into hepatocytes. The system of the transfected MDCKII cells also allowed for the identification of new competitive inhibitors potentially useful as antidotes in human mushroom poisoning. Moreover, it allowed the analysis of the inhibitory capacities of potential treatments, among them those widely used in the past, like penicillin.

Table 2 shows that silibinin, presently favored as the antidote in Europe with the exception of Italy, is among the most potent inhibitors of

OATP1B3. On the other hand, antamanide proposed by Wieland [10], and penicillin proposed by Floersheim [28] as antidotes, are indeed inhibitors for amanitin transport into cells, although with lower capacity than silibinin.

After the transportation of amatoxins into hepatocytes, the toxins enter the nucleus of the cells and bind to RNA polymerase II (RNAP II) with high affinity (K_D in the nM range). RNAP II is a key enzyme in all mammalian cells transcribing DNA into high nuclear RNA the precursor of messenger RNA, representing the message for all proteins in a cell. It was in 1970 that Meilhac et al. [29], among others, described that this enzyme is inhibited by amanitin. The structure of a complex between amanitin and the catalytic subunit of RNA polymerase II was elucidated by X-ray analysis in 2002 by Bushnell, et al. [30].

As it appears, binding of amanitin blocks the mobility of several enzyme domains involved in the catalytic process, as well as the movement of the enzyme on the DNA strand, resulting in a halt of transcription. Recovery of the enzymatic activity seems unlikely by the very low dissociation rate of the complex, and above all, by the rapid ubiquitinylation [31] of the catalytic subunit, inducing its degradation in the proteasome [32]. A block in transcription of mammalian cells leads to apoptosis *a* programmed cell death.

Clinical Presentation of Amanitin Poisoning: Phalloides Syndrome

Cyclopeptide mushroom poisoning recurs – at last in Middle Europe – from July–October every year. Since collecting mushrooms is a weekend activity, patients tend to seek medical care on Sundays or Mondays. Some people ingest dried or frozen mushrooms and can be poisoned at any time of the year. Signs and symptoms appear between 6 and 24 h after the mushroom meal. Most patients get sick 10–12 h after the meal. The symptoms are severe abdominal pain or cramps, vomiting, and cholera-like diarrhea persisting for the first day. This severe gastrointestinal phase is followed by an apparently

Table 2 Inhibition of OATP1B3-mediated uptake of (³H) *O*-methyl-dehydroxymethyl- α -amanitin in OATP1B3-exposing MDCKII cells [27]

	IC50 (μ M)	(Inhibition capacity (Silibinin = 1.0))
Penicillin G	25	0.02
CCK8	10	0.04
Bromosulphophthalein	3	0.13
Rifampicin	0.8	0.5
Antamanide	0.7	0.6
Silibinin	0.4	1.0
Cyclosporin A	0.3	1.3

improving clinical period of up to 24 h before the hepatic injury progresses to either acute hepatic failure or recovery.

This late onset of symptoms is a distinct and nearly pathognomonic diagnostic feature that, however, may be concealed in three situations. In the first, the amanitin-containing mushrooms were eaten in two meals exhibiting symptoms shortly after the second meal. In the second, the mushroom meal included mushrooms with a short incubation time for gastroenteritis. In the third, the mushroom meal was contaminated by bacteria (*Salmonella*, spp. *Bacillus cereus*) with a delayed onset of symptoms (food poisoning).

In all cases, commencing antidotal treatment should not be postponed even if it turns out not to have been necessary. Last, but not least, even edible mushrooms can produce symptoms with a delayed onset in some individuals. In these cases, however, the symptoms are distinctly milder.

A simplified day-by-day outline describes the course generally seen in fatal amanitin poisoning:

Time Schedule for Amatoxin Poisoning [8]

Day 1	Mushroom meal and symptom-free interval
Day 2	Emesis, abdominal cramps, and diarrhea
Day 3	Liver injury, coagulopathy, mild renal insufficiency
Day 4	Gastrointestinal bleeding, severe coagulopathy if not treated
Day 5	Hepatic encephalopathy Grade II–IV
Day 6	Complete kidney failure
Day 7	Death without liver transplant or human albumin dialysis

This pattern can be influenced by therapy. Thus, the occurrence of an early death due to circulatory failure can be avoided by rigorous fluid replacement. Bleeding can be managed by the administration of fresh frozen plasma or clotting factors. Renal failure, if severe, can be treated by hemodialysis. On the other hand, the onset of acute hepatic failure can be medically managed only for a short period of time.

Of course, not all amanitin poisonings are fatal. Therefore, a classification of severity is essential for deciding on therapeutic measures and prognosis. This cannot be done at admission to the hospital. The best day for a prognosis is the third day postexposure [33].

Severity Grading of Amanitin Poisoning

Grade I:	Patients exhibit gastrointestinal phase with typical delay but do not develop biochemical signs of liver or kidney dysfunction though other persons who have eaten the same meal may develop higher severity grade
Grade II:	Patients show delayed gastroenteritis with a mild rise in transaminases (two- to tenfold upper limit) but no coagulopathy
Grade III:	Patients develop severe hepatic injury, with transaminases > tenfold the upper limit of normal plus coagulopathy manifest by a rise in the international normalized ratio (INR) or a fall of prothrombin index
Grade IV:	Patients are characterized by a steep rise in transaminases and a steep decline in clotting function not improving after day 4, a steep rise in bilirubin and a rise in creatinine after day 3. This phase is usually fatal without liver transplant

It is obvious that Grade I and II patients have the best chances of surviving amanitin poisoning. It can be expected that supportive care with fluid and electrolyte replacement would be sufficient. However, as we cannot fully assess the severity of the poisoning prior to day three, antidotal treatment is indicated up to that time.

Grade III patients are at high risk and should be transferred to a center with the ability for hepatic transplant. Out of a 104 patients from our unit, only 6 could not be classified according to our severity grading: They showed a mild rise in transaminases (<10 times upper limit) but still a decrease in clotting function. All patients survived.

In the effort to differentiate between survivors and patients who need liver transplant, we compared the laboratory parameters of 23 patients who died from amatoxin poisoning with those of

104 patients who survived grade III intoxication [34], equivalent to acute liver injury (ALI) as defined by the US Acute Liver Failure Study Group registry [35].

Transaminases

In our comparison, AST peaked at day three and ALT at day four. AST returned to normal on days 4–6 in survivors. There was no significant difference in transaminases between survivors and fatal cases. Only 69% of the fatal cases had higher transaminases than the survivors. Therefore, the transaminases are not useful for prognosis [34].

Bilirubin

Bilirubin seems to be a rather late indicator for the prognosis. A rise above 5 mg/dl (85 μ mol/l) after day three was associated with a poor prognosis. About 82% of the fatal cases had higher bilirubin than the survivors.

Prothrombin Index

The behavior of the prothrombin index is of high prognostic value. An early and steep drop in prothrombin index (or a rise in INR) is a bad prognostic sign, especially if it does not recover after day 3–4.

There was, however, one interfering factor in our study. To avoid gastrointestinal bleeding, we treated coagulopathy early. Therefore, we saw few prothrombin indices below 20%. Nevertheless, 96% of the fatal cases had a prothrombin index lower than 25%, whereas only 4% of the survivors showed a prothrombin index below 25% [34].

Kidney Function

Severe nephrotoxicity caused by amatoxins has been mostly seen in animal experiments or in kidney perfusion models. In humans, nephrotoxicity is distinctly less than hepatotoxicity [36]. Due to the first-pass effect, the liver takes up in the early stage of the intoxication more of the amatoxins than any other organ. Only a small amount of amatoxins may penetrate into kidney cells as they have no OATP system, even though the major part of the toxins is excreted through this organ. Accordingly, early kidney injury

indicates a poor prognosis. Aside from being a direct nephrotoxin, there are two other mechanisms that can lead to kidney injury. One is prerenal azotemia caused by volume depletion in the early stage of the intoxication. The other is the hepatorenal syndrome in the late stage of the course. Kidney function due to hypovolemia, as indicated by elevated BUN, creatinine, and oliguria, can be normalized by fluid replacement. A slight elevation of serum creatinine on day three and beyond that fails to respond to fluid replacement points to a direct toxic effect on the kidney. Indeed, in our study 93% of the fatal cases had elevated serum creatinine (some very slightly) from day three onward. The combination of prothrombin index (<25%) plus the creatinine value > 106 μ mol/l (1.2 mg/dl) had a sensitivity of 100% for predicting death. All patients who did not meet these parameters survived. The specificity was 98%, as two patients survived with a prothrombin index <25 and creatinine > 106 μ mol/l (1.2 mg/dl).

These criteria are different from the “King’s College Criteria” (KCC) for paracetamol poisoning. In amatoxin poisoning, metabolic acidosis does not ensue before terminal circulatory failure, and this happens (with few exceptions) much later than 24 h. An elevation of serum creatinine portends a bad prognosis at much lower levels than 300 μ mol/l (3.9 mg/dl) as seen by KCC. Grade IV encephalopathy and coagulopathy are the excellent prognostic parameters in both intoxications.

Diagnosis of Cyclopeptide Mushroom Poisoning

History of ingestion of mushrooms known to contain cyclopeptides (*Amanita* spp., *Galerina* spp., *Lepiota* spp.)

History of ingestion of unknown mushrooms with onset of vomiting and diarrhea > 6 h after ingestion

Signs and symptoms of acute hepatic injury 1–3 days after mushroom ingestion

Identification of the mushroom by an expert

Measurements of amatoxins in urine

Identification of spores

The diagnosis procedure is based on three factors:

Identification of the mushroom
Signs and symptoms of the patient
Laboratory findings

Identification

The identification of the relevant mushroom can be made either by direct examination of the mushroom brought in by the patients or by the patient's description. One should bear in mind that the patient might have eaten several different species of mushrooms which might not be in the leftovers. The advice of an expert, a mycologist, or of a staff member in a poison control center should be obtained. This can be done by making a photograph and transmitting it to an expert mycologist or poison control center for a rough first identification. If no offending mushroom is available, a questionnaire can be useful. This should include asking for the shape of the cap (pileus), the stipe, gills, color, and the location where the mushroom was found. Poisonings by toxic *Amanita* spp. can be ruled out if the mushrooms were not taken from a forest from under a tree or a glade. *Amanita* poisoning is not possible if the collected mushrooms had pores and no gills under the pileus. If the patient indicates that they have ingested white-gilled mushrooms that showed a white or pale-green cap, it is highly suspicious that he or she has ingested a poisonous *Amanita* spp.

Clinical Presentation

All patients with signs of severe gastroenteritis occurring more than 6 h after the ingestion must be considered to have amatoxin poisoning until disproven. This clinical presentation is the leading characteristic of this intoxication.

Laboratory Findings

Laboratory tests are less important than are the clinical feature or the identification of the mushrooms. To be effective, treatment must be

commenced long before the diagnosis is verified. Therapeutic measures must never be postponed pending a laboratory result. If the mushroom cannot be identified macroscopically, it is prudent to use leftovers for microscopic search of spores, which will be always successful if parts of the pileus are within the leftovers. *Amanita* spp. have spores that are globose to subglobose, smooth, thin walled, and hyaline positive. They are 7–11 μm long and 6–9 μm wide. In Melzer's solution, the thin walls of the spores turn "amyloid," or blue black. Differentiation from *Agaricus* spores is easy, as *Agaricus* spores are dark brown and do not react with Melzer's solution (30 ml water, 1.5 g potassium chloride, 0.5 g iodine, and 20 g chloral hydrate).

The so-called newspaper test (Meixner's test) is only valuable for the exclusion of amatoxin poisoning if the offending mushroom is available and if the test result is negative. It can be performed in the remains of any part of the mushroom, provided it is unboiled. A piece of the mushroom is firmly pressed on an unprinted margin of a normal newspaper (not a magazine) which contains lignin and the spot is left to dry for 5 min. Then a drop of concentrated hydrochloric acid is placed adjacent to the spot. If the sample contains amatoxins, the overlap area will turn blue. This test is positive in all amatoxin-containing mushrooms. However, it is nonspecific since there are some mushrooms that will test positive but do not contain amatoxins [37, 38].

For detecting amatoxins in biological fluids such as serum, urine, gastric juice, or bile fluid, a sensitive assay is available in some countries. It is an ELISA from Bühlmann Laboratories AG Schönebuch, Switzerland. This test has a high sensitivity and can measure α -amanitin and γ -amanitin (not β -amanitin) in urine down to 1 ng/ml. There is agreement that values above 5 ng/ml in urine are judged as positive. There are other methods which can distinguish between α -amanitin and β -amanitin such as high-performance liquid chromatography and liquid chromatography – mass spectrometry, but they are not generally available. Attempts to determine serum concentrations of amatoxins are not useful as they can be negative by the time of admission to

the hospital. Detection of amatoxins in urine is possible for a longer period but may become negative by 48 h after ingestion. Very early, before symptoms appear, urine amatoxin assays may be negative [21–24]. By the time of hospital admission, amatoxin-poisoned patients may exhibit signs of dehydration, with hemoconcentration, hypokalemia, hyponatremia, hypoglycemia, and elevated BUN but with liver function tests near normal. However, by the second day, severely poisoned patients show a steep rise in transaminases and INR, whereas moderately poisoned patients develop a mild rise in transaminases without coagulopathy.

Treatment

Epidemiology/History

Before the 1980s, treatment of *Amanita* intoxication has followed the belief that the more treatment done, the better. Not to miss the potential benefit of a drug reported to be successfully used in case series, overtreatment by using the combination of many drugs was the rule [7]. Cytochrome C, steroids, vitamin C, and, since the 1960s, thioctic acid [39, 40] were often given in combination and were all believed to exhibit antidotal efficacy.

The mortality rate of amanitin poisoning on average was 30.2% between 1919 and 1958 (87 deaths of 288 cases) [3]. After the introduction of penicillin into therapy by Floersheim [41] in 1971 based on its efficacy in animal experiments [42], mortality fell to 22.4% (46/205) between 1971 and 1980 [43]. However, this improvement may have been due to advances in intensive care medicine. In France, from about 1930 to 1960 a serum antiphallinique [44] was on the market produced by the Pasteur Institute which turned out not to be useful and being a crude horse serum has caused anaphylactic shock [45].

In 1988 Faulstich et al. [46] demonstrated that a monoclonal amatoxin-specific Fab antibody did not neutralize, and even enhanced, hepato- and nephrotoxicity in a mouse model. Enjalbert et al. [47] reviewed retrospectively over a period

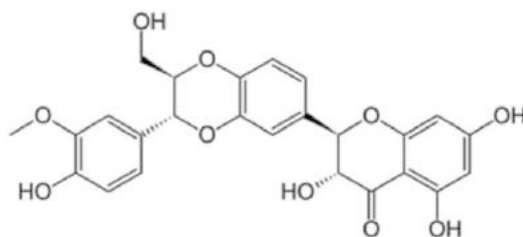


Fig. 3 Silibinin (From Wikipedia used under the creative Commons license)

of 20 years up to 2002 the outcome of amatoxin poisonings comparing different therapeutic regimes and concluded that the highest mortality/lowest efficacy was observed in the combination of benzylpenicillin with thioctic acid, with steroids and with any other drug. The only exception was the combination with silibinin. The lowest mortality rate was observed with silibinin (Fig. 3) or *N*-acetylcysteine (NAC) when each of them was used as monotherapy. There is little experience with the use of both of these antidotes simultaneously. Before silibinin was marketed, it was shown that it markedly reduced liver injury in beagle dogs: None of the dogs died when treated with silibinin, whereas 4 of 12 dogs died with signs of hepatic coma at the same dose of amanitin when they were not treated with silibinin [48]. The first experience with silibinin treatment in humans was described by Hruby et al. [49]. Of 18 patients with *Amanita phalloides* intoxication, 17 survived after treatment with a combination of penicillin plus silibinin. The one who died committed suicide by mushroom ingestion. In Portugal, the mortality rate between 1990 and 2008, without mentioning the kind of treatment, was 11.8% [50, 51]. According to the annual report of the American Association of Poison Control Centers [52] 2012, 4/44 (9%) patients died in the US in 2012. In Switzerland between 1995 and 2009, 5 of 32 (16%) patients died [53].

It may be that there are big differences in the toxicity of amanitin-containing mushrooms even in the same species from country to country. The Italians had the best results even with benzylpenicillin treatment alone. In a monocenter study (Florence) [54], they had only 2 deaths in 105 patients between 1988 and 2002 and 10 deaths

out of 242 patients (4.1%) on NAC treatment in Pavia between 2002 and 2012 [55]. In 11 patients treated with NAC in combination with benzylpenicillin all survived, one with liver transplant [56]. The worst results occurred in Australia where out of 12 patients, 9 of them having received silibinin 4 died (33%) [57].

These data are confusing. A multicenter prospective randomized study comparing different regimes as such as *N*-acetylcysteine versus silibinin cannot be done because it would likely require approximately 600 patients in each arm. A comparison of supportive treatment alone to silibinin or NAC cannot be undertaken for ethical reasons as empirical data indicate efficacy of silibinin, benzylpenicillin, and NAC.

A retrospective study published in 2008 [58] analyzed for the best antidotal treatment. After silibinin became available in 1980, penicillin treatment was still accepted so that a combination of silibinin + penicillin became the therapy of choice. Later, after realizing that silibinin and penicillin were both active in blocking the OATP, silibinin monotherapy was established. Included in the study were 614 patients, of which 388 had enough data for the evaluation. The patients came from the Toxicological department in Munich, from post marketing surveillance by the Madaus firm, and from Vienna, Mainz, Berlin, and Schweinfurt. 248 patients were treated with penicillin plus silibinin, 118 patients had a silibinin monotherapy. In the group that received the combination therapy, 8.8% died or had liver transplantation (21/1). In the group treated with silibinin only, 5.1% of the patients died or had liver transplantation (1/5). Though the risk of death in the silibinin mono-group was reduced by 40% the difference was statistically not significant. A longer period before the appearance of symptoms after the mushroom meal was associated with significant reduction of the risk of death (odds ratio, 6.17: 95% CI, 1.77–21.3; $p < 0.004$, <12 h: >12 h). A later start of silibinin therapy > 24 h versus < 24 h was associated with an increased frequency of death (OR, 3.0: 95% CI, 0.96–9.29; $p < 0.059$). This was true even though the patients with a shorter latency period exhibited

higher severity grades. From this study we concluded that early monotherapy with silibinin is efficacious. (Grade II-2 evidence) The ambiguity in all of these studies is that the distribution of patients with different severities in the different groups cannot be judged at admission and the influence of treatment before severity is assessed is not known. Nevertheless, the reduction of the mortality rate from over 30–20% with penicillin to 5–8% with silibinin argues for the efficacy of silibinin. In a highly sophisticated multidimensional multivariate statistical analysis using different logic including the data of Enjalbert [47], silibinin and NAC were found to be effective [59]. These statistics, however, including the majority of cases treated with silibinin in combination or alone comes from the firm producing silibinin [60]. The mortality rate was 7% (107 fatal cases of a total of 1491 cases).

Indications for ICU Admission in Cyclopeptide Mushroom Poisoning

Suspected cyclopeptide mushroom ingestion (gastroenteritis > 6 h) and elevated transaminases from day two- on $>$ tenfold upper limit

Severe dehydration and loss of electrolyte on the day one with increased hematocrit and/or BUN, and/or hypoglycemia, and/or hypokalemia and/or hyponatremia

Treatment of Cyclopeptide Mushroom Ingestion

Fluid and electrolyte resuscitation

Glucose solution for hypoglycemia and nutrition

Enhanced diuresis to keep up kidney function for elimination of amatoxins

Multiple doses of activated charcoal to reduce enterohepatic recirculation

Antidotal treatment with silibinin possibly in combination with NAC but not in combination with penicillin

Antidotal treatment with high-dose penicillin if silibinin is not rapidly available, possibly in combination with NAC

(continued)

If started on penicillin, switch to silibinin as soon as silibinin is available

Liver transplantation if necessary

Bridging with human albumin dialysis (MARS[®]) if patient is in coma until donor liver is available

Vitamin K + clotting factors + FFP if INR is > 6

Hemodialysis for renal failure

Treatment in Detail

Treatment of Dehydration

During the first 24 h after admission, volume replacement of 4–6 l is usually necessary. Fluid replacement must occur intravenously because of persistent vomiting and diarrhea. We recommend glucose (5–10%) with sodium and potassium (200–300 meq/24 h each) added. Because of volume depletion, fluid status and urine output should be monitored closely and serum potassium and sodium assayed and corrected as needed. As a rule, this approach will achieve initial stabilization. Clinically, the endpoints of fluid resuscitation are resolution of hypotension, normalization of the hematocrit and BUN, and increase in the central venous pressure. If hypoglycemia and hypotension persist, this may indicate inadequate resuscitation, early liver failure, or shock due to sepsis caused by the necrotic liver. Because in the Italian experience [54, 55, 61], forced diuresis was associated with good survival rate resuscitation to a brisk urine output is recommended by the authors (Grade III recommendation) as there is no doubt that maintaining glomerular filtration is important for the excretion of amatoxins. However, it is not clear if forced diuresis supported by loop diuretics such as furosemide enhances amatoxin clearance. Caution should be exercised, however, in cases of kidney failure due to the nephrotoxic effect of the amatoxins, in which fluid overload may occur and lead to cerebral edema, especially in combination with impending hepatic encephalopathy.

Removal of Toxin

The ability to do successful decontamination is strongly dependent on the time of admission to hospital. Only a small percentage of patients – two cases in our collective experience – arrived at the hospital during the early asymptomatic phase. One suicidal person and one patient with doubts about the ingested mushrooms sought help during this phase (<8 h). In these very rare cases, primary decontamination in the form of a high-dose activated charcoal and secondary decontamination with hemoperfusion is recommended by us. Activated charcoal should always, in our opinion, be given for primary and secondary decontamination. Charcoal binds amatoxins left in the intestine and interrupts enterohepatic circulation of the toxins. Our recommended dose is 50 g as a start and 12.5 g/h during the next 3 days. In some cases, a stomach tube may be necessary through which charcoal is continuously dispensed. If not using forced diuresis as discussed above, sufficient diuresis after volume replacement should be maintained. We recommended a rate volume replacement of 200 ml/h for 2–3 days [62].

In the 1980s, hemoperfusion was extensively used with the aim of removing amatoxins from the blood. Looking into more detail of the toxicokinetics, it became obvious that there is no toxin to be removed at that time when this therapeutic procedure can usually be started [23, 61, 63]. In 22 cases of amanitin poisoning in which we measured amatoxin levels in blood at admission, only three patients had measurable amatoxins, between 2 and 4 ng/ml. The amount of toxin removed by hemoperfusion in these patients was small. Hemoperfusion, hemodialysis, plasmapheresis, or human albumin dialysis are not, therefore, useful for secondary detoxification. One exception to that rule might be the very early presentation as seen in the suicidal patient who had taken a lethal dose of *Amanita phalloides* (five mushrooms) and survived when hemoperfusion was started before symptom onset [8].

As amatoxins are readily excreted through bile fluid, it might be reasonable to interrupt the

enterohepatic circulation of the toxins completely by suction of the duodenal fluid or even by inserting a nasobiliary tube into the ductus choledochus through the papilla Vateri and draining the whole bile fluid from the body. This was performed in a few cases [64] (Todd Mitchell personal communication). There may be some risk in this procedure, such as pancreatitis or bleeding from the papilla Vateri. A final conclusion about the efficacy of this procedure cannot yet be drawn. The most benefit may be from activated charcoal administration such that charcoal is present in the duodenum.

Antidotal Treatments

Benzylpenicillin, silibinin, and NAC are presently used as antidotes. Animal models and experiments in hepatocyte cell cultures [27] show that the uptake via OATP 1B3 is inhibited by many substances. This holds true both for penicillin and silibinin, but silibinin at the recommended dose is 50 times more potent than penicillin (see Table 2) in inhibiting amanitin uptake into the liver cell. The mechanism by which NAC may act is not clear. It is likely to be a combination of scavenging the toxin, antioxidant action, and reactivation of glutathione, as in paracetamol poisoning. There are no known adverse effects of silibinin at the dose blocking the transport system for the amatoxin uptake into the liver. In contrast, penicillin in effective doses may induce convulsions, especially if cerebral edema is imminent. In addition, penicillin may cause anaphylactic shock, interfere with coagulation, and induce pseudomembranous enterocolitis.

Due to these risks and the better results achieved with silibinin monotherapy, we recommend that penicillin should only be used if no, or until, silibinin is available. This might be a problem for the treatment outside of Europe where silibinin is not approved and therefore may not be readily available. In the US, silibinin is available as an investigational drug. A combination of penicillin as well as silibinin with NAC might be wise as NAC certainly has an antioxidative effect and can help to restore glutathione which is depleted in *Amanita* poisoning.

For dosing silibinin, we suggest – contrary to the instruction leaflet – a continuous infusion after a bolus. The bolus is sufficient to create therapeutic silibinin levels within one hour which might be of importance as many patients come in late. The bolus is 5 mg/kg body weight within one hour followed by 20 mg/kg body weight in a continuous infusion over the next 24 h. This dose is equivalent to the dose in the instruction leaflet, where administration in intervals is advised. There is no limit for the period of silibinin administration. In patients that can be classified as severity grade I–II (mild and moderate), the infusion can be terminated on day three. We recommend that all other patients should receive silibinin infusion until day six or until transaminase levels and INR are declining significantly. Silibinin treatment should also be used during the asymptomatic period in the few cases that present early after a suspicious mushroom meal. If no symptoms develop within 24 h, silibinin treatment can be terminated. It is essential that silibinin treatment be commenced in all cases in which amanitin poisoning is suspected.

The suggested dose for penicillin is 1,000,000 U/kg body weight on the first day and 500,000 U/kg body weight on day two and three. After the third day, penicillin treatment is no longer advised if the patient is progressing toward hepatic encephalopathy. From the abovementioned study comparing penicillin plus silibinin in combination to silibinin monotherapy, combination therapy seems not to be advantageous. Since both penicillin and silibinin are competitive inhibitors of the amanitin transporting system, they may interfere negatively with one another. Therefore our advice is to use silibinin alone if it is available.

In a mouse model, no change in survival or hepatic enzyme elevation was seen comparing amanitin poisoned mice given NAC treatment compared to control animals [65]. *N*-acetylcysteine has been used successfully, especially in Italy [55, 56].

The specific NAC protocol used in Italy is not exactly the same of that used in paracetamol poisoning. The differences are related to both NAC loading dose and duration of treatment (total

dose). They administer an intravenous loading dose of 150 mg/kg in no less than 90 min (to minimize the adverse effect anaphylactoid reaction), followed by the maintenance dose of 300 mg/kg/24 h (this is the so-called Pavia amatoxin protocol). This regimen of continuous infusion is started at Emergency Department admission in patients with suspected *Amanita* poisoning, and then:

- Is stopped if the urinary levels of alpha-amanitin are negative.
- Is continued if the urinary levels of alpha-amanitin are positive. The intravenous regimen of continuous infusion of 300 mg/Kg/24 h is subsequently.
 - Stopped 48–72 h in patients that don't develop hepatitis and with negativization of urinary alpha-amanitin levels.
 - Continued as long as the alpha-amanitin levels remain positive (even in the absence of hepatic damage) or as long as ALT decrease below 200 UI/L in patients that developed hepatic damage. In the Italian experience (Carlo Locatelli personal communication) in this last group of patients, the continuous infusion regimen of 300 mg/kg/die was continued for an average of 7 days (minimum 3 and maximum 21 days).

No adverse effects have been published from using NAC in this context, although anaphylactoid reactions can be expected with intravenous administration. Other substances such as steroids, vitamin C, cytochrome C, and thiocetic acid are no longer recommended. These interventions have not shown any additional benefit when combined with silibinin, penicillin, or NAC [47, 60]. In mouse/rat models picrothiza and cimetidine [66–68] showed some protective effects. Other non-penicillin antibiotics, like cephalosporins, were used instead of benzylpenicillin [69, 70], but there are too few cases to assess their efficacy. In cell culture experiments, all antibiotics used (benzylpenicillin, ceftazidime, and rifamycin) exhibited the same effect in inhibiting alpha-amanitin uptake into liver cells [71].

Hyperbaric oxygen therapy (HBO) has also been investigated in amanitin poisoning and seems to be useless. In a mouse model, HBO compared to normobaric condition did not exhibit better outcome after a toxic dose of amanitin [72].

Coagulopathy/Prevention of Bleeding

Coagulopathy in amanitin poisoning is due to a lack of hepatic synthesis of clotting factors. This is a sign of liver dysfunction. In amanitin poisoning, complications of gastrointestinal or intracerebral hemorrhage are typically seen from day three onward in grade III (severe ALI) intoxication. Absorption of blood from the intestine promotes hepatic encephalopathy due to ammonia production from blood proteins. Gastric hemorrhage was common in *Amanita* poisoning prior to modern therapy with proton pump inhibitors (PPIs). Because of this patients whose prothrombin index fell below 25% were treated with clotting factors or FFP. Further, these patients receive low dose of heparin and AT III in order to avoid DIC [73]. Since the introduction of PPIs, gastric bleeding has mostly disappeared in patients with *Amanita* poisoning. In most studies among all criteria for liver transplant (LTx) a prothrombin index below 10% was the best prognostic value for a lethal outcome [74, 75]. If the prothrombin index stays below 10%, or the INR is above 6 from day 3–4, we recommend the administration of clotting factors and LTx is indicated. We further recommend that vitamin K be given intravenously as soon as there are signs of a coagulopathy to allow resynthesis of clotting factors. (Grade III recommendation) PPIs such as omeprazole or pantoprazole appear to help to avoid gastric bleeding and we recommend that they be routinely administered.

Grades of Hepatic Encephalopathy

Prevention and Treatment of Hepatic Encephalopathy

There are four grades of hepatic encephalopathy (Table 3) based on intellectual functions (such as concentration), sense of time, memory, and the ability to calculate. Behavioral abnormalities like

Table 3 Grades of hepatic encephalopathy

Grade	
0	Normal level of consciousness but abnormal liver function
I	Sleeping disturbance, lack in concentration, slow reaction time, excitable, mood swings, disturbed motor skills, asterixis, degradation of writing
II	Lethargy, no sense for time, dyscalculia, muscle reflexes reduced, slurred speech
III	Disorientation, confusion, cloudy, loss of memory, aggression, delusion, muscle reflexes increased, nystagmus
IV	Coma, no reaction to pain, opisthotonus, mydriasis barely reacting to light

rapid mood changes, anxiety, aggression and paranoid thinking may also be present. Neuro-muscular disturbances manifest by hyperreflexia, may occur. As encephalopathy progresses, hand-writing capacity deteriorates, which can be monitored by a daily writing test. Asterixis, disturbed speech, and increased muscle tone are characteristic. In the final stage, the patient becomes comatose. The electroencephalogram (EEG) usually shows slow waves before the clinical manifestation of coma, and therefore we recommend EEG monitoring in grade III patients [76]. If the patient is in coma, intracranial pressure (ICP) should be measured either continuously by an implanted transducer once coagulopathy has been corrected or by Doppler noninvasive monitoring [77]. If irreversible brain damage has already ensued, LTx is not indicated. Glucose infusion, if necessary in combination with insulin, is the appropriate basic parenteral nutrient because it can prevent hypoglycemia and may be required for the regeneration of hepatocytes. Further, parenteral nutrition should contain branched-chain amino acids as they may help to prevent encephalopathy. 400 mg of rifaximin, given orally twice a day, will reduce the bacterial population of the colon and thus prevent the invasion of enterotoxins into the portal system. Lactulose decreases the bacterial ammonia production in the intestine leading to less absorption of ammonia and thus helps to prevent hepatic encephalopathy. The dosage is 10 g, four times a day.

Table 4 Criteria for liver transplantation

<i>King's College criteria for non-paracetamol poisoning</i>	
INR	> 6.5 on its own or
Serum bilirubin	> 300 μmol/l and
Jaundice to coma	>7 days and
Drug or infection in history	
<i>Clichy criteria</i>	
Encephalopathy grade	III to IV
Factor V	< 20% age < 30
Factor V	<30 age > 30
<i>Clichy (Escudé) criteria for Amanita phalloides</i>	
Ingestion to symptoms	< 8 h
Prothrombin index	< 10% ~ INR > 6
<i>Munich (Ganzert) criteria</i>	
Prothrombin index	< 25% under treatment with clotting factors from day 3 onward and
Creatinine	> 106 μmol/l from day 3 onward

Liver Transplant: Bridging Systems

If hepatic encephalopathy has developed to such a degree that the patient is not arousable and not reactive to painful stimuli (stage IV), liver transplant is inevitable. However, by then, it may be too late to organize LTx even on high urgency as intracranial pressure may lead to irreversible anoxic injury or brain death within a very short time. In contrast, patients have recovered from stage III encephalopathy [74] without transplantation. We recommend treating stage III or IV encephalopathic patients with a human albumin dialysis using the MARS® [78, 79] or by a fractionated plasma-separation system using PROMETHEUS® [80] (Grade II-3 recommendation). With these methods it may be possible to remove endogenous toxins which accumulate during liver failure, to lower intracerebral pressure, and to improve the circulatory insufficiency [81–83]. It should be stressed that these methods do not remove amatoxins, which do not bind to albumin and, as reviewed above, clear from the blood in the very early stages of intoxication. Various criteria have been used to decide on liver transplant before coma ensues. All criteria (see Table 4 criteria for liver transplant) have one sign in common: If the prothrombin index is below 10% or

the INR above 6, when not treated with coagulation factors or FFP, the sensitivity for fatal outcome is 100%. The specificity never reaches 100% because there are some cases that recover despite severe coagulopathy. Specificity reaches 100% if the severely impaired coagulation function persists. The KCC for paracetamol do not apply to amanitin poisoning because in amanitin poisoning kidney failure and metabolic acidosis are rarely seen early. KCC for non-paracetamol poisoning also do not fit because the time between jaundice and coma is never > 7 days in amatoxin poisoning. By this time the patient has either survived or is dead. The Clichy criteria do not apply because there are not enough data on the measurement of factor V and because encephalopathy grade III patients have survived in amanitin poisoning. The criteria of Escudie [74] do not fit because we have had patients who died with a longer asymptomatic period than 8 h. The Munich [34] criteria were developed especially for amanitin poisoning. (Table 4). Included in this study was the largest number of fatal amanitin poisonings compared to severe but survived poisonings. The combination of clotting function (prothrombin index <25% under clotting factors substitution) and impaired kidney function gave the best prognostic factor. The Munich and Clichy criteria were criticized by Ferreira [75]. But in their cases, liver transplant was done before encephalopathy or kidney insufficiency were reached, so the question remains as to what would have happened without liver transplant (post hoc fallacy).

The decision to pursue transplant is not to be made easily. Liver transplant is a major surgical intervention with attendant risks and requires a lifetime of immunosuppression. One should be as sure as possible that the patient would not likely survive without LTx, particularly because, as a rule, no long-term hepatic damage is expected. There is only one publication [84] that states chronic histopathological changes in liver biopsies 6 months after the intoxication. Other follow-up studies show complete recovery with the exception that kidney failure can persist in a few cases [85].

Special Situation Demanding Early LTx

About 10% [58, 74] of patients with *Amanita* poisoning die early in the course of disease. This is due to multiorgan failure with refractory shock. The reason is most likely a necrotic liver with endotoxins leaking into the circulation. Signs and symptoms of this condition include hypotension not responding to vasopressors, metabolic acidosis, and hyperdynamic circulatory failure with reduced peripheral resistance. Though not described specifically for amanitin poisoning, the only way to possibly save these patients is total hepatectomy followed by bridging using MARS[®] or PROMETHEUS[®] and liver transplantation as soon as an organ is available. This procedure was successful in patients with other causes of fulminant liver failure [86].

Auxiliary Partial Liver Transplantation

Single cases have been described in which partial orthotopic liver transplantation from a living donor for hepatic failure was performed [87]. To our knowledge this has never been done in amanitin poisoning. This procedure would allow the damaged liver to recover, and by weaning the immunosuppression after the recovery of their own liver, the graft will be rejected and disappear. This method seems to be best suited for children as their liver regeneration is best [88].

It may be reasonable to infuse silibinin during the perioperative period to avoid amanitin-induced damage to the new liver by redistribution of amatoxins from the explanted liver or kidney. This was described in two cases [89] in which the transplanted liver was injured and postmortem pathological examination of the implanted liver showed a similar histological picture as the patient's earlier explanted liver. This consideration was the reason that silibinin perioperatively is used in all cases transplanted in our center in Munich [90].

Successful liver transplantation in amanitin poisoning has been reported worldwide since 1985. The first liver transplantation in amanitin poisoning was performed in a child by Woodle [91]. This was followed by many more reports of

effective transplants [15, 90–94]. The survival rate of the graft and the patients is better than for other indications for hepatic transplant as in amanitin poisoned patients, other underlying diseases are absent.

Sequelae

Though histopathological changes in liver biopsies have been reported 6 months after surviving an amanitin poisoning [84], we have never seen this progress to chronic liver disease or cirrhosis. Several patients have come back to see us after years. Their liver function showed no impairment. But as there are no systematic investigations into this question, more follow-up studies might be needed. At discharge, of our patients some had slightly elevated ALT and bilirubin which later normalized.

Two cases are described in the literature [95–97] with severe bowel dysfunction after recovery from amanitin poisoning. The first case developed intractable diarrhea and dilatation of the colon requiring decompression by a catheter. The second case developed severe abdominal pain and diarrhea with pain and diarrhea for several weeks, after survival of the amatoxin poisoning. The histology revealed ulcerating ileocolitis. Follow-up histology after six months was normal [96].

In a few cases of survival of severe amatoxin poisoning, permanent kidney failure persists. An elderly patient permanently required hemodialysis and a second one had a renal transplant 4 years after liver transplantation [98].

Special Population

Immigrants

At least in Germany, it has become obvious that immigrants from Eastern Europe and the Middle East are at risk because of their tendency to forage for mushrooms and the likelihood of misidentifying a poisonous one [99]. As recently as 2015, a family of refugees from Syria was so poisoned [100]. The

reason this population is at risks is that they might not be aware of the danger of mushroom foraging or they may collect amatoxin-containing mushrooms that are similar to edible mushrooms in their home country. The same may come true for US people if their ancestry is from Germany, France, Italy, Russia, or Poland, as these countries have a fungophile tradition.

Pediatric Patients

Children are at greater risk than adults of experiencing fatal hepatic injury. While this is a terrible tragedy, it happens frequently. In these cases, parents may survive their intoxication, while their die. The mortality rate in small children was 50% [3, 53], before liver transplantation was available [3, 53]. There are many calls to Poison Control Centers when parents discover that their small children have eaten mushrooms while playing unattended outside in grassland or during a walk in a forest. In these cases, a rapid identification of the mushroom by an expert is required to both avoid overtreatment and to start antidotal treatment immediately if the suspicion of an amanitin-containing mushroom being ingested is high. Fortunately, in these cases the amount of mushroom eaten is usually not large.

Pregnant Patients

There are a number of case reports where pregnant women were poisoned by amanitin-containing mushrooms. In these cases, the toxic ingestion happened in the second trimester of pregnancy at the 22nd, 23rd, and 28th week [101–104] with no damage to the fetus. Even cases of first-trimester ingestion at the 11th week of gestation the birth and the development of the infant proceeded without incident [105]. Obviously the toxins of the mushrooms do not cross the placental barrier [105]. Therapeutic abortion might become necessary if the life of the mother is at jeopardy in early pregnancy [106]. In a retrospective review of 22 cases of pregnant women poisoned by amatoxin-containing mushrooms, the mean birth weight was lower than in controls. Two malformations, one due to alcohol abuse of the mother, were observed [107]. Abortion is

generally not indicated as normal fetal development would be expected, except in extreme cases.

Other Special Population

In collective review of *Amanita* poisonings [34, 58], a higher mortality rate was not seen in the elderly.

The Future

Polymyxin B in an in silico study turned out to protect RNAP II or even might free the polymerase from amanitin docked to it. In a mouse model, polymyxin B significantly decreased the amatoxin-induced hepatic and renal injury. When polymyxin B was administered 4,8,12 h post-alpha-amanitin exposure, 50% of the animals survived whereas in the control group, 100% died [108]. Future clinical studies will determine if this is an efficacious antidote.

Criteria for ICU Discharge in Cyclopeptide Mushroom Poisoning

Resolution of coagulopathy

Resolution of hepatic transaminases (not bilirubin, which may persist for longer)

Resolution of renal function

Common Errors in Cyclopeptide Mushroom Poisoning

Taking the symptoms for food poisoning or other origin not asking for mushroom consumption

Discounting the possibility of amatoxin poisoning because the ingestion of *Amanita phalloides*, *Amanita verna*, or *Amanita virosa* was excluded (other mushroom contain amatoxins like *Galerina* spp. and *Lepiota* spp.)

Discounting the possibility of amatoxin poisoning because the symptoms appeared

“too soon” (other mushrooms with short asymptomatic period coingested)

Discharging the patients after initial resolution of gastrointestinal symptoms (even if the patients want to be discharged)

Waiting for laboratory results and not starting antidotal treatment

Waiting too long to transfer the patient to a liver transplant center

Key Points in Cyclopeptide Mushroom Poisoning

Keep cyclopeptide mushroom poisoning in the differential diagnosis for a patient with gastrointestinal complaints, and ask all patients with gastroenteritis if they have consumed mushrooms.

Contact regional poison center for help in diagnosing and treating suspected cyclopeptide mushroom ingestion as they know where the antidote can be received from and where the mycologist experts are.

Provide initial and continuing treatment of fluid and electrolyte abnormalities, treat coagulopathy, and encephalopathy later on.

Treat as early as possible with available antidotes.

Make early contact with regional liver transplant center and consider early transfer to a transplant center.

Report cyclopeptide mushroom ingestion cases to local regional surveillance centers (in the US). Give warnings to the press.

To Be or Not to Be Depends on Early Therapy

A mushroom meal the eaters hits

Delayed by belly cramps and shifts

Please treat as promptly as you can

To be that woman or that man

That saves the mushroom eater's life

And all his children and his wife

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The mushroom species *Gyromitra* (formerly *Helvella*) *esculenta* grows throughout the northern hemisphere including North America, Europe, and Asia. It is commonly found in coniferous and hardwood forests. The species fruits in early spring (later at higher elevations), often where snow has recently melted. *G. esculenta* is a member of the fungus class Ascomycetes, meaning that it has no gills, tubes, or spines but develops its spores in saclike structures called *asci*. The mushrooms are moderately sized measuring 3–10 cm across, are brown to reddish brown, and have wrinkled caps, with a brainlike or saddle shape (Fig. 1). The stalk is white to brown in color, thick, and hollow, usually with a single chamber.

G. esculenta may be misidentified as Morchellaceae due to similar appearance. Morchellaceae (genera *Disciotis*, *Morchella*, and *Verpa*), or “true morels,” are highly sought for consumption yet capable of causing significant

gastrointestinal (GI) distress and neurological illness if consumed raw [1, 2]. *G. esculenta*, or “false morel,” contains gyromitrin, which is metabolized to the toxic monomethylhydrazine (MMH) (Fig. 2). Other mushrooms that contain gyromitrin are listed in Tables 1 and 2 [2–7].

Over 6,500 mushroom exposures were reported to the American Association of Poison Centers in 2013; 29 of these involved gyromitrin-containing species with no deaths [8]. *G. esculenta* was second only to *Amanita* spp. for mushroom-induced deaths during the first 72 years of the twentieth century [9]. A European review of 513 cases of gyromitrin toxicity reported a 14% mortality rate [10]. Despite its toxicity, *G. esculenta* has been sold for consumption, canned and raw, in some European markets.

Poisoning can occur after the ingestion of either raw or cooked *Gyromitra* mushrooms; however, their toxins are volatile and cooking decreases the toxicity. The boiling point of gyromitrin is 64 °C (147.2 °F) and of MMH is 87 °C (188.6 °F). Parboiling (repeated boiling with water exchanges) is utilized to prepare *G. esculenta* for consumption, though its efficacy for removing toxicity is not well established. Gyromitrin can be detected in dried, boiled, and lyophilized specimens [11, 12]. Several specific gyromitrin homologues have been identified in the steam during boiling. Toxicity from inhaling the steam or drinking the cooking water has been reported [11]. Drying the mushrooms in outdoor air at 20 °C (68 °F) over 14 days removed 98.9% of an intermediate metabolite, *N*-methyl-*N*-formylhydrazine (MFH) (see Fig. 2), and boiling 100 g of *G. esculenta* in 300 mL of water, pH of 7.8, for 10 min removed 81.3% of the toxin. Parboiling and acidifying the water promote removal of toxin [11].

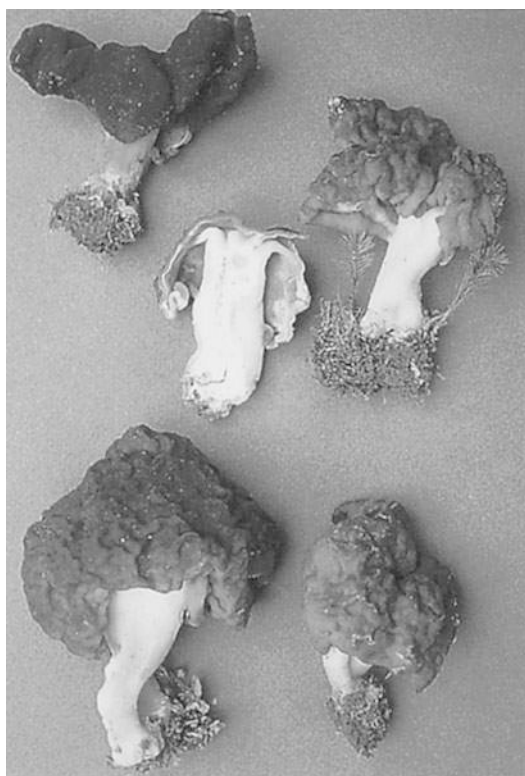


Fig. 1 *Gyromitra esculenta*, which contains the hepatotoxin gyromitrin (From Phillips R: *Mushrooms of North America*. Boston, Little Brown, 1991, with permission)

Biochemistry and Clinical Pharmacology of *Gyromitra* Toxins

In the nineteenth century, Bohm and Kulz [13] falsely identified helvellic acid as the compound responsible for the toxicity of *G. esculenta*. List and Luft [14] were the first to identify gyromitrin correctly (acetaldehyde MFH) in 1967 with subsequent structural confirmation via direct synthesis.

Fig. 2 Metabolism of gyromitrin

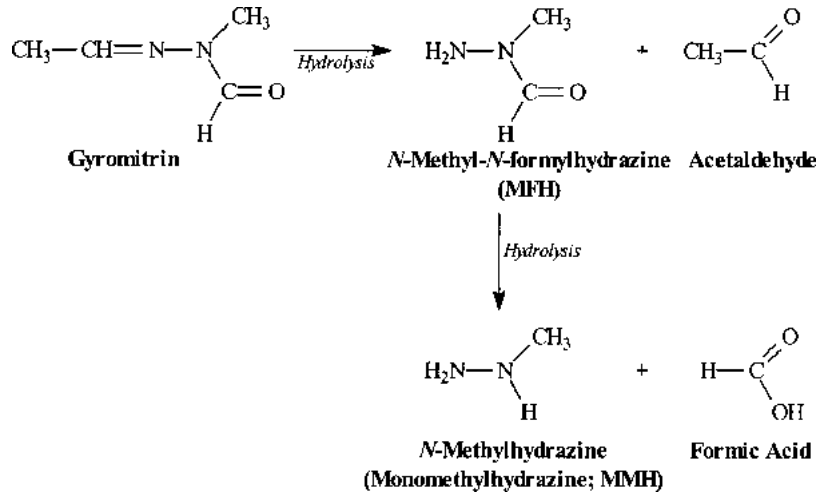


Table 1 Mushrooms known to contain gyromitrin^a

Scientific names	Common names
<i>Gyromitra ambigua</i> and <i>Gyromitra infula</i>	Hooded false morel
<i>Gyromitra esculenta</i>	False morel, beefsteak (brain) mushroom, elephant ears, turban fungus, lorchel

^aThere is low consensus among experts in terms of nomenclature and classification of these mushrooms [2–7]. A further discussion of the classification of mushrooms is provided in ► Chap. 107, “Overview of Mushroom Poisoning”

Under physiologic conditions, gyromitrin is metabolized rapidly to acetaldehyde and MFH (see Fig. 2). This reaction has been reproduced experimentally under conditions mimicking the gastric environment [15]. Subsequently, MFH is slowly hydrolyzed to MMH and formic acid. Metabolism of MFH by the hepatic mixed-function oxidase system has been studied and may explain gyromitrin’s hepatotoxic effects [16]. At this time, at least 11 structurally similar hydrazones (hydrazine homologues) have been identified in *G. esculenta* [11, 17].

Pathophysiology of Toxic Effects

Effect on Pyridoxine Metabolism

Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (CNS), is synthesized from the excitatory

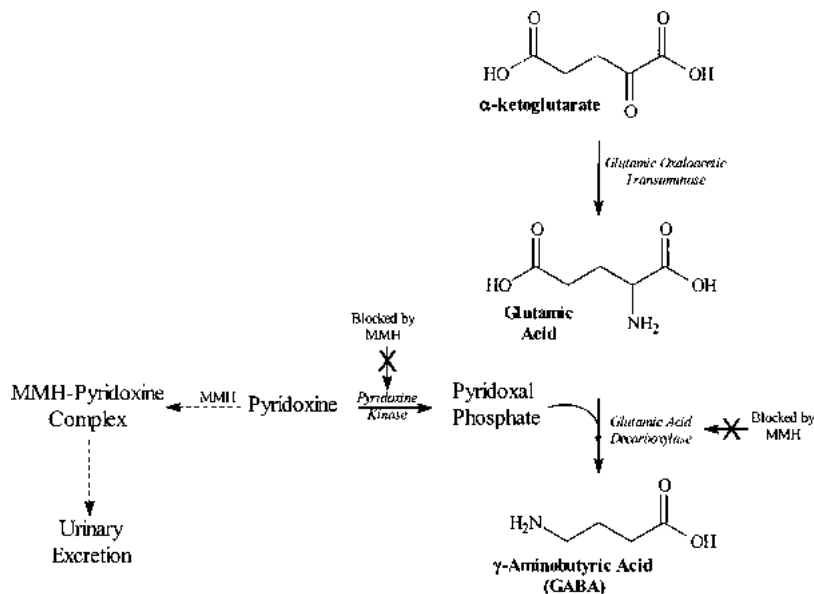
Table 2 Mushrooms thought to contain gyromitrin^a

Scientific names	Common names
<i>Cudonia circinans</i>	
<i>Cyathipodia macropus</i>	
<i>Gyromitra brunnea</i> or <i>Gyromitra fastigiata</i>	Brown false morel
<i>Gyromitra californica</i>	California false morel, umbrella false morel
<i>Gyromitra caroliniana</i>	Carolina false morel, big red mushroom
<i>Gyromitra gigas</i> (including <i>Gyromitra montana</i>)	Giant false morel, snow (snowbank) false morel
<i>Gyromitra korfii</i>	Bullnose
<i>Gyromitra sphaerospora</i>	Round-spored gyromitra
<i>Helvella crispa</i>	Common white helvella
<i>Helvella lacunosa</i>	Black helvella
<i>Leoptopodia elastica</i>	
<i>Leotia lubrica</i>	Slippery cap
<i>Neobulgaria pura</i>	Beech jelly-drop cup
<i>Otidea onotica</i>	Lemon-peel cup
<i>Sarcophaere crassa</i>	Violet star cup
<i>Spathularia flavida</i>	

^aThere is low consensus among experts in terms of nomenclature and classification of these mushrooms [2–7]. A further discussion of the classification of mushrooms is provided in ► Chap. 107, “Overview of Mushroom Poisoning”

neurotransmitter glutamate by the enzyme glutamic acid decarboxylase. This reaction requires pyridoxal phosphate, the activated form of pyridoxine (vitamin B₆), as a cofactor (Fig. 3). MMH inhibits glutamic acid decarboxylase, causing

Fig. 3 Inhibition of γ -aminobutyric acid synthesis by monomethylhydrazine



increased concentrations of glutamate and decreased concentrations of GABA. MMH also blocks the phosphorylation of pyridoxine by inhibiting pyridoxine phosphokinase. In addition, MMH binds and inactivates phosphorylated pyridoxine, inhibiting its role in other various reactions [18]. These effects on GABA synthesis account for the CNS excitation (e.g., seizures) seen with poisoning by gyromitrin-containing mushrooms.

Fast Versus Slow Acetylators and Difference in Toxicity

The ability to acetylate xenobiotics via hepatic metabolism varies within the human population and is genetically determined [19, 20]. There is a dichotomous distribution of acetylator phenotypes in humans, and people can be labeled as *slow* and *rapid* acetylators. After ingestion of *G. esculenta*, hydrazine compounds may be acetylated, which seems to protect against neurologic effects but to enhance hepatotoxicity. Formation of acetylhydrazine, the first step in the biotransformation of hydrazines, promotes formation of hepatotoxic alkylating radicals [20–24].

Oxidative Stress

Gyromitrin toxicity produces oxidative stress that overwhelms endogenous antioxidant systems that normally maintain methemoglobin (MetHb) concentrations of less than 3%. MetHb is formed by oxidation of hemoglobin's iron, converting it from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. MetHb is incapable of carrying oxygen and shifts the oxygen dissociation curve to the left, hindering oxygen delivery, thereby producing cyanosis and tissue hypoxia. Methemoglobinemia is discussed in detail in ► Chap. 30, "Toxicant-Induced Hematologic Syndromes."

Inhibition of Diamine Oxidase

Diamine oxidase (histaminase) is a regulatory enzyme responsible for the metabolism of histamine. It is found in rapidly proliferating tissues, such as intestinal mucosa and bone marrow. MFH noncompetitively inhibits diamine oxidase *in vitro* [25]. Inhibition of diamine oxidase can produce histamine concentrations that cause flushing, abdominal pain, nausea, vomiting, diarrhea, and headache. These clinical findings are similar to scombroid poisoning.

Mixed-Function Oxidase Inhibition

During the oxidation of gyromitrin and MFH, highly reactive nitrosamide intermediates are formed that are capable of decreasing hepatic cytochrome P-450 concentrations in rat models [16]. These nitrosamide metabolites may account for some inhibition of the mixed-function oxidase system and hepatotoxicity.

Inhibition of Folate Conversion to Folinic Acid

Folate is the inactive form of a B-complex vitamin essential for protein synthesis and erythropoiesis. Dihydrofolate reductase (Fig. 4), the enzyme that converts folate to folinic acid (the active form), is inhibited by the hydrazones in *G. esculenta*. Folinic acid (leucovorin) administration may maintain normal cellular catabolism.

Carcinogenicity and Embryotoxicity

There have been significant increases in neoplasm development reported in animals fed fresh *G. esculenta* or its prepared hydrazones [26–40]. MMH causes teratogenic effects in toad embryos [41] and has shown a dose-dependent decrease in pregnancy rates of exposed rats [42]. There is insufficient data to predict possible carcinogenic and mutagenic effects in humans.

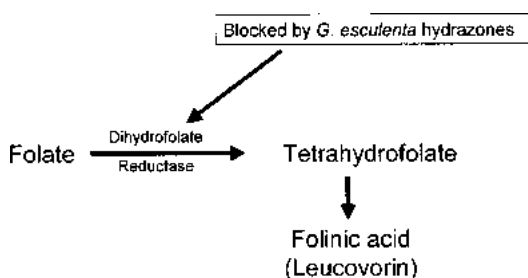


Fig. 4 Inhibition of tetrahydrofolate synthesis by hydrazones from *Gyromitra esculenta*

Clinical Presentation and Life-Threatening Complications

Interpersonal Differences in Dose Response: The Individual Threshold Dose

Individual responses to *G. esculenta* are varied and range from no effect to severe poisoning and death. Dose-dependent and interpersonal differences in response determine the minimal amount of ingested mushroom necessary to cause toxicity in any given patient. This phenomenon is known as the *individual threshold dose* [2, 43, 44]. Patient factors, such as age, size, health, and metabolic capability (i.e., slow versus fast acetylators); amount ingested; preparation technique; and amount of co-ingested food may affect the clinical course. Some report a kindling or sensitizing effect, where toxicity only occurs after repeated exposure. Others suggest that bioaccumulation of gyromitrin may lead to poisoning [21]. It has been observed that a person may eat *G. esculenta* for years but develop poisoning only after consuming a large, threshold amount.

There also is considerable variation in the potential of any gyromitrin-containing mushroom to cause toxicity. The toxicity of an individual mushroom is determined by several factors, including genetic strain, hybridization, environmental conditions (soil, temperature, light), age, and internal distribution of toxin. The altitude at which the mushrooms grow has been identified as a strong determinant of toxin content. Mushrooms grown at mid-range altitudes often contain five times more MMH than samples from higher elevations [45]. In North America, *G. esculenta* toxicity has been reported both east and west of the Rocky Mountains [46].

Systems Approach to Signs, Symptoms, and Complications

Clinical findings of *G. esculenta* toxicity are varied. Symptoms are typically delayed for

4–12 h, with reported onset ranging from 2 to 48 h. Latency variations may be partially explained by variations in the concentrations of the different mushroom toxins [1, 47]. The gyromitrin syndrome normally starts with GI symptoms, including abdominal pain and bloating, nausea, vomiting, and occasionally watery or bloody diarrhea; it can be accompanied by headache, myalgias, and fever. Hemolysis, methemoglobinemia, neurological complications, and hepatorenal failure may follow, though most patients manifest only GI symptoms and make a complete recovery within several days. In severe toxicity, GI distress progresses to neurologic, hepatic, and renal dysfunction. An asymptomatic interval between resolution of GI symptoms and the onset of neurologic or hepatorenal toxicity may occur. A high index of suspicion is warranted for severe, protracted illness when caring for gyromitrin-exposed patients [1].

Systemic Effects of Gyromitrin

The GI effects of gyromitrin poisoning can last for several days, with excessive fluid losses causing hypovolemia, hypotension, shock, and acidosis. Patients may develop tachycardia and hypotension secondary to hypovolemia from GI losses. Cardiovascular instability may indicate significant multiorgan dysfunction or shock. Neurologic effects appear later, often after resolution of gastric complaints, with or without an asymptomatic period. Patients may report headache, dizziness, or vertigo and exhibit ataxia, seizures, coma, delirium, or labile emotions.

Hepatic failure usually develops within 48 h of ingestion, if at all, and is manifested by elevated transaminases, coagulopathy, and jaundice. Abdominal examination may reveal right upper quadrant tenderness. Biopsy samples of rat liver and kidney tissue after death from gyromitrin poisoning reveal discoloration of tissue, inflammatory changes, and focal necrosis [47].

Infrequently, renal failure develops as a result of hemolysis, rhabdomyolysis, or prolonged hypotension [48]. Renal failure may occur as a

result of a gyromitrin-induced hepatorenal syndrome. Rhabdomyolysis and diffuse myalgias are possible.

Hypoglycemia and electrolyte abnormalities may develop from significant GI losses. Fever is a manifestation of systemic inflammatory response or a consequence of hepatic injury.

Gyromitrin induced oxidative stress may precipitate intravascular hemolysis and methemoglobinemia. Hemolysis can be assessed by measuring plasma free hemoglobin, haptoglobin, and hemoglobinuria. Significant hemolysis may cause splenomegaly. The skin may appear jaundiced (from hepatotoxic effects), pale (from dehydration, hypovolemia, or hemolysis), or cyanotic (from methemoglobinemia). Methemoglobinemia should be suspected in any patient who develops cyanosis unresponsive to supplemental oxygen. Although the effects and clinical findings from methemoglobinemia do not correlate well with cooximetry-derived MetHb concentrations, most patients develop significant clinical manifestations at MetHb levels greater than 30%. Methemoglobinemia is discussed in detail in another chapter.

Diagnosis

There is no readily available laboratory assay to confirm the presence of gyromitrin in either mushroom or biological samples. A history of *G. esculenta* consumption greatly assists the diagnosis and management of gyromitrin poisoning.

Differential Diagnosis of Gyromitrin Poisoning

Poisoning from other mushroom toxins (e.g., amatoxin, coprine, ibotenic/muscimol)
Bacterial food poisoning
Other toxic ingestions (e.g., acetaminophen, salicylate, iron, isoniazid, organophosphates)
Methemoglobinemia from non-mushroom source (e.g., benzocaine)
Gastritis/gastroenteritis
Biliary disease/cholelithiasis

(continued)

Hepatitis/fulminant hepatic failure
Sepsis
Encephalopathy or seizure disorder
Hydrazine (monomethylhydrazine) poisoning
from nonmushroom source (e.g., rocket
fuel)

Laboratory testing should include liver, renal, and metabolic panels; complete blood counts; creatine kinase; coagulation profiles; and methemoglobin fraction, serum haptoglobin measurement, and plasma free hemoglobin levels. Gyromitrin concentrations can be quantitated by gas chromatography–mass spectrometry but have not been shown to correlate with clinical status and are not available in a timely fashion [49].

Patients should be placed on a cardiac monitor and have vital signs and oxygen saturation assessed frequently. Pulse oximetry utilizes only two wavelengths and cannot reliably differentiate between different hemoglobin species. Cooximetry testing is required to accurately quantify methemoglobin concentration. This is discussed further in ► Chap. 30, “Toxicant-Induced Hematologic Syndromes.”

Treatment

Treatment is mainly supportive, with emphasis on controlling gastroenteritis and replacing fluid and electrolyte losses. Patients typically present at least 4 h after ingestion, which limits the utility of GI decontamination. If patients present within 1 h of ingestion, however, activated charcoal theoretically may be beneficial (Level of Evidence [LoE] III). However, there are no studies to indicate that it alters outcome. If the decision is made to administer activated charcoal, it must be done with caution in patients whose ingestion may result in seizures or altered mental status. Cathartics are not indicated. All symptomatic patients should be admitted for supportive care and treatment.

Antidotes

Methylene Blue

All patients with clinically significant signs or symptoms of methemoglobinemia (or MetHb levels >30%) should be treated with supplemental oxygen and methylene blue, unless contraindicated (LoE II-2). The dose of methylene blue is 1–2 mg/kg by intravenous push. Reversal of symptoms is expected to occur within 15 min. If necessary, a second dose can be administered, with a maximal total dose of 7 mg/kg. At higher doses, methylene blue can induce oxidative stress and worsen methemoglobinemia. Methylene blue is contraindicated in patients with known glucose-6-phosphate dehydrogenase deficiency because of increased risk of methylene blue–induced hemolysis [50]. If clinically indicated, such patients should undergo exchange transfusion to correct methemoglobinemia. The treatment of methemoglobinemia is discussed in ► Chap. 30, “Toxicant-Induced Hematologic Syndromes,” and the clinical pharmacology of methylene blue is reviewed in another chapter.

Folinic Acid (Leucovorin)

Hydrazines inhibit the conversion of folate to its active form, and patients should benefit from receiving the active formulation (folinic acid or leucovorin) based on treating other types of hydrazine poisoning (LoE III). The usual dose is 5–15 mg/day intravenously, intramuscularly, or orally for 5–7 days. Higher doses (≤ 1 mg/kg intravenously every 4 h) can be given for severely poisoned patients. Because the inhibition of dihydrofolate reductase is transient, it is generally thought that after 24 h folate can replace folinic acid treatment.

Thioctic Acid and *N*-Acetylcysteine

A historic case series mentions the use of thioctic acid (α -lipoic acid) in the successful treatment of *G. esculenta*–poisoned patients [51]. This compound, similar to *N*-acetylcysteine, is reported to have antioxidant effects. Although there is a theoretical advantage to using these compounds, to date there are no studies showing improved clinical outcome. *N*-acetylcysteine was shown to be

ineffective at reversing methemoglobinemia produced by other oxidants in human volunteers [51, 52]. Neither thioctic acid nor *N*-acetylcysteine is recommended.

Pyridoxine

The use of pyridoxine (vitamin B₆) has been shown to limit the severity of hydrazine-induced neurologic dysfunction from isoniazid and gyromitrin [20, 53–57] (LoE II-3). The optimal dose for gyromitrin-induced neurotoxicity is unknown; recommendations range from 1 to 70 mg/kg [52]. The empirical intravenous administration of 5 g of pyridoxine to adult patients who convulse after ingesting an unknown quantity of isoniazid or who fail to respond to conventional anticonvulsant therapy is well established [57] (LoE III). Some have recommended giving this dose to gyromitrin exposed patients with seizures [1].

It seems reasonable to administer 25 mg/kg of pyridoxine intravenously once to all patients with known or suspected acute gyromitrin toxicity and to repeat doses if seizures occur or continue. If the patient has seized, 70 mg/kg (up to 5 g) should be given (LoE III). Administration of pyridoxine at doses greater than 500 mg/day for extended periods (≥ 6 months) is associated with the development of sensory neuropathy and other adverse effects but should not occur with short-term use [56, 58, 59]. The clinical pharmacology of pyridoxine is discussed in ► Chap. 163, “Pyridoxine.”

Other Treatments

Hemodialysis

Gyromitrin-induced renal failure should be managed in a standard fashion, including the use of hemodialysis. Usual guidelines for initiating hemodialysis in acute-onset renal failure should be followed.

Intravenous Fluids and Serum Alkalinization

Patients may develop significant dehydration secondary to GI losses and decreased fluid intake. Barring contraindications, aggressive fluid resuscitation should be provided to replace fluid

deficits, compensate for ongoing losses, and ensure adequate urine output (>0.5 mL/kg/h). Insertion of a urinary catheter may help assess urine output accurately. Hypovolemia should be managed with normal saline or lactated Ringer's solutions, with close monitoring of electrolytes and renal function. Rhabdomyolysis can be treated with urinary alkalization (LoE II3), as well as hydration, with a goal of a urine pH > 6.5 (LoE III) to help prevent the renal tubular deposition of myoglobin–Tamm-Horsfall protein complexes and acute renal failure [60]. Urinary alkalization can be accomplished by placing 150 mEq of sodium bicarbonate in 1 L of 5% dextrose in water, with an infusion rate of 200 mL/h in adults. Adding this amount of sodium bicarbonate to saline-containing fluids could produce hypernatremia. Urinary alkalization by this technique is best accomplished if the patient is not hypokalemic, which should be anticipated because bicarbonate administration will reduce serum potassium.

Treatment of Seizures

Treatment of gyromitrin-induced seizures includes the administration of benzodiazepines and pyridoxine, if necessary barbiturates (except, perhaps, phenobarbital, as discussed below) and propofol can be administered. These agents are GABA-agonists that decrease neuronal excitation. Pyridoxine overcomes the gyromitrin-induced inhibition of GABA synthesis (see Fig. 3). Benzodiazepines bind to the GABA_A chloride channel, increase GABA binding to its receptor, and increase the rate of GABA chloride channel opening. Barbiturates and propofol enhance GABA's actions at GABA chloride channels by prolonging the duration the channel remains open. At high concentrations, some barbiturates can directly open GABA chloride channels. Phenobarbital induces P-450 enzymes and increases the microsomal metabolism of gyromitrin, theoretically causing more hepatotoxicity [16]. The use of phenobarbital in the treatment of a gyromitrin-poisoned patient is therefore not recommended.

Phenytoin blocks voltage-gated sodium channels and inhibits the spread or propagation of

seizure activity but does not increase GABA concentrations within the CNS [61]. This mechanism is effective at preventing the spread of abnormal focal CNS electrical activity but is not expected to abort the diffuse neuronal involvement in gyromitrin-induced seizures. Therefore, the use of phenytoin is not recommended.

Vitamin K

Gyromitrin-induced hepatotoxicity can decrease vitamin K–dependent coagulation factors (factors II, VII, IX, X and proteins C and S). Pharmacologic correction for this effect can be administered in the form of vitamin K, at doses of 0.5–10 mg intravenously, intramuscularly, or orally, depending on the severity of the hepatotoxicity. A dose of only 0.5 mg intravenously should be used for patients requiring medical anticoagulation because reversal of vitamin K effects, which are long lasting, can be difficult to overcome [62]. The prophylactic use of vitamin K in patients with hepatotoxicity but not coagulopathy is controversial and not recommended.

Observation Time

Patients presenting after known or suspected *G. esculenta* ingestion should be observed clinically for at least 12 h after ingestion. Asymptomatic or minimally symptomatic patients can be discharged home if they have adequate support, outpatient follow-up, and instructions to return if symptoms progress. A regional poison control center may be able to assist with telephone follow-up. All patients with any of the following should be admitted to the hospital: signs or symptoms of toxicity (gastroenteritis, liver or renal dysfunction, seizures); significant comorbidities (cardiac disease or renal failure); and those at age extremes. Severely ill patients need intensive monitoring and care.

Special Populations

Theoretically, patients with smaller body surface areas (i.e., children and small adults) or significant comorbidities (i.e., hepatitis, anemia,

cardiac disease) are at increased risk for toxicity. A pregnant patient who ingests *G. esculenta* may place the fetus at risk due to maternal dehydration, shock, hepatotoxicity, methemoglobinemia, and other sequelae of gyromitrin poisoning. The treatment of pregnant patients should focus on the mother, given the potential benefits to fetal and maternal outcome. The teratogenic and embryotoxic risks of *G. esculenta* are unknown.

Patients with glucose-6-phosphate dehydrogenase deficiency are at increased risk for hemolysis. They may develop significant hemolysis, anemia, methemoglobinemia, and hypovolemic shock from either gyromitra poisoning or the use of methylene blue.

Indications for ICU Admission in Gyromitrin Poisoning

Hemodynamic compromise
Neurologic instability (coma or seizure)
Hemolysis (especially in patients with glucose-6-phosphate dehydrogenase deficiency)
Significant methemoglobinemia (e.g., dyspnea, tachypnea, dysrhythmia, confusion, seizures)
Toxicity in patients with significant comorbidity (e.g., acute coronary syndrome, renal failure)
Severe gastrointestinal symptoms with significant fluid imbalance

Key Points in Gyromitrin Poisoning

Gyromitrin can lead to significant morbidity and death.
Clinical onset generally in 6–12 h.
Gastrointestinal symptoms predominate early.
Most patients develop gastrointestinal complaints only and recover within several days. A transient asymptomatic period may occur.
Progression to hepatorenal or neurologic disease (or both) within 48 h may occur.
Hemolysis, methemoglobinemia, hepatorenal failure, jaundice, seizures, and coma can occur.

Criteria for ICU Discharge

Resolution of hemodynamic instability.
 Resolution of end organ damage (e.g., stabilization of comorbidities).
 Correction of fluid/electrolyte derangements, hemolysis, and/or methemoglobinemia.

Important Points Regarding Gyromitrin Poisoning

Acetylation status can determine neurological and hepatic effects.
 Oxidative stress can result in hemolysis and methemoglobinemia.
 Inhibition of histaminase can result in severe gastroenteritis.
 Inhibition of GABA synthesis may result in seizures.

Common Errors in Treating Gyromitrin Poisoning

Failure to consider the diagnosis.
 Failure to recognize potential severity of poisoning.
 Failure to recognize methemoglobinemia.
 Interpreting asymptomatic interval as Non-poisoning.
 Failure to identify patients with G6PD deficiency.
 Treating G6PD-deficient patients with methylene blue.
 Giving excessive or prolonged pyridoxine.

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Part XXI

Natural Toxins: Plants and Herbals

Philip Aplin

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While critical care physicians commonly encounter cases of life-threatening drug and pharmaceutical toxicity, their exposure to significant plant and herbal toxicology is likely to be a rare occurrence. Poison center data indicate that calls related to plant ingestion are actually quite common but that the vast majority are not serious [1, 2].

However, there are a number of important plants and herbal products that a critical care physician should be aware of as having the potential for serious toxicity, and even death. The following chapter will highlight these plants in particular. Some types of plants and their effects are dealt with in greater detail in dedicated chapters of this book. It can be said that the level of evidence for therapeutic interventions in plant toxicology is low and are overwhelmingly case report/case series based. Randomized clinical trials are rare.

Also worthy of note is the obvious geographic variance in the distribution of plants around the world. This chapter will focus on the well-known poisonous plants and herbs, and it will not go into detail on their distribution, identification, or appearance. Identification of a plant suspected of causing poisoning or toxicity is obviously critical

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in being able to determine the possible clinical course and management. In general, common names should not be relied upon for identification. Common names of plants are often confusing, and very different plants may have very similar common names (e.g., *Atropa belladonna* known as deadly nightshade and *Solanum nigrum* known as black nightshade). The use of a plant's botanical name will clarify any potential confusion. The best way to identify a plant is for as much of the plant as possible to be brought in with the patient, digitally photographed, and the image sent to an expert botanist via the regional poison center.

Exposure to plants will of course vary depending on geographic location, but it can be generalized that serious poisoning from plants is a far greater problem in the developing than the industrial world. For example, yellow oleander poisoning (*Cascabela thevetia*) is a major cause of death due to deliberate self-harm in Sri Lanka [3]. Exposure to plants can occur unintentionally as commonly seen in children exploring their environment or adults mistakenly thinking a toxic plant is edible. When an adult undertakes deliberate ingestion of a toxic plant, it is far more likely to result in serious clinical effects than accidental exposures in a child. Deliberate plant ingestion by an adult may be for recreational, medicinal, or self-harm intent. Estimation of an ingested dose or toxic amount of plant material is often extremely difficult due to variation in toxic concentrations between species, part of a plant, location, and time of the year. Some plants are also not uncommonly ingested as teas, which is effectively a hot water extraction of plant material.

The following table indicates the main plant/plant groups that will be covered in this chapter. They are grouped according to their main toxic component or mechanism of action. It is not a complete list of toxic plants, and it is important for an acute care physician to be aware of the toxic plants and herbs present in their own local environment.

The following table introduces most of the plants to be discussed in this chapter:

Group	Toxin	Plant's botanical/ common name
1. Cytotoxins	(i) Cytotoxic toxalbumins	<i>Ricinus communis</i> /castor bean <i>Abrus precatorius</i> /rosary pea
	(ii) Colchicine	<i>Colchicum autumnale</i> /autumn crocus <i>Gloriosa superba</i> /glory
	(iii) Cyanide	<i>Prunus</i> spp. and <i>Rosaceae</i> spp./apricot, bitter almond
2. Anticholinergic	(i) Atropine/scopolamine/hyoscine	<i>Atropa belladonna</i> /deadly nightshade <i>Datura stramonium</i> /Jimsonweed <i>Brugmansia</i> spp./angel's trumpets <i>Duboisia</i> spp./corkwood tree
3. Digoxin-like alkaloids	Thevetin	<i>Cascabela thevetia</i> /yellow oleander
	Oleandrin	<i>Nerium oleander</i> /common oleander
	Digitoxin	<i>Digitalis purpurea</i> /foxglove
	Convallatoxin	<i>Convallaria</i> spp./lily of the valley
	Cerberin	<i>Cerbera manghas</i> /sea mango
4. Sodium channel effects	Aconitine	<i>Aconitum napellus</i> /monkshood or wolfsbane <i>Delphinium</i> spp./larkspur
	Veratridine	<i>Veratrum</i> spp./false hellebore
	Grayanotoxins	<i>Rhododendron</i> spp.
	Taxines	<i>Taxus</i> spp./yew

(continued)

Group	Toxin	Plant's botanical/ common name
5. GABA antagonists	Cicutoxin	<i>Cicuta virosa</i> /water hemlock
		<i>Oenanthe crocata</i> /hemlock water dropwort
6. Nicotinic receptor effects	Coniine	<i>Conium maculatum</i> /poison hemlock
	Anabasine	<i>Nicotiana glauca</i> /tree tobacco
	Cytisine	<i>Laburnum</i> spp./golden chain
7. Hepatotoxins	Pyrrolizidine alkaloids	<i>Symphytum</i> spp./comfrey
	Thujone	<i>Mentha pulegium</i> /pennyroyal
	Catechins	<i>Camellia sinensis</i> /green tea
	Hypoglycemic agents	<i>Blighia sapida</i> /akee
		<i>Atractylis gummifera</i> /blue thistle or chardon a glu
8. Oxalate toxicity	(i) Insoluble oxalates	<i>Philodendron</i> spp./fruit salad plant
		<i>Colocasia</i> spp./elephant ear
		<i>Dieffenbachia</i> spp./dumb cane
		<i>Zantedeschia aethiopica</i> /arum lily
	(ii) Soluble oxalates	<i>Rheum</i> spp./rhubarb
		<i>Carambola</i> spp./star fruit
9. Dermatologic/ocular toxins		<i>Euphorbia</i> spp./spurges
		<i>Toxicodendron</i> spp./poison ivy and rhus
10. Miscellaneous		<i>Cleistanthus collinus</i> /oduvan

GABA gamma amino butyric acid, *spp.* species

Treatment Summary

Treatment for most plant poisoning is symptomatic and supportive. Gastrointestinal decontamination has not been studied specifically in plant poisoning, and a risk assessment should be made on a case-by-case basis. Many significant plant poisonings are accompanied by prominent gastrointestinal (GI) disturbance and potentially by a rapid decline in conscious state or other aspiration risk which clearly should be kept in mind when considering agents such as activated charcoal. The administration of activated charcoal has not been shown to improve outcome in most plant-poisoned patients.

Antidotes have a limited but important role in some cases of plant toxicity. Physostigmine has a place in reversing the effects of serious anticholinergic poisoning. Cyanide antidotes may be indicated in ingestions of large quantities of cyanogenic-containing plant material, and there is good evidence to support the use of digoxin immune Fab in cardiotoxicity from oleander poisoning [4] (Grade I data). All these will be covered in more detail in this and later chapters of this book.

Cardiac Glycosides

Poisonings from plants containing digoxin-like alkaloids are one of the most important potentially life-threatening presentations that an acute care physician may be faced with. The clinical features are similar to pharmacologic digoxin poisoning, and the management should be thought of along the same lines including the use of digoxin Fab in cases of serious toxicity. Important plants that contain cardiac glycosides are listed below:

- Common oleander (*Nerium oleander*)
- Yellow oleander (*Cascabela thevetia*)
- Lily of the valley (*Convallaria majalis*)
- Foxglove (*Digitalis purpurea*)

- Sea mango (*Cerbera manghas*)
- Odollam tree (*Cerbera odollam*)
- Red squill (*Urginea maritima*)
- Christmas rose (*Helleborus* spp.)

Cardiac glycosides (bufenolides) derived from toad skin secretions are also found in Chinese herbal products such as Chan Su.

These toxins act like digoxin in blocking cellular Na^+/K^+ ATPase resulting in increased vagal tone and intracellular sodium and calcium flux causing late depolarizations, increased automaticity, and hyperkalemia. The clinical manifestations feature GI upset and cardiac dysrhythmias, typically bradycardia, varying degrees of heart block and ventricular dysrhythmias. The most important biochemical finding is hyperkalemia caused by decreased intracellular potassium transport, a marker of serious toxicity. There may be some cross-reactivity of plant digoxin-like glycosides with laboratory digoxin assays, depending on the assay technique [4], but the level will not correlate with the degree of toxicity, and patients should be managed according to clinical presentation. The amount of plant material required to cause toxicity varies widely between plants.

Ingestion of a small number of seeds of yellow oleander (*Cascabela thevetia*) can cause death in an adult. Yellow oleander toxicity has been studied to a greater degree than any other plant poisoning. This is due to an epidemic of intentional yellow oleander seed ingestion as a method of suicide in Sri Lanka since the 1980s [5]. Such was the scale of the problem that a randomized controlled trial of digoxin Fab in yellow oleander poisoning was undertaken in Sri Lanka. This study showed that digoxin Fab was effective in restoration of sinus rhythm more quickly and in more patients than the control group [4]. Another randomized placebo-controlled study undertaken in Sri Lanka suggested potential benefit of multidose activated charcoal [6] (Grade 1 data).

Good supportive care is an essential accompaniment of any use of an antidote. Given the potential benefit of multidose activated charcoal, it follows that a single dose of charcoal should be given to alert patients with early presentation, meaning within the first hour or two post-

ingestion (Grade III recommendation). Severe hyperkalemia, particularly if accompanied by EKG changes, should be treated by conventional methods if digoxin Fab is not immediately available. Calcium has traditionally been considered to be contraindicated in digoxin poisoning; however, this is controversial and discussed in other relevant chapters in this book. Atropine can be given for severe bradycardia and AV block, and cardiac pacing is appropriate if bradycardia is refractory, though this may be ineffective. Ventricular dysrhythmias appear to be relatively uncommon in yellow oleander toxicity [7]. In the absence of anti-digoxin Fab, lidocaine may be tried along with standard American Heart Association Advanced Cardiac Life Support (ACLS) principles. Cardiopulmonary bypass or venoarterial extracorporeal membrane oxygenations are indicated as in other cases of toxin-induced cardiac arrest or severe hemodynamic instability resistant to other treatment. A more detailed discussion of plant cardiac glycoside poisoning is contained in a separate chapter of this book.

Cyanogenic Plant Toxicity

Cyanogenic glycosides are principally contained in the plant family *Prunus* that contains the well-known species apricot, bitter almond, cherry, plum, and pear. The seeds or kernels of these plants contain the toxin, amygdalin, also known commercially as Laetrile. When metabolized by the enzyme emulsin (also contained in the seeds and present in the gastrointestinal tract (GIT)), amygdalin releases cyanide [8] that can be absorbed systemically and cause cyanide toxicity with sufficient dose. Reports of clinically significant cyanide toxicity from plants most commonly involve excessive consumption of apricot and bitter almond kernels, which have been used as an alternative cancer therapy [9]. The effects of cyanide and clinical manifestations of cyanide poisoning are well known: dyspnea and metabolic features of a severe raised anion gap lactic acidosis due to cellular inhibition of oxidative phosphorylation. Central nervous system (CNS) effects of headache, confusion, seizures, and

coma, as well as cardiovascular effects of tachycardia and hypertension, progressing to bradycardic and shock, are also classically described. Treatment includes supportive care, consideration of GI decontamination with activated charcoal with airway protection by an endotracheal tube given the potential for rapid CNS deterioration in significant ingestions and antidote therapy. However, while of theoretical benefit if administered within the first hour after ingestion, activated charcoal has not been shown to alter the outcome in these patients. The antidote options are (1) sodium nitrite/thiosulfate combination, (2) high-dose hydroxocobalamin (vit B-12 precursor), or (3), rarely, Kelocyanor. In Germany 4-aminophenol is commonly used as methemoglobin producer in the treatment of cyanide poisoning. In one pediatric case series of cyanide poisoning from apricot kernel ingestion, all 13 patients had a good recovery [10]. All underwent gastric lavage and received activated charcoal. Nine patients had a lactic acidosis treated with sodium bicarbonate. Four required mechanical ventilation, hypotension in two, coma in two, and convulsions in one. Six patients received antidote treatment. Detailed consideration of these antidotes and cyanide poisoning is contained in other chapters of this book.

Plants Containing Insoluble Oxalate

Severe local mucosal irritation from contact with plant material containing insoluble oxalate crystals is the most common plant exposure reported to some poison centers [11]. This is because these plants are commonly found indoors and available to be ingested by young children exploring their environment.

The plants with the potential for this toxicity belong to the *Araceae* family. They are numerous and include the fruit salad plant (*Philodendron* spp.), elephant ear (*Colocasia* spp.), dumb cane (*Dieffenbachia* spp.), and the arum lily (*Zantedeschia aethiopica*).

The oxalate crystals are packaged in spear-like raphides within an injectable cell that releases the crystals and other enzymes into the mucous

membranes when the leaf of the plant is bitten [12]. The effect is severe local pain and possible swelling, but systemic oxalate toxicity is not observed. The pain associated with exposure to even small amounts of these plants typically limits further ingestion. Hence, the majority of cases are minor featuring significant oral discomfort that settles with local cooling and analgesia. The potential exists for more severe pharyngeal and laryngeal injury if larger quantities of plant material are chewed and swallowed and clinical signs of severe mucous membrane swelling, inability to swallow, dysphagia, and stridor should raise the possibility of potential upper airway obstruction. Eye exposures require irrigation and may require evaluation for corneal injury.

Soluble oxalates contained principally in the leaves of plants such as rhubarb have the potential to be absorbed from the GIT and cause deposition of calcium and magnesium oxalate crystals in the kidney with resulting hypocalcemia, hypomagnesemia, and renal impairment. This is a problem seen principally in animals not humans.

Dermatologic and Ocular Irritants

Spurges: This diverse group of plants has a common feature in producing a milky white sap that causes severe eye pain on topical exposure with a keratoconjunctivitis that can result in desquamation of the corneal epithelium and secondary uveitis. However, with good eye care as in a chemical eye injury and ophthalmology follow-up, the outcome is good, and the cornea generally heals without scarring [13].

Poison oak, *Rhus* spp., and poison ivy: Many plants may cause a variety of skin reactions. However, members of the *Toxicodendron* family, poison ivy, poison oak, and other *Rhus* trees are notorious for causing a severe, and often delayed, onset hypersensitivity dermatitis due to contact with urushiol compounds present throughout these plants. Depending on the individual's sensitivity, the time of onset varies from hours to a week after exposure. Treatment involves topical and oral steroids with resolution typically taking 10–14 days [14].

Nicotine-Like Toxins

Poison hemlock (*Conium maculatum*) is a widely distributed plant found in diverse settings, especially in wooded areas, along waterways, ditches, and roadsides. It can be mistaken for other edible plants in the same family such as wild carrot, parsley, and fennel. The distinguishing feature of poison hemlock is the purple spots on the stems and characteristic unpleasant “mousey” odor when crushed.

The principal toxin contained in poison hemlock is coniine which is structurally similar to nicotine and acts by activating, then blocking, nicotinic receptors throughout the nervous system [4, 15]. As these receptors are found in the parasympathetic and sympathetic nervous system and at the neuromuscular junction, the clinical manifestations are potentially diverse, but the main threat to life is respiratory muscle paralysis and CNS depression resulting in respiratory failure and death without appropriate supportive care. Deaths have been reported in Australia due to mistaken identity [16], and most famously Socrates is thought to have been poisoned and died after being forced to drink a concoction of poison hemlock. Poison hemlock is described in more detail in the chapter devoted to this plant.

There are a number of other plants with the potential for causing similar toxicity due to the action of nicotine-like toxins. These include tobacco (*Nicotiana tabacum*), wild tobacco (*Nicotiana glauca*), and golden chain (*Laburnum* spp.). Treatment is mainly supportive, particularly of ventilation, and while atropine may improve bradycardia and hypotension, it will not reverse the neuromuscular effects. Charcoal is not recommended without airway protection due to the propensity for CNS depression and seizures in these cases.

GABA Receptor Antagonists

Water hemlock (*Cicuta virosa*) (Fig. 1).

This is a well-known plant in the US and Europe and is also known as cowbane. The principal toxin is cicutoxin which is found throughout



Fig. 1 *Cicuta virosa* (Original book source: Prof. Dr. Otto Wilhelm Thomé, *Flora von Deutschland, Österreich und der Schweiz*, 1885, Gera, Germany. This image is in the public domain. Accessed at: http://biolib.mpgz.mpg.de/thome/band3/tafel_056.html)

the plant, but particularly in the roots. The plant may be mistaken for a wild variety of parsnip and accidentally ingested. Only small quantities of root are required to cause potentially serious toxicity [17]. Cicutoxin is a potent pro-convulsant, probably mediated by GABA receptor antagonism in the brain. As a result its main clinical effect is seizure activity, which may be resistant to standard anticonvulsant therapies such as benzodiazepines due to their reliance on GABA [18]. Following ingestion, GI upset is common followed soon after by sweating, salivation, confusion, and status epilepticus with the potential for all of the associated complications of prolonged seizures, including acidosis, rhabdomyolysis, renal failure, and hyperthermia. Treatment is supportive with aggressive and multiple anticonvulsant medications often required in an intensive

care setting to control seizure activity. The treatment of such seizures is discussed in detail in the ► Chap. 20, “Toxicant-Induced Seizures.” Due to the rapidity of seizure onset, GI decontamination with activated charcoal should only be considered once the airway is secured. Water hemlock poisoning is described in detail in the chapter devoted to this agent.

Hemlock water dropwort (*Oenanthe crocata*): Also known as “dead man’s fingers,” this plant is similar in appearance to poison hemlock and water hemlock and belongs to the same Apiaceae family. Ingestion of this plant is also usually due to mistaken identification of the roots/tubers as being edible. The clinical effects are similar to water hemlock poisoning, i.e., principally seizure activity. Treatment is supportive as outlined in water hemlock poisoning.

Sodium Channel Toxins

Aconitine: Mainly encountered as herbal preparations, aconitine is a potent alkaloid derived from all parts of the aconitum plant (*Aconitum napellus*) also known as wolfsbane or monkshood, a small blue/purple flowering plant. The highest concentration of aconitine is found in the roots [19]. This is a widely used herbal remedy, particularly in Chinese traditional medicine. Poisoning may occur through ingestion or topical absorption [20]. Aconite produces its effects by opening of voltage-sensitive sodium channels in the myocardium, nerves, and muscle leading to prolonged depolarization and premature excitation [21]. Clinical features occur soon after ingestion. GI symptoms are common if taken orally, but the most characteristic symptoms are paresthesias and numbness of the lips and mouth, limb and muscle weakness, bradycardia, hypotension, and a variety of cardiac dysrhythmias, the most lethal being ventricular tachydysrhythmias potentially leading to cardiac arrest [19]. These ventricular dysrhythmias can be resistant to antidysrhythmic drugs and cardioversion/defibrillation [19]. Treatment is supportive and should proceed along standard ACLS guidelines. In addition the use of extracorporeal cardiac support should be strongly

considered in cases of cardiac arrest or cardiogenic shock due to aconite poisoning.

Veratrum alkaloids: Plants belonging to the genus *Veratrum* or false hellebores and *Zigadenus* or death camas contain a number of veratrum alkaloids including veratridine that act on voltage-gated sodium channels to increase permeability to Na^+ and Ca^{++} [22]. Ingestion usually results from misidentification as an edible plant such as the common camas or sego lily. The main clinical effects following ingestion are vomiting, bradycardia, and hypotension [23]. Neurological symptoms are generally mild. Treatment is supportive involving fluids, atropine, and, in severe cases, vasopressor support.

Rhododendron: Similar toxins to aconitine and veratridine are present in *Rhododendron* spp., called grayanotoxins. Poisoning from these plants in humans is rare except for cases of toxic honey ingestion in Turkey made from nectar derived from *Rhododendrons*. The principal clinical effects are vomiting, bradycardia, hypotension, neuromuscular weakness, and paresthesias. Ventricular dysrhythmias and conduction blocks responsive to atropine have been noted in case reports [24, 25]. Treatment is supportive.

Yew (*Taxus* spp.): The yew tree is commonly found in cooler climates throughout the world and is characteristically found surrounding churches and graveyards in the United Kingdom. All parts of the tree are toxic apart from the soft fleshy aril of the fruit. However, the seed contained at the center of the fruit is toxic. The main alkaloid toxins are known as taxines A and B which act to alter sodium and calcium channel conductance in cardiac myocytes. It causes a delay in action potential depolarization rate similar to the effect of class I antidysrhythmics [26]. Yew also contains taxanes which are spindle poisons that are used as chemotherapeutic agents [27]. Ingestion of plant material typically causes GIT effects, but principally it is the cardiovascular effects that are the most important clinical manifestation. Initial bradycardia may be followed by QRS prolongation, ventricular tachycardia, hypotension, cardiogenic shock, and cardiac arrest. The yew leaves or needles are most commonly ingested either accidentally by children or deliberately by adults as it

is a well known and readily available toxic plant in some parts of the world. An estimated dose of around 50 g of yew needles in an adult has the potential for serious toxicity and death [28]. Management is essentially supportive using ACLS principles. Atropine may be useful in bradycardia, and cardiac pacing for severe conduction disturbances and digoxin Fab have been used in some cases [29] though there is no good evidence they are effective. Prolonged CPR and extracorporeal cardiac support may result in patient survival in cases of cardiac arrest or cardiogenic shock.

Anticholinergic Plant Toxicity

A number of plants contain anticholinergic compounds such as atropine, hyoscyne, and scopolamine that when ingested cause features of the anticholinergic toxidrome. These plants include Jimsonweed (*Datura stramonium*), deadly nightshade (*Atropa belladonna*), henbane (*Hyoscyamus niger*), and angel's trumpet (*Brugmansia* spp.), among others (Fig. 2).

Due to the fact that these plants are often deliberately ingested for their hallucinatory effects, they are relatively common plant poisonings encountered in emergency departments, and often more than one patient will present at a time. The anticholinergic toxidrome consists of hallucinations and delirium, pupillary dilation, dry flushed skin, tachycardia, hyperthermia, and urinary retention. Seizures and cardiac arrhythmias are uncommon. Injuries may be sustained due to the psychotic state inducing risk-taking behavior and self-harm. All parts of these plants contain tropane alkaloids in varying concentrations [30]. In the case of *Datura*, it is the seeds that are usually ingested, whereas with *Brugmansia* it is as a tea brewed from the leaves. Clinical effects develop rapidly in these later cases. Treatment of affected patients initially involves providing a reassuring low-stimulus environment, benzodiazepine sedation for agitation, and, in severe cases, consideration of the use of the antidote physostigmine, an anticholinesterase inhibitor that will effectively reverse the anticholinergic effects. Notably physostigmine has a



Fig. 2 *Brugmansia Feingold* (<https://commons.wikimedia.org/w/index.php?curid=142315> under a Creative Commons license)

much shorter half-life than the tropane alkaloids. Physostigmine also has potential value as a diagnostic agent in suspected cases of delirium due to anticholinergic plant poisoning. Decontamination using activated charcoal can be considered following a risk assessment on a case-by-case basis in early presenting cases. However, given the altered mentation exhibited by these cases, the risk of charcoal administration in patients with unprotected airways is potentially significant. Activated charcoal has not been shown to alter the outcome in these patients. Further, the anticholinergic toxidrome induced by these plants can be reversed by physostigmine. The usual intravenous dose is 2 mg over 2 min. The use of physostigmine in anticholinergic poisoning is discussed in greater detail in ► Chap. 23, “Anticholinergic Syndrome.” The clinical pharmacology of physostigmine is reviewed in ► Chap. 161, “Physostigmine.” Even in the absence of treatment, however, the clinical effects from these poisonings usually resolve within 24 h [31].

Cellular Poisons

Ricin: The castor bean plant (*Ricinus communis*) is the source of the potent biologic toxin ricin. It is derived from the seeds of the plant which have a characteristic variegated brown and black appearance and a hard outer shell. This shell must be broken for ricin to be released. Ricin is a cellular toxin that acts by inhibiting ribosomal protein synthesis [32]. The effects depend on the route of exposure. The toxicity of ricin by the inhaled or injected route is approximately 1,000 times greater than when ingested [33]. If swallowed whole without being chewed, the seeds will pass through the gut with no or only minor symptoms. When chewed, or deliberately crushed, ricin can be released but is probably poorly absorbed from the intestine. Even so, historically death has been reported with ingestion of as few as two seeds [34]. The effects following ingestion are principally gastrointestinal with the potential for significant fluid and electrolyte losses, and hepatic and renal dysfunction may also be found [35]. Parenterally injected ricin leads to multi-organ failure with an LD₅₀ in mice of 5–10 µg/kg [36], while inhaled ricin produces noncardiogenic pulmonary edema at tiny doses if the particle size reaches the lower airways [37].

Treatment of ricin poisoning is entirely supportive in all cases. Activated charcoal can be considered in recent ingestions. However, the administration of activated charcoal has not been shown to alter the outcome in patients who have ingested ricin. Ricin poisoning is covered in more detail in ► Chap. 114, “Toxalbumins.”

Abrin: The attractive red and black seeds, often made into necklaces and bangles, of the tropical/subtropical plant *Abrus precatorius* or rosary pea (Fig. 3) contain the potent toxin abrin which is very similar in structure and mechanism of action to ricin [38]. Similar toxicity can be expected if chewed or crushed seeds are ingested [39]. Abrin poisoning is discussed in detail in ► Chap. 114, “Toxalbumins.”

Colchicine: *Colchicum autumnale*, commonly known as autumn crocus or meadow saffron, is the plant source of the drug colchicine. Usually as a result of mistaken identification as the edible



Fig. 3 *Abrus precatorius* (rosary pea) Forest and Kim Starr – USGS plants of Hawaii

wild garlic plant *Allium ursinum*, ingestion of any part but most commonly the leaves of *Colchicum* can result in potential serious and fatal colchicine poisoning [40]. Colchicine is a well-known cellular poison preventing microtubular formation and inhibiting mitosis. High turnover organ systems such as the GI tract and bone marrow are preferentially affected. Hence, ingestion of sufficient quantities of the *Colchicum* plant will present in the same fashion, with initial GI symptoms, bone marrow suppression, and multisystem organ failure occurring in a dose-dependent fashion. Treatment is supportive. As recommended in ingestions of unknown or potentially serious amounts of colchicine tablets, activated charcoal should be administered to all cases as even small reductions in the amount of colchicine absorbed may affect outcome (Grade III recommendation). Multidose activated charcoal can be considered; however, there is no evidence that it enhances outcome in colchicine-poisoned patients and colchicine is not considered to be one of the toxins amenable to enhanced elimination by this treatment in a major position statement issued by major clinical toxicology societies (<http://www.clintox.org/documents/positionpapers/MultipleDoseActivatedCharcoal.pdf>). Colchicine toxicity may also occur from ingestion of tubers of the colchicine-containing plant *Gloriosa superba* or glory lily.

Plants Causing Hypoglycemia

Akee (Blighia sapida): This is the national fruit of Jamaica and commonly eaten. However, ingestion of the unripe fruit of this tropical plant is potentially deadly and the cause of “Jamaican vomiting sickness” characterized by GI distress, marked hypoglycemia, coma, convulsions, and liver dysfunction. The main toxin is hypoglycin A and acts by interfering with long-chain fatty acid metabolism. Hypoglycemia does not explain the whole clinical picture; other compounds may account for some of the CNS effects seen with akee poisoning [41]. Treatment is supportive plus intravenous dextrose.

Chardon a glu (Atractylis gummifera): Commonly known as blue thistle, it is a significant plant poison in North Africa due to misidentification with an edible plant, *Scolymus hispanicus* or Geumina. It also causes hypoglycemia along with CNS and hepatotoxicity due to atractyloside toxins that interfere with oxidative phosphorylation [42].

Miscellaneous

Cleistanthus collinus: Commonly known as oduvan, this important toxic plant has been responsible for many deaths in southern India due to deliberate ingestion as a method of self-harm [43]. All parts of the plant are toxic but mainly the leaves are ingested. The toxicity of the plant has been attributed to a number of complex compounds with the clinical effect being the characteristic metabolic derangement of a distal renal tubular acidosis manifest by a normal anion gap hypokalemic metabolic acidosis and also cardiac dysrhythmias, respiratory failure, and shock [44]. Management focuses on correction of hypokalemia and acidosis and cardiorespiratory support. Activated charcoal may be given with the usual considerations; however, it has not been shown to alter the outcome in these patients.

Herbs and Essential Oils

Herbal products are widely available over-the-counter products, the use of which has grown

enormously over the past 20 years. Consumers of alternative health products may not be aware of the potential side effects and toxicity of these agents or disclose that they are taking them to healthcare professionals. Varying regulations exist between countries controlling herbal products, but cases of miscalculation, adulteration, and contamination and lack of standardization are all reported in the literature. Herbal preparations may also include essential oils which are often concentrated extracts of plant material and potentially toxic in small volumes. Though the number of herbal preparations is huge, only the most important herbal product-related toxicity will be covered in this introductory chapter.

As the toxicity of herbal preparations often affects the liver, a good history of the potential use of these products is important in the workup of patients with otherwise unknown causes of liver dysfunction.

Pyrrolizidine alkaloids are contained in a number of plants and appear to be the causative toxins in cases of hepatic veno-occlusive disease associated with herbal preparations. The plant species containing these alkaloids include *Symphytum* (comfrey), *Heliotropium*, *Senecio*, and *Crotalaria*. The dose required to cause toxicity is difficult to define due to varying content in plant species and individual variation in susceptibility. The toxic effect is a form of sinusoidal obstruction similar to the hepatotoxicity seen with bone marrow transplantation [45]. Pulmonary damage is sometimes also seen. Presentations may range from an acute hepatitis to a more chronic picture resembling Budd-Chiari syndrome [46]. Hepatotoxicity has also been reported from the ingestion of green tea, particularly with more concentrated extracts and multicomponent forms [47], chaparral, germander, the Chinese herbal product Jin Bu Huan, clove oil, and pennyroyal oil (*Mentha pulegium*). Particularly in the case of pennyroyal oil-induced hepatotoxicity, the use of *N*-acetylcysteine may be beneficial as glutathione deficiency may enhance toxicity [48] (Grade III recommendation).

Other herbal toxins to note include:

	Potential for drug interactions and enhanced serotonergic effects
Yohimbe/ma huang	Sympathomimetic effects secondary to ephedrine
Wintergreen (oil of)	Salicylate toxicity
Eucalyptus oil	CNS depression and risk of aspiration
Clove oil	CNS depression, aspiration risk, and hepatorenal failure noted in pediatric case reports [49]

This is not a complete list, and practitioners should also be aware of the varying regulations and quality controls that exist for these products throughout the world when dealing with patients with potential toxicity from over-the-counter preparations.

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Exposure to plants with anticholinergic properties can result in emergency department and intensive care unit (ICU) admissions due to hallucinations, delirium, agitation, seizures, hyperthermia, and rhabdomyolysis among other clinical manifestations of toxicity [1–3]. Alkaloid-containing plants of the *Solanaceae* (nightshade) family, especially *Datura* spp., have been used since antiquity as analgesics, hypnotics, aphrodisiacs, hallucinogens, and as herbal remedies. Homer likely referred to *Datura* in the *Odyssey* [4]. Dioscorides, in *De Materia Medica*, described dose-dependent *Datura* toxicity [5]. Cleopatra lured Caesar with this plant and Marc Antony’s troops suffered confusion and fatalities after eating the plant when retreating from Parthia in 38 AD. An outbreak of *Datura* poisoning occurred in colonial Virginia in 1676, during Bacon’s Rebellion [3]. In his work, *The History and Present State of Virginia*, Robert Beverly described behaviors consistent with anticholinergic delirium among soldiers who were sent “to quell the Troubles”:

The *James-Town* Weed (which resembles the Thorny Apple of Peru, and I take to be the Plant so call’d) is supposed to be one of the greatest Coolers in the World. This being an early Plant, was gather’d very young for a boil’d Salad, by some of the Soldiers sent thither, to quell the Troubles of Bacon; and some of them eat plentifully of it, the Effect of which was a very pleasant Comedy; for they turn’d natural Fools upon it for several Days: One would blow up a Feather in the Air; another wou’d dart Straws at it with much Fury; and another stark naked was sitting up in a Corner, like a

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Monkey, grinning and making Mows at them; a Fourth would fondly kiss, and paw his Companions, and sneer in their Faces, with a Countenance more antick, than any in a *Dutch Droll*. In this frantick Condition they were confined, lest they should in their Folly destroy themselves; though it was observed, that all their Actions were full of Innocence and good Nature. Indeed, they were not very cleanly; for they would have wallow'd in their own Excrements, if they had not been prevented. A Thousand such simple Tricks they play'd, and after Eleven Days, return'd to themselves again, not remembering any thing that had pass'd. [6]

Unintentional outbreaks of anticholinergic delirium have occurred with poisoning from contaminated flour [7–9], when food has been prepared with berries mistaken for edible varieties [10–12], when leaves have been prepared in a salad [13], or when plant parts have otherwise been prepared in food [14–16], brewed in tea [17–20], or used as a herbal remedy [21, 22]. Outbreaks have also occurred due to recreational use as a hallucinogen [1, 2, 11, 17–19, 23–33]. Six hundred and ten single exposures to anticholinergic plants were reported to the National Poison Data System in 2014; most were unintentional (454 of 610 [74%]) [34]. Pre-teen children (≤ 12 -years-old) accounted for most exposures (381 of 610 [63%]) [34]. Most patients were not treated in a healthcare facility (419 of 610 [69%]) [34]. A minority of patients developed moderate clinical effects (80 of 610 total single exposures [13%] with 80 of 191 treated in healthcare facilities [42%]) or major clinical effects (8 of 610 total single exposures [1%] with 8 of 191 treated in healthcare facilities [4%]) [34]. No fatalities were reported [34]. This chapter will focus on patients with anticholinergic plant poisoning who require care in healthcare facilities, especially in the ICU. The term, anticholinergic in this chapter will be restricted to its common connotation which is antimuscarinic.

Anticholinergic Plants

Anticholinergic plants are members of the *Solanaceae* family. This family includes foods (e.g., tomatoes, potatoes, paprika, eggplants, red

peppers), tobacco, and ornamentals (e.g., petunias) [5, 35]. These plants grow in temperate and tropical climates and include the genera *Atropa*, *Datura*, *Duboisia*, *Hyoscyamus*, and *Mandragora* [36]. The pharmacologically active components are the tropane (belladonna) alkaloids: atropine (D,L-hyoscyamine) and scopolamine (L-hyoscyne). The L-isomer of atropine (L-hyoscyamine) is predominantly responsible for atropine's pharmacological action.

Atropa belladonna

Atropa belladonna, deadly nightshade, is perhaps the best known of the *Atropa* genus (Fig. 1). It is native to continental Europe and Great Britain and is cultivated in the United States as an ornamental [37, 38]. Its roots, leaves, and fruits contain tropane alkaloids, including 98% atropine with only small amounts of scopolamine [10, 21, 39]. It grows as a bush with purple-black berries. These berries, which contain as much as 2 mg of atropine per berry, may be mistaken for edible berries [10, 12].



Fig. 1 *Atropa belladonna* (Photo courtesy of Julian White © Rights remain with the Photographer)

Datura Species

Datura stramonium, also known as Jimson weed, locoweed, thornapple, and other common names, is the most geographically widespread of the potentially toxic *Solanaceae* [29] (Fig. 2). It is a large annual shrub with dark green ovate-oblong leaves and a white tubular flower that blooms from July to September, followed by the growth of a fruit consisting of a four-lobed, spiny pod [11]. Each of these pods contains 50–100 kidney-shaped seeds 2–3 mm in size that change from yellow to tan to black as they mature. All parts of the plant contain anticholinergic compounds, though the amounts of atropine and scopolamine can vary depending on the part of the plant, the age of the plant, and the time of year [38, 40–42]. Each seed contains about 0.05–0.1 mg of atropine, or about 6 mg per pod [2, 40]. *Datura stramonium* is used as a hallucinogen, commonly by ingesting the seeds, but also by smoking the leaves or brewing in a tea [2, 17, 18, 28, 29, 31–33, 43]. Accidental poisoning has occurred

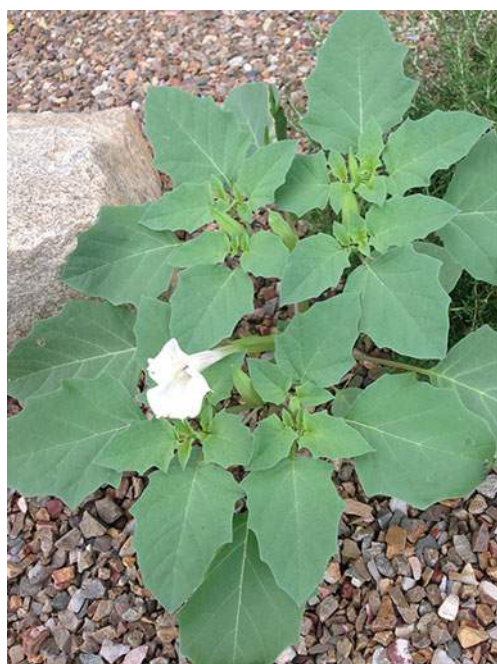


Fig. 2 *Datura stramonium* (Photo courtesy of Robert French © Rights remain with the Photographer)

from use as an herbal tea or herbal therapy [11, 18, 41, 44, 45]. Young children have been poisoned after ingesting seeds when playing with the seed pod [46–48]. Fatalities have been reported [49, 50].

Angel's trumpet, or sacred *Datura*, is referred to variously as *D. sauveolens*, *D. candida*, *D. innoxia*, *D. meteloides*, *Brugmansia candida*, and *B. sauveolens* [19]. It grows wild throughout the southeastern United States, the Caribbean, and South America and is a common garden ornamental plant [24]. It is an evergreen bush 2–8 m high, with trumpet-shaped, purplish-to-white flowers measuring 20–50 cm that hang straight down [19, 24, 38, 51, 52]. Exposure is typically from use as a hallucinogen by brewing tea, ingesting the leaves and flowers, or steeping the leaves and blossoms in water and alcohol to yield a “magic drink.” Angel's trumpet may also be mistaken for a herbal tea, herbal remedy, or an edible plant [19, 22, 24, 27, 52–54].

Toxic effects of Chinese herbal medicines and Chinese proprietary medicines account for 0.2% of the acute medical admissions in Hong Kong [51]. Some are derived from *Datura* spp. that are native to south Asia and China [55], including *D. metel*, *D. innoxia*, *D. tabula*, and *D. fastuosa*. They are used to treat asthma, chronic bronchitis, seizures, psychosis, and pain [51]. Yangjinhua is made from the dried flowers of *D. metel*, containing the tropane alkaloids in the following proportion: 85% scopolamine and 15% atropine [55]. Yangjinhua may be smoked, given orally, or administered intravenously [55].

Duboisia Species

Duboisia hopwoodii, *D. leichhardtii*, and *D. myoporides*, known collectively as corkwood, are plants native to Australia [56]. These plants are farmed as a source of scopolamine and atropine [57, 58]. Occupational exposure to plant material has resulted in a syndrome characterized by mydriasis and cycloplegia dubbed “cork-eye” and intentional ingestion has resulted in systemic toxicity [59].

Fig. 3 *Hyoscyamus niger* from Kohler’s Medicinal Plants, 1887, Bera-Untermhaus, Germany (in public domain)



Hyoscyamus niger

Hyoscyamus niger, henbane, (Fig. 3) is a foul-smelling annual or biannual herb that is native to Europe and northern Africa but is also distributed widely in North America [38, 60, 61]. All parts of the plant, including the roots, leaves, and fruits contain atropine and scopolamine [38, 62]. It has been used intentionally as a hallucinogen and inadvertent poisoning has occurred when mistaken for parsnip [16].

***Mandragora* Species**

Mandragora species are widespread around the Mediterranean [15]. Historically, these plants were characterized by supposedly human-shaped or phallus-shaped roots, which were thought to have occult properties [35, 36]. However, in addition to the root, the leaves, seeds, and berries contain varying concentrations of tropane

alkaloids. Outbreaks of anticholinergic poisoning have occurred when this plant has been mistaken for an edible plant [63, 15].

The toxicity of *Mandragora*, commonly known as mandrake, should not be confused with that of *Podophyllum peltatum*, which is sometimes known by a similar common name, American mandrake. *Podophyllum peltatum* contains podophyllotoxin (see Chap. 71, “Antitubulin Agents: Colchicine, Vinca Alkaloids, and Podophyllin”) [64].

Biochemistry and Clinical Pharmacology

Atropine	
T _{1/2}	2–4 h [65]
Vd	2.3–3.6 L/kg [65]
pKa	9.8 [65]
log Kow	1.83 [66]

Scopolamine	
$T_{1/2}$	2–6 h [67]
Vd	1.4–2.0 L/kg [67]
pKa	8.2 [67]
log Kow	0.98 [66]

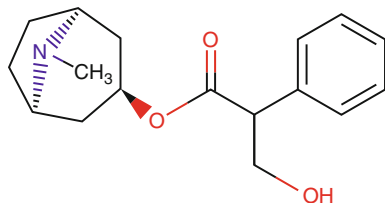


Fig. 4 Atropine [68]

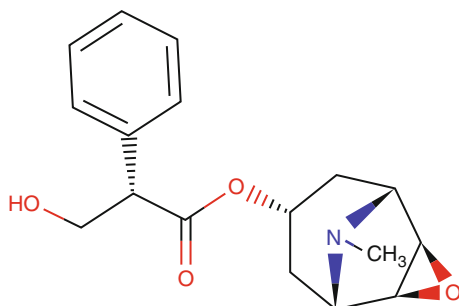


Fig. 5 Scopolamine [69]

The tropane alkaloids, atropine and scopolamine, are responsible for the pharmacological and toxicological actions of anticholinergic plants (Figs. 4 and 5).

Atropine and scopolamine are rapidly absorbed from the gastrointestinal tract. Clinical effects typically occur within 5–10 min after the ingestion of teas and 1–3 h after ingestion of leaves or seeds [19, 70]. Slow dissolution of the plant parts, along with anticholinergic slowing of the gastrointestinal tract, prolongs absorption [28]. Unabsorbed alkaloids have been found in the stomach 24 h after ingesting anticholinergic plant parts and the anticholinergic effects last much longer than predicted by known absorption and elimination rates of pure atropine and scopolamine [2, 26, 28]. Atropine and scopolamine are widely distributed throughout the body.

Elimination is by hepatic metabolism and renal excretion. Twenty percent to 50% of atropine is excreted unchanged in the urine, in contrast to only about 1–5% of scopolamine [10, 11, 26, 71].

Pathophysiology of Toxic Effects

Atropine and scopolamine compete with the neurotransmitter acetylcholine at a common binding site on all five muscarinic acetylcholine receptor subtypes. Muscarinic acetylcholine receptors are located throughout the central nervous system, primarily in the brain, in organs innervated by the parasympathetic division of the autonomic nervous system, and in the skin at postganglionic, sympathetically innervated sweat glands.

Clinical Presentation and Life-Threatening Complications

Anticholinergic plants can cause central and peripheral manifestations of the anticholinergic syndrome (see Chap. 23, “Anticholinergic Syndrome”). Peripheral effects include mydriasis, flushing, tachycardia, dry skin, dry mouth, decreased gastrointestinal motility, urinary retention, and hyperthermia; central effects are usually hallucinations and delirium. Atropine and scopolamine block the cholinergic actions on the sphincter muscle of the iris and the ciliary muscle of the eye, resulting in mydriasis and loss of accommodation [72].

The severity and duration of clinical effects depend on the route, form (e.g., tea ingestion, flower/leaf smoking), and dose, with some variation in content among the different anticholinergic plants. The progression of symptoms can be related to the equivalent dose of atropine and scopolamine. Time to onset of clinical effects varies with the route and the plant involved, beginning within 5–10 min if a tea or broth is ingested or delayed for 1–3 h if seeds or leaves are ingested [19, 24]. Signs and symptoms may last several days (up to 11, in Beverly’s historical account) [2, 6].

Altered mental status is the most prominent and frequent manifestation, present in all 27 patients in one report [28]. More common CNS effects are restlessness, bizarre behavior, delirium, disorientation, and combative behavior; seizures and coma are unusual. Patients characteristically pick at imaginary objects in the air, on clothing, or on bed sheets and have fragmented, mumbling, rapid, and incomprehensible speech [2, 11]. Patients may be able to answer questions appropriately with one to two words, but their disorientation and confusion are revealed when responding in sentences. Severely affected patients may be mute [70]. Hallucinations or delusions were the most frequently reported adverse effect, occurring in 50% of 122 *D. stramonium* exposures that were reported in Texas between 1998 and 2004 [1]. Hallucinations commonly feature the family or friends, natural colors, simple objects, visual misperceptions, and the sensation of flying [11]. The hallucinations are sometimes perceived as small objects or people and described with the term Lilliputian, referring to the little people described in Jonathan Swift's *Gulliver's Travels* [16, 40, 73]. Auditory hallucinations are less common [11, 29, 53]. Patients are often amnesic for events, after recovering [11, 29, 53]. Particularly characteristic of belladonna alkaloid intoxication is undressing behavior, presumably due to the subjective symptoms associated with flushing and hyperthermia, combined with loss of inhibitions [24, 29, 70, 74]. Neurologic examination may reveal hyperreflexia, clonus, myoclonus, and sometimes dorsiflexor Babinski responses. Coma with decerebrate posturing [11, 29] or decorticate posturing has been reported [75, 76]. Neurological findings in the comatose patient may suggest focal lesions [76]. Convulsions and flaccid paralysis may occur in severe cases [24].

Cardiovascular abnormalities are ordinarily limited to sinus tachycardia; mild hypertension and widened pulse pressure are seen in some cases [19, 24, 25, 30, 54]. Mydriasis occurs early in intoxication and is often one of the last signs to resolve. Blurred vision and dilated pupils may present as the only manifestations of a minor exposure or from anisocoria following monocular contact with plant parts ("Gardener's mydriasis")

[27, 77]. Urinary retention and gut hypomotility may present as early or late complications. Vomiting may be present early, particularly with accidental ingestion of large amounts, such as in foods and teas [12, 20]. Dysphagia and dysarthria result from severe mouth and throat dryness. Renal insufficiency or failure may occur due to rhabdomyolysis and dehydration.

Complications of severe anticholinergic plant poisoning include aspiration pneumonitis due to loss of airway protection, particularly in patients with seizures [10, 52]. Severe agitation, myoclonus, and seizures, coupled with hyperthermia and dehydration, create a risk of rhabdomyolysis and resultant renal injury [3, 12, 78]. Delirium could put patients at risk of traumatic injury. There are few reports of death associated with anticholinergic plant ingestion [17, 49, 50, 54, 79].

Diagnosis

Anticholinergic plant poisoning is a clinical diagnosis. There are no routinely available tests that can be used to confirm ingestion of an anticholinergic plant. The diagnosis is made by obtaining a history, often from indirect sources, and performing a careful and complete physical examination. Resolution of delirium after administration of physostigmine is virtually diagnostic of anticholinergic toxicity.

Clusters of cases, such as simultaneous onset of symptoms in family or friends who have shared a meal, or the onset of the anticholinergic syndrome in a group of adolescents or young adults suggests the diagnosis [12, 15, 19, 20, 24, 25, 27, 30, 31, 33, 63]. Routine immunoassays for drugs of abuse and comprehensive drug screens do not detect the belladonna alkaloids. Qualitative and quantitative assays of blood, urine, hair, gastric contents, and plants by gas chromatography-mass spectrometry or thin-layer chromatography can detect atropine and scopolamine, but these assays are not routinely available [10, 24, 28, 49, 53, 70, 80, 81].

Nonspecific laboratory abnormalities that have been reported include transient elevations of lactate dehydrogenase, hepatic transaminases,

calcium, phosphorus, prothrombin time, and white blood cell count [19, 28, 29]. Serum creatine kinase levels, urinalysis, and renal function tests may reveal rhabdomyolysis, myoglobinuria, and renal failure. These findings may occur as a result of hyperthermia and/or agitation [3, 12, 82].

Sinus tachycardia is the typical electrocardiographic feature [16, 20, 40]. Mikolich reported electroencephalogram findings in six patients who presented after ingestion of *D. stramonium* seeds and who had no observed seizures. Diffuse slowing was seen in three of the patients, rhythmic bursts of high-voltage sharp waves in two, and marked loss of alpha activity one. These electroencephalograms returned to normal in all cases. The observed changes may be due to hyperthermia or to the antagonistic actions of toxic alkaloids on cholinergic pathways in the reticular activating system [29].

Differential Diagnosis

The differential diagnoses to be considered when faced with a comatose patient, a convulsing patient, or with a patient who is agitated, delirious, hyperthermic, and tachycardic includes toxic, metabolic, infectious, traumatic, and psychiatric causes. Common possibilities include overdose of pharmaceuticals with anticholinergic, sympathomimetic, or serotonergic properties; ingestion of recreational drugs; or ingestion of anticholinergic plants. Withdrawal syndromes, stroke, seizure, hypo- or hyperglycemia, fluid and electrolyte abnormalities, hepatic encephalopathy, hyperthyroidism, CNS infections, and psychoses must also be considered [2, 14, 16, 27, 40, 75, 76, 83, 84].

The presence of characteristic peripheral and central manifestations of anticholinergic toxicity may help differentiate anticholinergic plant poisoning from other potential diagnoses [40]. For example, hyperthermia and agitation may be seen with cocaine, amphetamine, or other sympathomimetic drug intoxications, or with serotonergic drug intoxications. However, these conditions typically cause diaphoresis. This is distinctly unusual for anticholinergics that typically produce dry axillae and dry mucous membranes. Ileus and

urinary retention are also characteristic peripheral findings. Undressing behavior, mumbling, rapid, incomprehensible speech, and visual hallucinations are characteristic of the central effects of anticholinergic toxicity and strongly support the diagnosis of anticholinergic toxicity.

Diagnostic studies that may be helpful in the differential diagnosis include blood glucose, urine drugs-of-abuse screening, complete blood cell count, serum chemistries, creatine kinase, transaminases, ammonia and lactate levels, salicylate and acetaminophen levels, thyroid function tests, brain imaging, and electrocardiograms. Lumbar puncture can be used for diagnosing or excluding CNS infection. CT scans may assist with evaluation of head trauma or CNS hemorrhage. With appropriate caution, a diagnostic trial of physostigmine may help establish the diagnosis of anticholinergic toxidrome and possibly avoid unnecessary diagnostic testing. Lack of response to physostigmine makes anticholinergic poisoning much less likely as a potential cause of delirium.

Treatment

A common scenario is an agitated, delirious patient being restrained by emergency or security personnel. Treatment priorities include, in some cases, protecting the airway to prevent aspiration and controlling agitation to prevent complications, such as hyperthermia, rhabdomyolysis, myoglobinuric renal tubular injury, and traumatic injury to the patient or to staff. Physical restraints may be needed but should be avoided for prolonged periods because of the risk of developing rhabdomyolysis. Should physical restraint be required, patients must also be adequately sedated in order to avoid potential injury caused by fighting against the restraints.

Rapid-acting benzodiazepines are often used as first line therapy to treat agitation and prevent seizures (Grade III recommendation). Benzodiazepines have the advantage of being a nonspecific means of controlling agitation when the diagnosis is unclear. While benzodiazepines may be effective in controlling agitation, they do not reverse

delirium. Adverse effects include over-sedation, aspiration, and potential delay in recovery to baseline mental status when compared with the administration of physostigmine, as addressed below [78].

Although intact Jimson weed seeds have been found in vomitus and gastric lavage fluid for many hours after ingestion [28, 85], gastric lavage is difficult, can increase agitation, and is associated with several life-threatening complications such as aspiration pneumonitis, aspiration pneumonia, and esophageal or gastric perforation [86]. It does not shorten the length of ICU stay, overall length of hospitalization, or otherwise improve outcome [85, 87]. Administration of activated charcoal carries the risk of emesis, aspiration, and corneal abrasion [88]. These modalities are contraindicated in patients with altered mental status unless the airway is protected and, generally, are not indicated in the management of anticholinergic plant poisoning.

Physostigmine is a naturally occurring carbamate compound that acts as a short acting acetylcholinesterase inhibitor. It is a specific antidote for anticholinergic toxicity. Physostigmine acts by increasing the concentration of acetylcholine at muscarinic and nicotinic receptors by reversibly inhibiting acetylcholinesterase at the synaptic cleft and neuroeffector junctions [53, 89]. In contrast to other carbamate cholinesterase inhibitors, it is a tertiary amine and crosses the blood-brain barrier, reversing the central as well as peripheral effects of cholinergic blockade. Published guidelines recommend that physostigmine be stocked by facilities that accept emergency patients and be immediately available for the treatment of anticholinergic toxicity [90].

Although a subject of controversy in the past [91–94], physostigmine is considered indicated as an initial treatment to reverse agitation and delirium caused by anticholinergic toxicants, including anticholinergic plants [53, 78, 89, 94, 95] (Grade II-3 recommendation). In a retrospective comparison of therapy with physostigmine versus benzodiazepines in anticholinergic toxicity, physostigmine controlled agitation in 96% of cases (versus only 24% with benzodiazepines) and reversed delirium in 87% of patients (versus no

reversal with benzodiazepines). Side effects of physostigmine were limited to diaphoresis, vomiting, diarrhea, and asymptomatic sinus bradycardia to a rate of 51 beats per minute in one case [78]. In ambiguous cases, physostigmine administration can be used as an aid in diagnosis [40, 89].

Prior cautions against the use of physostigmine were based on reports of dysrhythmias, asystole, and seizures that were temporally associated with its administration, typically in the setting of cyclic antidepressant toxicity [92, 96–98]. Levy reported a case of atrial fibrillation and non-sustained ventricular tachycardia that occurred 45 min after a 2 mg dose of physostigmine in the treatment of anticholinergic symptoms due to Jimson weed seed ingestion [99]. Given the length of the interval between the administration of physostigmine and the reported dysrhythmia, a cause-and-effect relationship seems unlikely. Physostigmine was effective and complications were not reported in several other case reports of anticholinergic plant poisoning and case series that included patients with anticholinergic plant poisoning [2, 15, 24–26, 29, 52, 54, 74, 75, 97, 100–102]. Nevertheless, physostigmine should be used with appropriate caution and administered in a monitored, critical care setting such as an intensive care unit or a monitored area of an emergency department. A reasonable indication for the use of physostigmine is for cases who are not adequately managed with low doses of benzodiazepines. Physostigmine is contraindicated in the presence of severe or clinically active asthma, gangrene, mechanical obstruction of the intestine or urogenital tract, or any significantly vagotonic state. Cholinergic signs may be observed, and bradycardia and seizure can be seen if physostigmine is administered too quickly [103].

Physostigmine is available as physostigmine salicylate in 2 mg ampules, the concentration is 1 mg/mL [103]. In adults, an initial dose of 0.5–1 mg slow IV push with a minimum delay of 10–15 min before re-dosing has been recommended (in children 0.01–0.02 mg/kg) [104]. Physostigmine should be given slowly at a rate of no more than 1 mg per minute in adults and 0.5 mg per minute in children [103]. The half-life

of physostigmine is 18–36 min [105] and the duration of action is about 45–60 min [103]. Anticholinergic effects frequently reemerge after the effects of a physostigmine bolus wanes. Continuous infusion of physostigmine was described in a published case of prolonged and recurrent anticholinergic delirium due to a mixed-drug overdose [106].

Patients who have ingested anticholinergic plants; who present with agitation, delirium, seizure, or hyperthermia; and who receive physostigmine require either ICU care or a prolonged stay in the emergency department for intensive monitoring for worsening anticholinergic toxicity and its consequences and to observe for adverse effects of treatment.

Indications for ICU Admission in Anticholinergic Plant Poisoning

Delirium unresponsive to benzodiazepines and physostigmine
Hallucinations
Repeated doses of physostigmine required to control delirium
Respiratory failure
Airway compromise
Seizures or symptomatic dysrhythmias (both rare)

Criteria for ICU Discharge in Anticholinergic Plant Poisoning

Resolution of delirium and hallucinations
No physostigmine or sedatives required for at least 4–6 h
Resolution of associated respiratory or renal failure

Key Points in Anticholinergic Plant Poisoning

1. Anticholinergic plants are used as hallucinogens.
2. Anticholinergic plants may be mistaken for edible berries or foods.

3. Delirium, hallucinations, tachycardia, dry mouth, and mydriasis are the most common clinical effects.
4. Seizures, rhabdomyolysis, respiratory failure, and renal failure are potential serious complications.
5. There is no routinely available diagnostic test to confirm the diagnosis; however, resolution of delirium after administration of physostigmine is virtually diagnostic of anticholinergic toxicity.
6. Physostigmine is specific therapy for anticholinergic plant toxicity.

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When Withering wrote his classic *An Account of the Foxglove and Some of Its Medicinal Uses* in 1785 [1], he recognized the beneficial uses of foxglove (*Digitalis purpurea*); but in the section “Effects, Rules and Cautions,” he described what is now the well-known toxicity of digitalis: “occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death.”

Intoxication from cardiotoxic plants may result from direct ingestion of plant parts, such as leaves, flowers, nectars, seeds, or roots, or may result from teas (decoctions and infusions) brewed from the plant. In some cases, toxicity has occurred from drinking water from a vase that contained the cut flowers of foxglove or lily of the valley or, according to common folklore, from roasting hot dogs on a branch from oleander [2]. Herbal products, especially those contained in traditional medicines, may contain cardiac glycosides [3–5] or alkaloids from *Aconitum* spp. [6, 7]. Cardiotoxic alkaloid-containing toxic honey was implicated in poisonings in 400 BC. Xenophon reported the poisoning of Greek soldiers by honey made by bees from the nectar of wild rhododendron [8].

Type and Activity of Plant Toxin

Plants producing cardiac toxins may be separated into characteristic groups based on the type and the activity of the plant toxin. These groups include (1) digitalis and digitalis-related compounds, (2) aconitine and related alkaloids, (3) grayanotoxins, and (4) *Veratrum* alkaloids. Table 1 lists common plants and the nature of their cardiotoxic components [2, 9–14].

Digitalis and Digitalis-Like Glycosides

Digitalis, digoxin, and related cardiac glycosides are found naturally in several plant species around the world (see Table 1) [15]. Medicinally important glycosides are obtained from the foxglove

plant. Other plants, such as oleander, lily of the valley, Christmas rose, and sea onion, also contain potentially toxic cardiac glycosides.

Foxglove (*Digitalis* spp.) is a biennial plant commonly grown in North American gardens, but it originates from Southern Europe and Central Asia. During the first year of growth, the plant produces a basal rosette of large oval leaves. In the second year, flowers are borne on a large stalk that matures from the bottom to the top. Each flower is cup shaped with darker spots on the lower inside of the tubular-shaped flower. Blooms vary in color from dark pink or purple (*Digitalis purpurea*) to yellowish or whitish (*Digitalis lanata*). The entire plant is toxic, and poisoning has resulted from consumption of teas brewed from foxglove leaves [16, 17]. In some cases, the leaves during the first-year growth were mistaken for comfrey (*Symphytum officinale*) [2].

Oleander is native to tropical and subtropical climates and comprises two related plants, *Nerium oleander* and *Cascabela thevetia*. *N. oleander* is a tall evergreen shrub frequently grown indoors as an ornamental plant in temperate North America, but it also can be grown outdoors, where it may reach heights of 25 ft. The dark, leathery leaves are arranged in whorls of three, and the flowers, borne in clusters with five petals each, are usually pink, peach, red, or white. Yellow oleander (*C. thevetia*) is similar in shape, with yellow or orange flowers, and produces black fruits with a central stone (seeds). Oleander is particularly enticing to small children because of its lovely flowers and seed pods that are easily accessible [18]. All parts of the plant are toxic; reported cases of toxicity include consumption of oleander leaves [19] or oleander tea derived from the leaves [20] and the ingestion of seeds. In some countries (e.g., Sri Lanka), the ingestion of the seeds of yellow oleander is a common means of suicide [21].

Sea mango (*Cerbera manghas*) is a small tree in the Apocynaceae family found along the coasts of South Asia and Southeast Asia, Polynesia, and Northern Australia. It has been reported as an agent in self-poisonings in Sri Lanka [22] and in Taiwan [14].

Lily of the valley (*Convallaria majalis*) is a small perennial plant with two elliptical, pointed leaves and flowers borne on a single, small stalk. Blooms

Table 1 Cardiotoxic plants

Class	Common name	Scientific name	Toxin
Cardiac glycosides	Purple foxglove	<i>Digitalis purpurea</i>	Digitoxin
	Grecian foxglove; wooly foxglove	<i>Digitalis lanata</i>	Digitoxin, digoxin
	Oleander	<i>Nerium oleander</i>	Oleandrin
	Yellow oleander; be still tree	<i>Cascabela thevetia</i> (<i>Thevetia peruviana</i> , <i>T. neriifolia</i>)	Thevetin A and B
	Christmas rose	<i>Helleborus niger</i>	Helleborin, helleborein
	Lily of the valley	<i>Convallaria majalis</i>	Convallotoxin, convallarin, convallamarin
	Squill or sea onion Sea mango	<i>Urginea maritima</i> <i>Cerbera manghas</i> <i>Cerbera venenifera</i> <i>Cerbera odollam</i>	Scillaren, scillarenin Cerberin
Aconitum alkaloids	Monkshood; wolfsbane	<i>Aconitum</i> spp. (<i>A. napellus</i>)	Aconitine alkaloids
	Larkspur	<i>Delphinium</i> spp.	Delphinine
Grayanotoxins	Rhododendron, azalea	<i>Rhododendron</i> spp.	Grayanotoxin 1 or andromedotoxin
	Japanese pieris; lily of the valley bush	<i>Pieris japonica</i>	Grayanotoxin 1 or andromedotoxin
	Mountain-laurel	<i>Kalmia latifolia</i> ; other <i>Kalmia</i> spp.	Andromedotoxin
<i>Veratrum</i> alkaloids	Indian hellebore; American white hellebore; false hellebore; green hellebore	<i>Veratrum viride</i>	Germidine, germitrine, veratridine, veratrosine, veratramine
	Corn lily	<i>Veratrum californicum</i>	
	Death camas; black snakeroot	<i>Zigadenus venenosus</i>	Zygacine, zygadenine, protoveratrine

are small, cup shaped, white, and fragrant and are located along only one side of the flower stem. Bright red berries form later in the season along the flower stalks. Lily of the valley is reported by the Poisons Information Centre as a common plant exposure for children in Helsinki [23], and accidental ingestion has resulted in intoxication [24, 25].

Hellebore, or Christmas rose (*Helleborus niger*), is an herbaceous perennial from the buttercup family, with compound leaves and white or sometimes purplish flowers that bloom in the spring or winter. Although the plant contains cardiac glycosides, reported poisonings are rare [2]. This plant should not be confused with the *Veratrum* spp., which sometimes are called *false hellebore* (see later).

Squill (*Urginea maritima*) or sea onion is a perennial plant with lilylike leaves and small white flowers borne off terminal clusters.

Ingestion of the bulbs has produced effects consistent with cardiac glycoside toxicity [26].

Aconitum and Related Alkaloids

Monkshood, aconite, or wolfsbane (*Aconitum* spp., e.g., *Aconitum napellus*), a perennial plant originally native to Europe, is found within North America. The plant grows 3–4 ft tall from a tuberous root and has deeply divided palmate leaves. The flowers are borne off a long spike, each flower containing five petaloid sepals, with one shaped in the form of a monk's hood. Blooms vary in color, including purple, blue, and combination of purple and white. Related species are grown in China and Japan. *Aconitum carmichaelii* and *Aconitum kusnezoffii* are the main source of medicinal aconite drugs, *ts'ao wu* (*wu t'ou*) and *fu tzu* (*ch'uan wu*) [10, 27].

Delphinium and larkspur (*Delphinium* spp.) are perennial, biennial, or annual plants similar in appearance to monkshood with deeply divided leaves; various species grow from 6 in. to 6 ft tall. The flowers are usually borne off multiple racemes or flower clusters, each flower, commonly blue, containing a long “spur” off the back, hence the name *larkspur*.

Aconitine and delphinium alkaloids are under investigation as potential analgesic and anti-inflammatory drugs [28–30], and *Aconitum* roots currently are used in preparations of Chinese and Japanese medicines for the treatment of rheumatic and neurologic diseases [31, 32]. This usage frequently results in unintentional, potentially fatal, toxicity [6, 7, 31–36].

Grayanotoxins

Rhododendrons (*Rhododendron* spp.) are large evergreen shrubs with leathery leaves and large, showy flower clusters, each flower containing protruding stamens. Bloom colors are highly variable, depending on the hybrid, but can be pink, purple, maroon, or red. The related azaleas are either evergreen or deciduous small shrubs, with additional flower colors of white, orange, salmon, or crimson. Japanese pieris (*Pieris japonica*), also known as the *lily of the valley bush*, is an evergreen with dark, leathery leaves, bearing chains of white, urn-shaped flowers in the spring. Although native to Japan, this small shrub is found frequently in gardens of North America. Mountain-laurel, *Kalmia latifolia*, and other *Kalmia* spp. are small, evergreen shrubs that produce clusters of white to pinkish, bell-shaped flowers.

Toxic diterpenoids (grayanotoxins, also known as andromedotoxins, rhodotoxins, or acetylandromedol), mainly grayanotoxin I or andromedotoxin, are responsible for poisonings attributed to toxic honey, which is produced by bees collecting pollen from *Rhododendron* spp. [37, 38]. Toxic honey, known in Turkey as *deli bal* or *tutan bal*, is ingested as a treatment for gastritis and peptic ulcers [8]. Sucking azalea nectar from the flower may pose less of a hazard [39].

Veratrum Alkaloids

Indian hellebore, also called *American white hellebore*, *false hellebore*, or *green hellebore* (*Veratrum viride*), is an herbaceous perennial with oval, alternately arranged leaves. Each leaf has prominent parallel veins, and the flowers, borne in terminal clusters, are greenish white. Related species, such as *Veratrum californicum* (or corn lily), have white flowers [2]. Confusion of *Veratrum* spp. with other plants, particularly gentian, has led to ingestion of the plant or of wine made from *Veratrum album* [40–43]. Death camas (black snakeroot, *Zigadenus venenosus*, and other species) is a perennial plant in the lily family with grasslike leaves grown from a bulb. Creamy white flowers are clustered together and borne off a single central stalk. Toxicity arises from ingestion of the bulbs [44], frequently mistaken for wild onion [45].

Biochemistry of Cardiotoxic Substances in Plants

Plant Cardiac Glycosides

The plant cardiac glycosides, known as *cardenolides*, have a characteristic chemical structure consisting of an aglycone or genin (i.e., a steroid nucleus joined to a lactone ring) attached to one to four sugar moieties (Fig. 1). The aglycone is essential for the pharmacologic activity of the glycoside, whereas the sugar moieties, specific for each cardenolide, affect the water and lipid solubility and the potency [18, 46].

The foxglove plant produces several cardiac glycosides, most notably digoxin from the Grecian foxglove (*D. lanata*) and digitoxin from the purple foxglove (*D. purpurea*) and from *D. lanata* [12].

D. lanata contains the precursor glycosides, lanatosides A, B, and C. After mild alkaline hydrolysis to remove an acetyl group and enzymatic hydrolysis to remove glucose, digitoxin and digoxin are produced from lanatosides A and

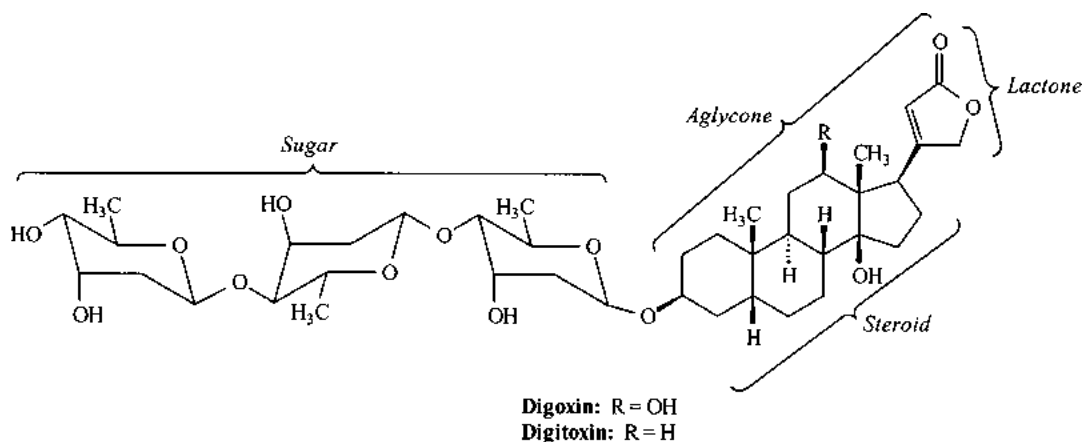
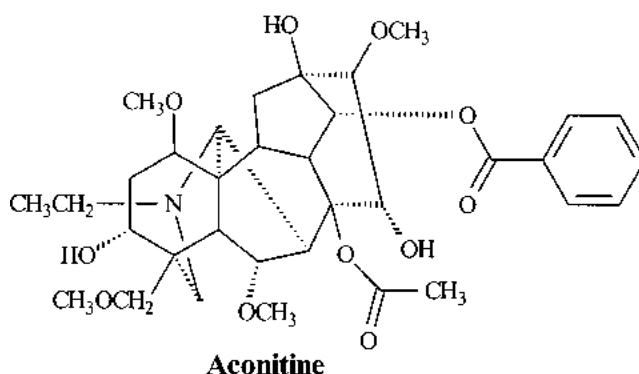


Fig. 1 Chemical structures of plant glycosides, including major component divisions

Fig. 2 Chemical structure of aconitine



C. D. purpurea contains the precursor purpurea glycoside A, which contains no acetyl groups, and enzymatic hydrolysis is sufficient to produce digoxin [12]. Because digitoxin is less polar than digoxin, it avidly binds to serum albumin, which results in a longer distribution phase than digoxin [12].

Oleandrin and thevetin A have a structure similar to digitoxin but with varying sugar residues attached at the number three carbon of the "A" ring on the steroid nucleus [18]. The genins for thevetin B and digitoxin are identical, with the only difference being that in thevetin B a thevetose and gentiobiose are conjugated to oxygen at the number three carbon [47]. Oleandrin and, to a lesser extent, oleandrogenin bind to albumin [48].

Latex from *C. manghas* contains cardenolides such as cerberin, neriifolin, and cerebroside.

Aconitine and Related Cardiotoxic Alkaloids

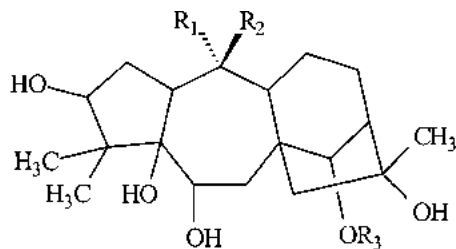
Compounds derived from *Aconitum* spp. (principally the tubers or root stock) are diterpenoid alkaloids (i.e., a nitrogenous base formed from some C₂₀-terpenoid precursors) (Fig. 2) [31]. The most toxic alkaloids are aconitine, mesaconitine, and 3-acetylaconitine. The presence of a benzoylester side chain at carbon 14 produces the arrhythmic effects attributed to these three alkaloids [31]. The alkaloids contained within the plant vary depending on the species and the geographic location, with some species being more toxic than others [49]. Raw tubers are "processed" by boiling or steaming *bushi* under high pressure in Japan and China to produce *kako-bushi*. This process reduces the toxicity of the parent alkaloids by producing less toxic pyro-type aconitine alkaloids [50].

Grayanotoxins

Grayanotoxins are diterpenoids with a perhydroazulene skeleton [51] found primarily in the leaves of shrubs in the heather family (e.g., rhododendrons, azaleas, and mountain-laurel). Grayanotoxins I, II, and III differ by virtue of (1) a hydroxyl group off carbon 10 in grayanotoxins I and III, which is a carbonyl in grayanotoxin II, and (2) a hydroxyl moiety at carbon 14 in grayanotoxins II and III, which is esterified to an acetyl in grayanotoxin I (Fig. 3). The content of grayanotoxin I in a fresh leaf from *Rhododendron ponticum* was estimated at 0.024% [52].

Veratrum Alkaloids

Veratrum alkaloids are steroid-like, polycyclic, nitrogen-containing structures [11]. Veratrine is a mixture of alkaloids, with veratridine being one of the major components. All *Veratrum* alkaloids are based on a steroid nucleus, with a fused two-ring, *N*-containing heterocycle added across the 13–17 bonds (Fig. 4). Protonation of this nitrogen makes these drugs primarily cationic at physiologic pH. The steroid 3-position oxygen exists as a hydroxyl, in weakly active cevine, esterified to veratric acid in moderately potent veratridine and to methyl-butenoic acid in the highly potent cevadine. The 6–7 hydroxyl groups on these molecules account for their (limited) aqueous solubility, whereas differences in potency result primarily from varied substituents at the 3-hydroxyl position.



Grayanotoxin I: R₁ = OH; R₂ = CH₃; R₃ = COCH₃

Grayanotoxin II: R₁R₂ = H₂C=; R₃ = H

Grayanotoxin III: R₁ = OH; R₂ = CH₃; R₃ = H

Fig. 3 Chemical structures of grayanotoxins

Pathophysiology

Plant Digitalis Glycosides

Digitalis compounds exert a positive inotropic effect on the heart and have arrhythmogenic activity. Cardioactive steroids are specific inhibitors of the membrane protein sodium pump (Na⁺,K⁺-ATPase) [53]. Na⁺,K⁺-ATPase effectively moves ions across membranes and maintains transmembrane Na⁺ and K⁺ gradients with energy generated from the hydrolysis of adenosine triphosphate (ATP). The enzyme is composed of three subunits (α, β, and γ), with the α subunit containing the Na⁺,K⁺, and ATP-binding sites and the binding site for cardiac glycosides [53]. Inhibition of the pump by cardiac glycosides reduces active Na⁺ efflux, resulting in increased intracellular [Na⁺] and effectively lowering the Na⁺ gradient-dependent driving force that powers plasmalemmal sodium-calcium exchange. The net effect is an increased intracellular calcium concentration, leading to an elevated amount of calcium released during cardiac systole and increased force development, the positive inotropic effect (Fig. 5). By a totally different mechanism, these cardiotoxic steroids are thought to modify the ion selectivity of the voltage-gated Na⁺ channel to a state of “promiscuous permeability” or “slip-mode conductance” (meaning calcium follows sodium), allowing the usually impermeant Ca²⁺ to enter cells through Na⁺ channels. This Ca²⁺ influx promotes Ca²⁺ release from the sarcoplasmic reticulum [54]. The steroidal alkaloid veratridine also increases the calcium conductance of voltage-gated Na⁺ channels, suggesting the possibility of a generalized action of steroid-containing drugs on this ion channel. The positive inotropic effect of cardiac glycosides results from the increases in intracellular calcium effected by both of these mechanisms since more calcium is now available for the myocardial contractile elements.

With toxicity, cardiac glycosides can cause many possible arrhythmias (see ► Chap. 38, “Digitalis Glycosides”). Junctional pacemakers can discharge at an increased rate, leading to nonparoxysmal atrio-ventricular junctional tachycardia [53]. Enhanced

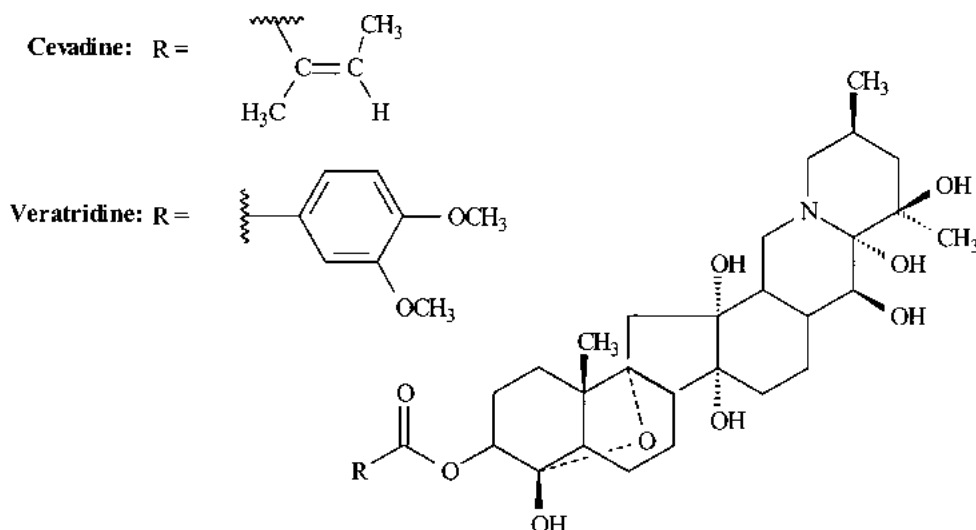


Fig. 4 Chemical structures of *Veratrum* alkaloids

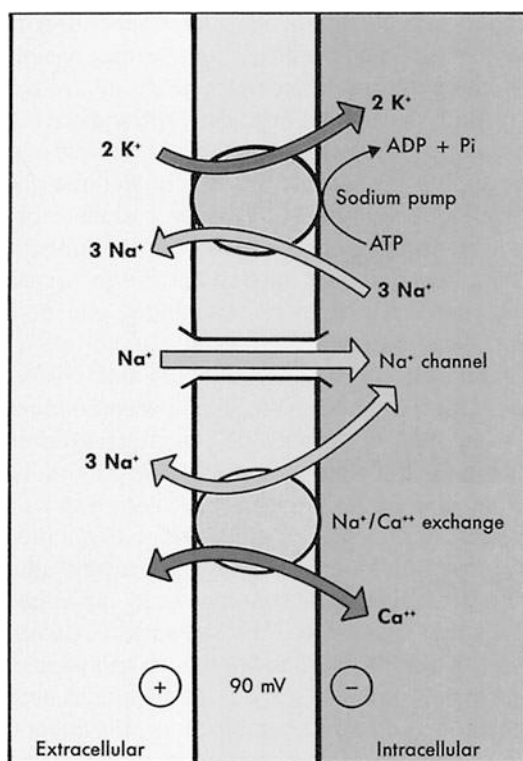


Fig. 5 Membrane ion flux of Na^+ and Ca^{2+} in the heart. Glycoside-induced inhibition of Na^+, K^+ -ATPase secondarily inhibits the Na^+ influx- Ca^{2+} efflux exchange reaction (From Ref. [96], p. 217)

automaticity and impaired conduction, such as an atrioventricular block with an accelerated junctional pacemaker, are consistent with digitalis toxicity. Sinus bradycardia, sinoatrial arrest, and heart block (second-degree or third-degree atrioventricular block) also are associated with toxicity. Oleandrin, the major cardiac glycoside found in oleander, also functions as a Na^+, K^+ -ATPase pump inhibitor and produces pathophysiologic changes similar to those of digoxin overdose (see ► Chap. 38, “Digitalis Glycosides”). As with digitalis, severe poisoning produces conduction defects in the sinus node (sinus bradycardia, sinus arrest, or exit block), atrioventricular node (second-degree or third-degree heart block), or both. Higher serum cardiac glycoside levels correlate with involvement of both nodes [55]. There may be decreased atrioventricular conduction and bradycardia secondary to increased vagal tone resulting from increased carotid sinus baroreceptor firing in response to sodium/calcium influx and increased vagal outflow. Acute cardiac glycoside toxicity produces systemic hyperkalemia secondary to Na^+, K^+ -ATPase pump inhibition, with a shift of potassium extracellularly from all tissues in the body (e.g., release from skeletal muscle). Cardenolides from *Cerbera* species (cerberin,

neriifolin, and cerebroside) also cause cardiac dysrhythmias and hyperkalemia due to inhibition of the Na^+/K^+ ATPase [22].

Aconitine, Grayanotoxins, and Veratridine

Although digitalis and digitalis-like compounds primarily inhibit the Na^+/K^+ -ATPase pump, aconitine, grayanotoxins, and veratridine are “activator” agents that open sodium channels [56]. The cardiac conduction tissues and the autonomic nerves innervating the heart are affected by these activators; both actions contribute to the clinical presentation. Aconitine and veratridine bind within the transmembrane region, known as *neurotoxin receptor site 2* [57]. This binding produces persistent activation of the voltage-gated Na^+ channel (Fig. 6) at the resting membrane potential and concomitant inhibition of channel inactivation. A persistent Na^+ permeability, a relatively constant inward current, and depolarization of the excitable cardiac membrane result. Persistent channel opening also produces prolonged phase 3 depolarization in cardiac

myocytes, inducing afterpotentials with generated automaticity.

Similarly, grayanotoxin I and α -dihydrograyanotoxin and *Veratrum* alkaloids (veratrine with a steroidal skeleton, jervine, veratramine, or those with a cevanine skeleton, protoveratrine A, protoveratrine B, veratridine) increase the resting sodium permeability by holding transmembrane sodium channels open at rest [51]. As a result of this permeability increase, the resting membrane depolarizes, resulting in spontaneous action potentials that produce neurotransmitter release and cardiac dysrhythmias. This persistent, toxin-modified sodium permeability, if present in cardiac membranes, results in prolonged atrial and ventricular action potentials, often followed by oscillatory afterpotentials [58]. If enough of the sodium channels are bound by toxin, the resulting depolarization is so large that the remaining toxin-free channels become inactivated, and the membrane becomes refractory, preventing further conduction.

Specific diterpenoid alkaloids from *Aconitum* and *Delphinium* spp. most likely cause hypotension and bradycardia through activation of autonomic reflexes [59]. This activation produces an end result at the level of the carotid sinus similar to

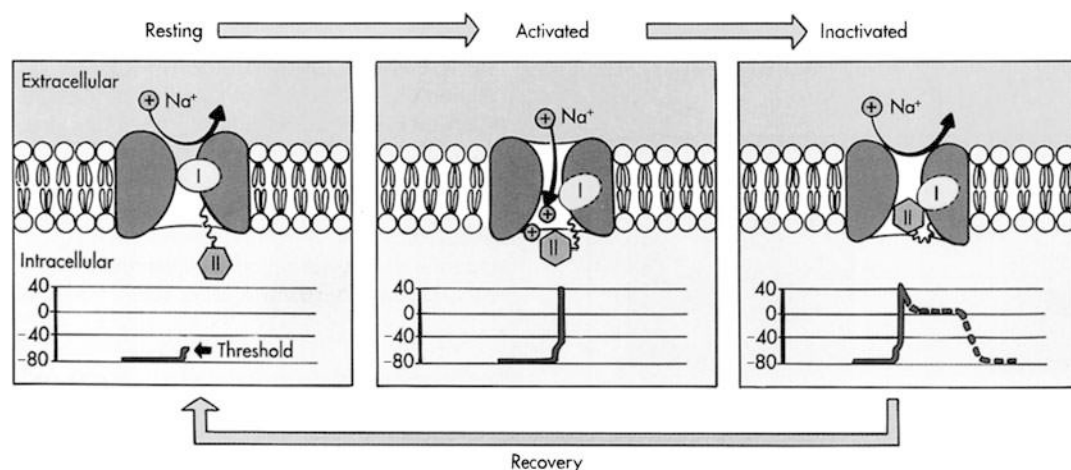


Fig. 6 Postulated conformational arrangements of cardiac Na^+ channels compatible with the concept of resting, activated, and inactivated states. Transitions between resting, activated, and inactivated states depend on membrane

potential and time. Aconitine, veratridine, and related toxins maintain the channel in the activated state. Potentials for each state are shown under each channel schema as a function of time (From Ref. [96], p. 198)

that of digoxin: reflex stimulation of vagal tone manifested chiefly as decreased heart rate and atrioventricular block. *Veratrum* intoxication also produces vagal reflex hypotension and bradycardia through a similar mechanism, most likely secondary to withdrawal of peripheral α -adrenergic tone [60]. Neuronal responses to systemic activator alkaloids include a range of positive and negative symptoms as nerves that are “weakly affected” show spontaneous repetitive firing and exaggerated transmitter release, whereas “strongly affected” nerves show depolarizing block. Perioral innervation manifests both effects, with paresthesia (positive) and numbness (negative) occurring simultaneously in the lips and tongue. Aconitine also is thought to have other ion (e.g., K^+) channel effects that produce a prolonged QT interval and possibly torsade de pointes [36].

Clinical Presentation and Life-Threatening Complications

Plant Cardiac Glycosides

Manifestations of oleander poisoning are the same as those of digitalis glycosides poisoning (see ► Chap. 38, “Digitalis Glycosides”), although differences in bioavailability of the plant-derived glycosides make the clinical course less predictable. Early after an overdose, oleander poisoning causes nausea, vomiting, decreased appetite, and diarrhea, as well as weakness and dehydration. Patients may have changes in consciousness, with lethargy progressing to confusion and coma. Seizures also have been described after oleander ingestion [61]. Visual disturbances and yellow-green vision may occur [20, 62].

Cardiac dysrhythmias and conduction disturbances may supervene at any time; bradydysrhythmias and tachydysrhythmias may be seen [5, 61, 63]. Bradycardia may be more common; in one review of 170 cases of yellow oleander poisoning, atrioventricular block was seen in 52.4% of patients, and bradycardia was seen in 49.5% [64]. Atrioventricular block or complete dissociation may produce complex junctional or reentrant dysrhythmias [62, 63, 65], which may

degenerate into life-threatening ventricular tachycardia or fibrillation or sudden cardiac arrest [20]. Electrolyte disturbances, related to paralysis of the cellular Na^+, K^+ -ATPase pump, are manifest as hyperkalemia with peaked T waves on electrocardiogram (Fig. 7).

Aconitine and Related Cardioactive Plant Alkaloids

Aconite is one of the most potent plant-derived toxins known, with severe poisoning caused by 5 mL of the tincture, 0.2 mg of aconitine, or 1 g of the cured plant [66]. Aconitine has systemic toxicity, with gastrointestinal disturbances present within hours after poisoning, including the early onset of nausea, hypersalivation, and vomiting. Neurotoxicity may include numbness, ataxia, dysarthria, perioral paresthesias, weakness of the extremities, and deteriorating consciousness leading to seizures and coma [34].

Characteristic bradydysrhythmias and hypotension support the diagnosis. Ventricular ectopy can be life-threatening, with ventricular tachycardia or fibrillation or both preceding asystole. Cardiac conduction disturbances include QRS widening, a prolonged QT interval, and bundle branch block. Toxicity progresses rapidly, with life-threatening cardiotoxicity evident often within 2 h of the ingestion. Death results from direct myocardial depression and cardiovascular collapse or from a malignant dysrhythmia [34, 35].

Metabolic disturbances, such as metabolic acidosis, hypokalemia, and hyperglycemia, are sometimes seen [35]. In addition, serum creatine kinase may also be elevated [35].

Grayanotoxins

Grayanotoxins cause dose-dependent manifestations that are similar to the manifestations associated with poisoning by *Veratrum* alkaloids. Grayanotoxin poisoning from mad honey ingestion has been associated with sudden onset of vomiting, chest pain, nonspecific ST elevation, and bradycardia, mimicking an acute myocardial

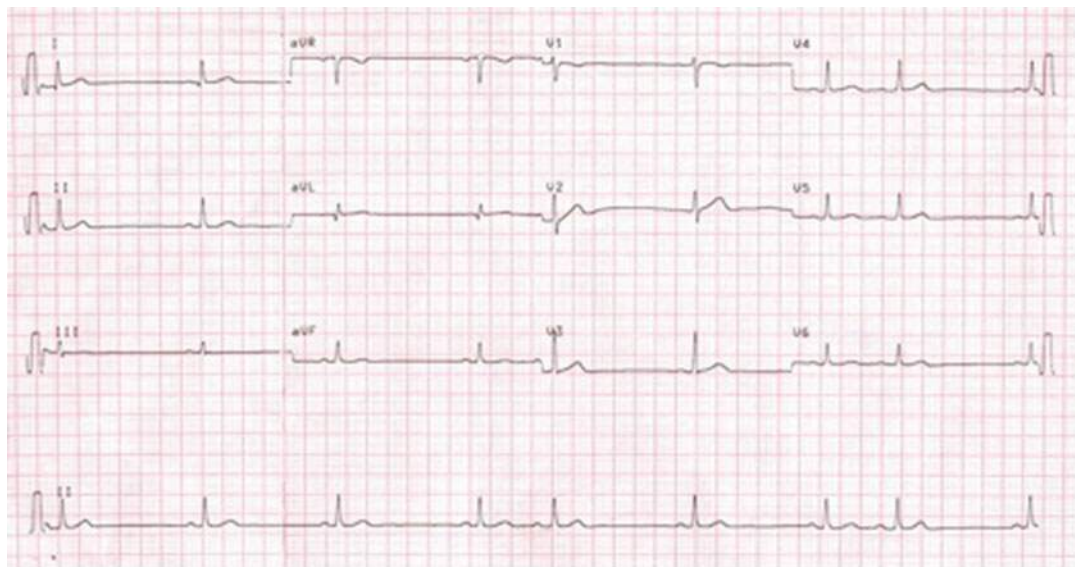


Fig. 7 ECG tracing in an adult woman who ingested yellow oleander and suffered AV conduction abnormalities and dropped beats typical of digitalis-related compounds (Courtesy of Dr. Raja Selvaraj)

infarction [67]. In one report of 23 victims of grayanotoxin-contaminated honey in Turkey, the most common clinical effects included hypotension, bradycardia, nausea, and vomiting. Sweating, faintness, weakness, dizziness, chills, exhaustion, impaired consciousness, and blurred vision also were common [68]. Victims of massive overdoses may develop seizures, severe cardiac conduction delays, and life-threatening ventricular ectopy [38]. Complete (third-degree) atrioventricular block has been documented in a case of mad honey intoxication [69]. In another case, atrial fibrillation with slow ventricular response was observed [70]. Grayanotoxins are rapidly metabolized and excreted [71]. Patients who are supported through the severe gastrointestinal and cardiovascular toxicity usually survive and become symptom-free 1–5 days later [8, 69, 70].

sweating, dilated pupils, blurred vision, respiratory depression, light-headedness, headache, and syncope are reported commonly by victims [41]. Myalgias, weakness, muscle spasms, paresthesias, and myoclonus have been reported [42]. Cardiovascular effects include hypertension or hypotension, bradycardia, and sinoatrial or atrioventricular blocks. Ventricular dysrhythmias may occur with massive overdoses [41, 42]. In one case series of four patients, who mistook white hellebore for wild garlic while foraging, symptoms included nausea and vomiting, confusion and dizziness, hypotension, and bradycardia; one patient had inverted T waves and transient blindness. All survived, becoming symptom-free within 24 h [72].

Diagnosis

Laboratory Detection of Plant Toxins

Veratrum Alkaloids

Poisoning by the glycoalkaloids from ingestion of hellebore causes symptoms within 30–60 min of the exposure. Nausea and repeated vomiting with intense abdominal pain and sometimes diarrhea herald the onset of toxicity. Paresthesias, salivation,

Detection of cardiac glycosides from plants is viable with existing analytical methodologies. Clinical laboratories capable of performing immunoassay procedures can detect digitalis compounds because they cross-react with assays used for therapeutic drug monitoring. Detection of

oleandrin in serum using digoxin immunoassays has been reported using various technologies FPIA (fluorescence polarization immunoassay), MEIA (microparticle enzyme immunoassay), and two turbidometric immunoassays. However, a chemiluminescent assay (Bayer Diagnostics, now a part of Siemens Diagnostics) showed no cross-reactivity [73–76]. While FPIA methodologies showed the highest cross-reactivity with oleandrin, Abbott Laboratories have discontinued the assays. Alternative assays are available, and, for example, the Dimension Vista digoxin assay (Flex Reagent Cartridge, Siemens Diagnostics, Deerfield, IL) can detect oleandrin comparable to FPIA assays. EMIT assays are also capable of detecting oleandrin [77]. However, since immunoassay methodologies vary in their ability to detect cardiac glycosides, they should be used for a qualitative assessment of exposure rather than for quantitative purposes.

Squill ingestion has produced apparent serum “digoxin” levels of 1.59 ng/mL by enzyme immunoassay [26]. Similarly, convallatoxin from lily of the valley has been identified through digoxin immunoassays that cross-react. Cross-reactivity was tested using several assays and analyzers: two different chemiluminescent assays, one on the Siemens Immulite 2000 analyzer and one using a microparticle immunoassay on the ci8200 Abbott Architect analyzer; an Elecsys electrochemiluminescence immunoassay on a Roche Cobas e601 analyzer; a latex agglutination assay on the Roche Cobas c501 analyzer; and MEIA on the Abbott AxSYM analyzer [78]. Cross-reactivity was variable, but the Abbott Architect showed the highest sensitivity for detecting convallatoxin.

However, specific identification of cardiac glycosides, such as digoxin, digitoxin, deslanoside, digoxigenin, and digitoxigenin, may require sophisticated applications, such as high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS) [79] or HPLC-ion-spray-mass spectrometry [80]. Similarly, oleandrin has been assayed in cases of oleander poisoning using HPLC [81] or HPLC-MS with serum concentrations of 1.1 ng/mL [82]. For medico-legal investigations, detection of oleandrin

should be confirmed by tandem mass spectrometry or other more sophisticated methodologies such as liquid chromatography-three-dimensional quadrupole mass spectrometry equipped with sonic-spray ionization [83]. Specimens are also stable in serum-separated tubes and therefore can be sent to reference laboratories for further analysis without concern for a decline in toxin concentration [84]. Chromatographic methods have been used to detect grayanotoxins (andromedotoxins) in material obtained from the rumen contents of poisoned sheep and goats [52] and in honey responsible for poisoning humans [8]. There is interest in developing a quantitative grayanotoxin assay that can correlate blood or urine concentrations with the clinical severity of “mad honey poisoning” [85]. Similarly, thin-layer chromatography and ionization spectrometry have been used to detect *Veratrum* alkaloids in wine produced from *V. album* [43]. Detection of aconitine in the blood, serum, and plasma is most helpful if poisoning is suspected. Applications using various chromatographic techniques, particularly liquid chromatography, in conjunction with mass spectrometry, have been used [86, 87]. Although these methods may confirm the presence of one of these toxins, they are unavailable in most clinical laboratories.

Treatment

Resuscitation and Supportive Care

Patients with life-threatening poisoning from plant cardiotoxins may require advanced cardiac life support. The initial approach should be carried out according to current algorithms established for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) by the American Heart Association [88].

Decontamination

If the patient presents to medical care having ingested a cardiotoxic plant, he or she might benefit from gastrointestinal decontamination with activated charcoal in an attempt to reduce

absorption of cardiotoxins. Activated charcoal is the preferred agent because it should effectively adsorb cardiac glycosides, aconitine, veratrine, and other active toxicants while they are still in the stomach. Studies have confirmed the ability of charcoal to bind oleandrin [89–91]. However, the administration of activated charcoal has not been documented to be of benefit in these patients [90]. Also giving charcoal by mouth to a drowsy patient with an unprotected airway risks pulmonary aspiration, which can be a life-threatening complication. The ► [Chap. 14, “The Assessment and Management of Hypotension and Shock in the Poisoned Patient”](#) provides greater detail on the administration of activated charcoal. Multiple-dose activated charcoal was found to be safe and of some benefit in one randomized controlled trial in the treatment of patients suffering yellow oleander poisoning (level of evidence [LoE] I) [92].

Indications for ICU Admission in Plant-Derived Cardiac Glycoside Poisoning

History of massive overdose and early onset of clinical effects
 History of overdose and unusually susceptible patient (e.g., extremes of age, underlying congenital or acquired cardiac disease)
 Life-threatening cardiac rhythm disturbances (or potentially life-threatening with evidence of progression)
 Life-threatening cardiac conduction disturbances or asystole
 Life-threatening hemodynamic instability
 Severe metabolic disturbances (e.g., hyperkalemia)
 Progressive deterioration in level of consciousness
 Seizures or coma

Extracorporeal Removal Techniques

Patients are unlikely to derive any benefit from hemodialysis in cardiotoxic plant poisoning, given the large molecular size of these alkaloids

and other natural compounds. The value of hemoperfusion has not been established.

Specific Treatments

Cardioversion or transcutaneous cardiac pacing may be lifesaving for patients with cardiac toxicity from plants (LoE III). In the series by Eddleston and associates of 66 patients with yellow oleander poisoning, six patients (10%) required a temporary pacemaker [65].

Antidysrhythmic agents have been suggested for malignant arrhythmias associated with aconite poisoning but with mixed success [5]. Successful management of hyperkalemia also may resolve cardiac conduction disturbances (LoE III).

Vasopressors, such as norepinephrine, may be needed in addition to intravenous fluids to treat refractory hypotension. Standard anticonvulsants, such as benzodiazepines, are a rational choice of treatment for aconite-associated seizures.

Antidotes

Digoxin Fab-specific antibodies have been used successfully to treat patients with significant poisoning by oleander or other cardiac glycoside-containing plants (LoE I) [65, 93, 94]. In a randomized controlled trial, Eddleston and associates [65] showed that Fab fragments resolved dysrhythmias and bradycardia after yellow oleander poisoning rapidly, often within 2 h of administration. These authors note that the relatively short half-life of Fab fragments (16 h) and continued absorption of cardiac glycosides from ingested oleander seeds may account for recrudescence symptoms. The lower affinity of Fab fragments for oleandrin and other natural toxicants than for digoxin may account for recurrent dysrhythmias seen in some patients. In Eddleston’s series, recrudescence of oleander-related bradycardia was noted in three patients 48 h after the initial administration of Fab antibodies [65]. In the context of oleander poisoning, an empirical dose of 800 mg

Table 2 Indications for digoxin immune FAB in plant-derived cardiac glycoside poisoning

For the treatment of life-threatening complications of history-confirmed oleander, foxglove, or other plant-derived cardiac glycoside poisoning:
Severe ventricular arrhythmias (e.g., ventricular tachycardia or fibrillation)
Progressive bradyarrhythmias (e.g., severe sinus bradycardia or second-degree or third-degree heart block not responsive to atropine)
Potassium concentrations >5 mEq/L in the context of severe poisoning

Note: Each vial of Digibind contains 38 mg of digoxin-specific Fab fragments, which bind approximately 0.5 mg of digoxin or digitoxin. Plant-derived cardiac glycosides have lower binding affinities for the Fab, however. Patients poisoned by plant-derived cardiac glycosides may require a substantially increased dose of the antidote over that conventionally used in the treatment of digitalis poisoning, and they may require repeated administration in patients with normal renal function

of Fab fragments may be given as a starting dose. This is a larger dose than is typically used in the initial treatment of pharmaceutical digoxin poisoning and is recommended because of the lower binding affinity of the antibody to the natural cardiac glycosides. Suggested indications for the administration of digoxin immune Fab are listed in Table 2. Although this has not been formally studied, we suggest that the pediatric dose should be similar to that for adults, with appropriate adjustment of total fluid volume.

Of note, a newer digoxin immune Fab, a digoxin-specific antibody (Protherics Inc, Brentwood, Tennessee) approved by the US Food and Drug Administration in 2001, has also been studied for the treatment of chronically digoxin-poisoned patients and appears to be safe and effective [95].

Criteria for ICU Discharge in Plant-Derived Cardiac Glycoside Poisoning
With coma, seizures, or gastrointestinal upset: normalization of consciousness, resolution of gastrointestinal symptoms, and no

evidence of progressive cardiac disturbances after at least 24 h of monitoring
After administration of the antidote: stable heart rate and rhythm for at least an additional 48 h of continuous cardiac monitoring with no evidence of recrudescent cardiac toxicity
After administration of the antidote: resolution of hyperkalemia and associated electrocardiogram findings and on monitoring for at least an additional 48 h, no evidence of rebound hypokalemia or recrudescent hyperkalemia

Special Populations

Pediatric Patients

Because of their smaller size and lower weight, children receive larger weight-based doses of the toxins when they ingest poisonous plants. Because most of the life-threatening clinical effects associated with aconite, *Veratrum* alkaloids, grayanotoxins, and cardiac glycosides are dose dependent, children are theoretically a more vulnerable group. In addition to their smaller size, the oral behaviors, natural curiosity, and developmental immaturity of toddlers place them at a higher risk for inadvertent poisoning by plants.

Elderly Patients

The relative instability of the cardiovascular system of some elderly patients and their diminished capacity to detoxify and eliminate toxins place them at high risk for toxic effects from plants. The elderly already may be on cardiac medications and have underlying cardiac disease, which may compound the adverse effects of poisoning from plant cardiotoxins.

Other Special Populations

Immigrant populations and others who practice herbal medicine constitute a group at higher risk for inadvertent poisoning by cardiotoxic plants.

Key Points in Plant-Derived Cardiac Glycoside Poisoning

1. Cardiotoxic plant poisoning can occur in plant foraging individuals who make mistakes, suicidal patients, those experimenting with herbal tea or alternative therapies, or children.
2. Plant-derived alkaloid toxins may or may not be detected by conventional laboratory assays. Management of symptomatic patients with a history of poisoning should not be delayed.
3. Digoxin Fab antibody administration may be helpful in the management of patients with significant oleander or foxglove poisoning.
4. Multiple and varying cardiac rhythms, with conduction disturbances, ventricular excitability, and ST segment depression, and poor response to atropine and other initial management measures are poor prognostic signs.

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Poison hemlock (*Conium maculatum*) is regarded as one of the most poisonous plants worldwide. This plant is a member of the family of Apiaceae (Umbelliferae). The term *Umbelliferae* originates from *umbellula*, which means “little shade,” referring to the parasol-shaped clusters of flowers. Other members of this family include celery (*Apium graveolens*), lovage (*Levisticum officianale*), angelica (*Angelica archangelica*), carrots (*Daucus carota*), and parsnip (*Pastinaca sativa*). Poison hemlock has been misidentified as the aforementioned edible species and consumed, leading to toxic exposure [1]. However, this misidentification occurs infrequently because of the plant’s “mousy” odor, bitter taste, and burning in the mouth after ingestion.

Poison hemlock was the official poison of ancient Greece and was used by executioners during this period [2]. It typically was mixed into a concoction containing conium juice, opium, and other alkaloids. This type of extract is believed to have been administered to Socrates in 399 BC, when he was condemned to death. The ability of the hemlock to induce a motor paralysis was elegantly documented by Socrates’ student Plato, who was at his bedside during his death: “The man who administered the poison kept his hand upon Socrates, and after a little while examined his feet and legs; then pinched his foot hard and asked if he felt it. Socrates said no. Then he did the same to his legs; and moving gradually upwards in this way let us see that he was getting cold and numb [3].”

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Fig. 1 Poison hemlock (*Conium maculatum*). (From Graeme KA, Braitberg G, Kunkel DB, et al: Toxic plant ingestions. In Auerbach PS [ed]: Wilderness Medicine, 4th ed. Philadelphia, Mosby, 2001, p 1114, with permission.)

Poison hemlock typically grows to a height of about 2 m. The stem is large and hollow and contains purple spots that are considered an identifying characteristic – hence one of its common names, *spotted hemlock* [1]. Its foliage and leaves are three times divided (tripinnate), similar to a fern (Fig. 1). Poison hemlock develops white flowers that are organized into a flowering head in which the pedicles, individual flower stems, all spring from one point; this is called an *umbel*. Its long, solid white taproot also is characteristic of this species. Poison hemlock can grow anywhere adequate moisture is supplied; it is often found in pastures and meadows and alongside streets and streams. Hemlock can be found throughout the world, although most ingestions occur in North and South America, Europe, western Asia, and Australia. *C. maculatum* is native to Europe and Asia and was introduced to America as an ornamental plant [4]. Poison hemlock growing in the southern climates is thought to be more poisonous than that in temperate regions. Ancient Greeks considered the poison hemlock growing in Macedonia to be the most toxic substance [5].

Toxicity can follow ingestion of any part of the plant, including leaves, stems, roots, flowers, or seeds. Severe toxicity has occurred in children, when the stems were used as whistles [6]. Toxicity is reduced, but not eliminated, when the plant is dried [4]. Toxicity in humans has occurred after consumption of small birds (skylarks, chaffinches, robins) that recently ingested hemlock

buds [7]. Powdered *C. maculatum* has also been reported for sale on the internet [8]. Overall, most exposures are unintentional and dose limited and exposures are more frequent in children.

The active alkaloids in poison hemlock are physiologically and structurally related to nicotine. The syndrome caused is the result of direct effects on nicotinic receptors. Other plants, such as those of the genus *Nicotiana* (which includes tobacco plants), act in a similar fashion.

Poison hemlock has many common names throughout the world, such as *cicuta* (Argentina, Colombia, Chile), *hemlock* (England), *grande cique* (France), *giftjeks* (Norway), *odort* (Sweden), *wild carrot* (Australia), *cigue maculee* (Canada), and *doku-ninjin* (Japan) [8, 9]. Poison hemlock should be distinguished from water hemlock (*Cicuta maculata*).

Biochemistry

The biologic activity of the plant originates from the simple alkaloids found within poison hemlock. Hemlock, similar to other alkaloid containing plants, is bitter tasting. Ten piperidine alkaloids have been identified from *C. maculatum*: λ -coniceine, coniine, *N*-methyl coniine, conhydrine, pseudoconhydrine, conhydrinone, *N*-methyl pseudoconhydrine, 2-methylpiperidine, 2-n-pentyl-3,4,5,6-tetra-hydropyridine, and 5-hydroxy-2-n-pentyl-piperidine [4, 10]. The two principal toxins, λ -coniceine and coniine, are thought to be responsible for both the acute and chronic clinical manifestations of poison hemlock intoxication. These are the two alkaloids found in greatest proportion within the plant and are the focus of the following discussion (Fig. 2) [4]. They are synthesized combining eight two-carbon-acetate units. Reduced nicotinamide-adenine dinucleotide phosphate-dependent λ -coniceine reductase catalyzes the synthesis of coniine [11]. This is a reversible reaction, allowing for the interconversion between the two alkaloids [12]. These substances are structurally similar to nicotine (see Fig. 2), a pyrrolidine alkaloid, and stereospecifically bind to cholinergic ligand-gated sodium channels at nicotinic sites. Similar to nicotine,

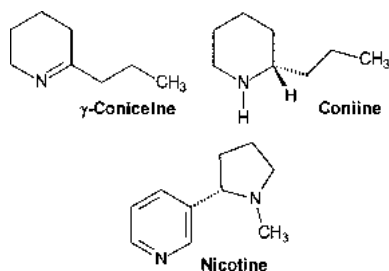


Fig. 2 Chemical structures of major alkaloids in poison hemlock. The chemical structure of nicotine is shown for comparison

coniine and related alkaloids have an initial excitatory effect followed by a depressant effect on the central nervous system.

Additionally, twenty-four different steroids have been recently identified in *C. maculatum*. The clinical implications of these compounds have yet to be determined [13].

Coniine and λ -coniceine are present in the plant at varying concentrations and proportions depending on the season, nutrients available, and amount of rainfall. During dry, sunny seasons, the average fruit size and toxin amount increases. During rainy seasons, the λ -coniceine alkaloid predominates [14]. The relative concentrations of these two alkaloids also change as the plant matures [12]. λ -Coniceine is the predominant alkaloid in the leafy parts of poison hemlock and in the early stages of development from flower to fruit [12]. The overall change in λ -coniceine to coniine is associated with rapid growth of the fruit. The peak in λ -coniceine concentration precedes the peak of coniine concentration. As the fruit approaches the final stage of maturation, the coniine content declines, and there is another slight increase in the λ -coniceine concentration [12]. The percentage of total alkaloid weight compared with plant weight varies from 0.009% in dry stems to 0.750% in dry seeds harvested in the midwinter. Fresh secondary growth material is midway between, at 0.075% [15]. Determination of the median lethal dose based on ingested plant weight will vary depending on the season, part of plant ingested, and degree of plant maturation.

Conhydrine, similar to λ -coniceine, is an oxidation product of coniine [14]. Conhydrine

concentrations peak at approximately the same time as λ -coniceine, which is during the rainy season. *N*-methyl coniine, another minor alkaloid, concentrations increase when coniine is at its peak. It is not clear how coniine is converted to *N*-methyl coniine. However, coniine and *N*-methyl coniine predominate in mature seeds [12].

Pathophysiology

Pharmacokinetics of Poison Hemlock

Volume of distribution: 1 L/kg

Protein binding: <5%

Mechanism of clearance: excretion in the kidneys and lungs; metabolized in the liver

Active metabolites: none known

The physiologic effects of coniine are complex and dose dependent. Most toxicity occurs when coniine and related alkaloids enhance the nicotinic actions of acetylcholine by depolarizing voltage-gated nicotinic acetylcholine receptors in the central nervous system, at neuromuscular junctions, postganglionic autonomic nerves, and the adrenal medulla. Muscarinic effects of acetylcholine are typically unaffected. The N_M type nicotinic receptors are found at the skeletal neuromuscular junction, and the N_N variety is found at nerve terminals (Fig. 3). The alkaloids' agonist properties on nicotinic receptors are the predominant mechanism responsible for the clinical effects. Receptor stimulation results in sodium channel influx, leading to membrane depolarization and action potential propagation. Although the effect on the nicotinic receptor-controlled structures is initially stimulatory, it is followed shortly thereafter by depressant, curare-like, antagonistic effects [2]. The resulting effects have been referred to as the *nicotinic syndrome* (Table 1).

The most striking effects of these alkaloids are observed in spinal reflexes. Convulsive activity, induced by local application of coniine to the spinal cords of frogs, was thought to be the result of direct agonist action on the motor neurons

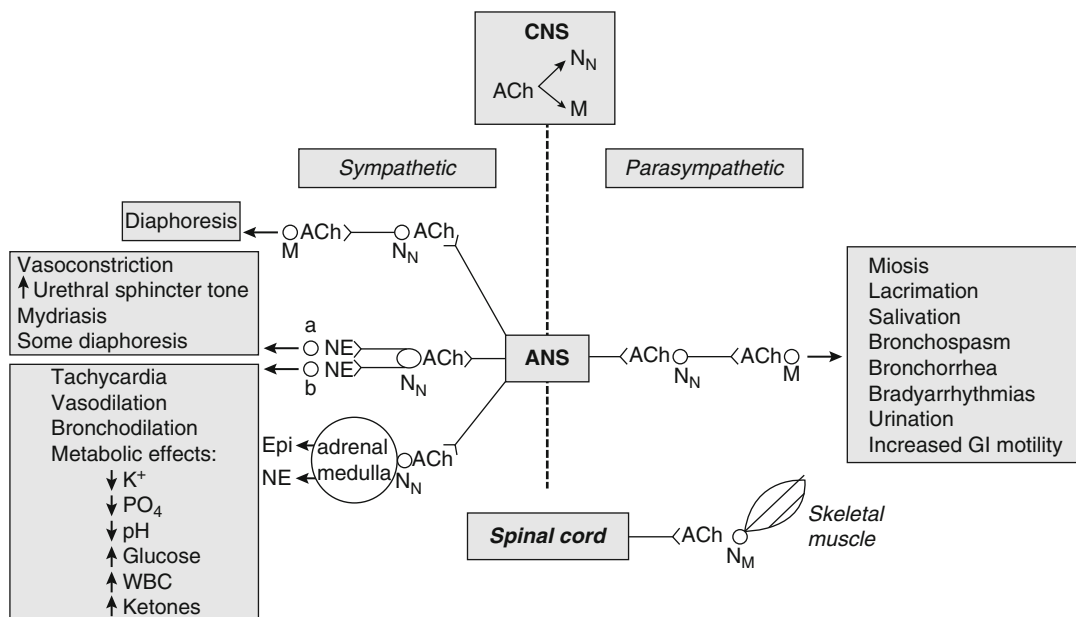


Fig. 3 Nicotinic and muscarinic receptors of the central nervous system (CNS), autonomic nervous system (ANS), and peripheral skeletal muscles. Direct nicotinic agonists (e.g., arecoline, coniine, cytisine, lobeline, nicotine) stimulate nicotinic receptors; however, prolonged depolarization at the receptor causes eventual blockade of nicotinic receptors. ACh, acetylcholine; Epi, epinephrine; GI,

gastrointestinal; M, muscarinic receptor; N_M, nicotinic receptor at skeletal muscle; N_N, nicotinic receptor in nervous system; NE, norepinephrine; WBC, white blood cell count (From Graeme KA, Braitberg G, Kunkel DB, et al: Toxic plant ingestions. In Auerbach PS [ed]: Wilderness Medicine, 4th ed. Philadelphia, Mosby, 2001, p 111, with permission.)

Table 1 Nicotinic syndrome

Early stage	Late stage
Hypertension	Hypotension
Tachycardia	Bradycardia
Vomiting	Paralysis
Diarrhea	Coma
Muscle fasciculations	
Convulsions	

From Graem KA, Braitberg G, Kunkel DB, et al.: Toxic plant ingestions. In Auerbach PS (ed): Wilderness Medicine, 4th ed. Philadelphia, Mosby, 2001, p 1114 with permission

within the cord [16]. Based on these kinds of initial experiments, it was previously believed that the main action of coniine was strychniniform (i.e., causing convulsive activity of spinal origin) [2]. However, experiments with intact animals have shown that hemlock alkaloids and strychnine have predominantly antagonistic properties [16]. The paralyzing effect of hemlock alkaloids

is the result of the ascending neuromuscular blockade, similar to that of curare [2].

Reportedly the toxic dose in humans is approximately 60 mg of coniine, and the fatal dose is approximately 150–300 mg [17]. Ingestion of a 1 in. sq. piece of hemlock has been reported to be lethal in a child [3]. However, reports of toxic and lethal dosages are inherently prone to error.

Clinical Presentation and Life-Threatening Complications

The clinical effects after poison hemlock ingestion are biphasic. There is an initial stimulatory phase, followed by a more pronounced state of skeletal motor depression, associated with muscle weakness, paralysis, and respiratory arrest (see Table 1).

There is usually a short latent period between ingestion and onset of clinical manifestations. The first symptoms to occur are typically direct gastrointestinal irritation of the mucosa of the oropharynx, esophagus, and stomach. Gastrointestinal irritation is followed in approximately 30 min by profuse salivation, nausea, and vomiting [18], manifestations of initial cholinergic nicotinic stimulation. These episodes of emesis theoretically help to limit further exposure and toxicity.

Cardiovascular effects are typically minor. Large doses of coniine, λ -coniceine, and *N*-methyl coniine in isolated animal heart preparations cause decreased inotropy [16]. However, these effects are not seen in intact animals. In the late stages of significant poison hemlock ingestion, bradycardia, hypotension, and shock may occur.

Fasciculations of skeletal muscle and tonic-clonic contractions of separate limbs are characteristic during the initial excitatory phase. These skeletal motor effects are mediated by spinal cord and neuromuscular junction stimulation and may lead to rhabdomyolysis [2, 7]. In several cases with rhabdomyolysis, this was associated with myoglobinuria and renal failure; all these cases were due to secondary poisoning following consumption of birds that had eaten hemlock and, where tested, had high coniine levels [7].

The excitatory phase is followed by ascending muscular weakness and paralysis, with painful hypotonic skeletal muscles [7]. Affected individuals are often lethargic, and muscle weakness may lead to respiratory arrest requiring mechanical ventilation. Respiratory failure can be prolonged, lasting up to two weeks or in less-severe cases may recover completely in as little as 24 h [19, 20]. Death is usually secondary to progressive paralysis and respiratory arrest. Severe toxicity treated with ventilatory support and supportive care has led to recovery without sequelae [3].

Diagnosis

Poisoning by poison hemlock should be a diagnostic consideration in any patient with nicotinic signs and symptoms (see prior section) or

ascending paralysis after ingestion of “plant material.” No specific diagnostic tests are routinely available.

Signs of rhabdomyolysis (myoglobinuria and serum creatine phosphokinase elevations) are often present [21]. Transient elevations in liver enzymes often occur, but typically resolve as the patient recovers [21].

Alkaloids from poison hemlock are excreted by the lungs and kidneys, giving the breath and urine of poisoned animals a “mousy” odor characteristic of the plant. Analysis for coniine can be performed on urine or serum samples. The most commonly useful method for diagnostic confirmation is obtaining a portion of the plant that has been ingested. Analysis of the plant specimen by gas chromatography–mass spectrometry for the presence of the piperidine alkaloids confirms the diagnosis. Variable results have been demonstrated with mass spectrometry utilizing patient urine, blood, and serum [1, 19, 22, 23]. Analysis of cerebrospinal fluid has also been suggested [19]. In cases in which poisoning has occurred after ingestion of toxic bird flesh, coniine has been isolated from the animal specimens [7].

Treatment

There is no specific antidote for poison hemlock. Supportive care is the mainstay of treatment. If the patient presents early after ingestion, gastrointestinal decontamination with orogastric lavage may be considered because of the potency of these toxins (Level III evidence). Some clinical toxicologists recommend a dose of activated charcoal in the hope that it may decrease toxin absorption if it can be administered within 1 h of ingestion, although there are no data showing that this, or lavage, alters the clinical course or outcome. Mechanical ventilation may be required for patients who are severely poisoned. In one case series of 11 hemlock-poisoned patients, three required ventilatory support, and all three subsequently died [7]. The use of forced diuresis, hemoperfusion, and hemodialysis has been reported, but no clinical or experimental support is available for these techniques [7] (Level III).

Aggressive volume replacement with maintenance of brisk urine output is indicated in patients at risk for rhabdomyolysis. Vasopressor agents are required when there has been an inadequate response to volume resuscitation. Bradycardia can be treated per standard protocols. Based on the time frames for which toxicity would be expected, patients not exhibiting systemic signs or symptoms after 6 h of ingestion may be safely discharged home.

Indications for ICU Admission in Poison Hemlock Toxicity

Respiratory depression
Seizure-like activity
Change in mental status
Large ingestion
Pediatric patients with signs of ingestion

Special Populations

Animal studies suggest potential teratogenic effects associated with chronic exposure to poison hemlock. Observations in different animal species have found malformations predominantly of the limbs, including limb rotation; permanent flexure of the carpal or elbow joints, with or without scoliosis; and sometimes cleft palate and lip [15]. No human data are available regarding teratogenicity.

Common Misconceptions About Poison Hemlock

1. Poison hemlock is nontoxic.
2. Poison hemlock is the same as water hemlock (see ► [Chap. 115, “Water Hemlock”](#)).

Key Points in Poison Hemlock Toxicity

1. Ingestion of any part of the plant can lead to severe toxicity.
2. The main alkaloids are coniine and λ -coniceine.

3. Patients with overdoses present with nicotinic and curare-like symptoms.
4. No specific antidote is available.
5. Treatment is supportive without specific antidotes.
6. With survival, there are typically no long-term sequelae.
7. There are possible teratogenic effects.

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Toxalbumins are complex proteins found in certain plant species that are toxic when ingested, inhaled, or administered parenterally. The most common plants containing toxalbumins are *Ricinus communis*, *Abrus precatorius*, and *Robinia pseudoacacia*. Although *R. communis* and *A. precatorius* concentrate the toxin within their seeds, the toxic lectins of *R. pseudoacacia* are found in the bark, seeds, leaves, and roots of the plant. The toxalbumins are summarized in Table 1. The primary toxins in these plants are ricin, abrin, and robin. They are classified as ribosome-inactivating proteins (RIP) and will be described in further detail later in the chapter.

***Ricinus communis* (Castor Bean)**

R. communis is native to Mexico and Africa and is easily cultivated in throughout the United States for castor oil, use in cosmetics, industrial lubricants, and paints, as well as an ornamental plant; it also grows wild quite ubiquitously. These large, leafy plants can grow 10–12 ft and produce brown spiculated pods, each containing three hard, shiny, almond-shaped brown striped or spotted seeds (Fig. 1). The seed is composed of three components: castor oil, which contains ricinoleic acid; pulp, which is rich in glycoproteins; and a fibrous portion, which contains the highest concentration of the toxalbumin ricin, up to 5% by weight [3]. The seeds also contain a separate toxin, a red cell agglutinating protein [8–10].

The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of Centers for Disease Control and Prevention.

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Table 1 Toxalbumins

Scientific name	Common name	Toxin	Location of toxin	Geography	Clinical manifestations
<i>Abrus precatorius</i>	Crab's eye, jequirity bean, rosary pea	Abrin	Seeds	India, South America, Florida, Caribbean	GI, pulmonary, shock
<i>Ricinus communis</i>	Castor bean plant, mole bean	Ricin	Seeds	Mexico, Africa, Southern United States	GI, pulmonary, shock
<i>Robinia pseudoacacia</i>	Black locust	Robin, phasin	Bark, leaves, buds	United States, Canada, Mexico	GI, CNS
<i>Jatropha multifida</i>	Coral plant, physic nut	Ricin	Seeds, fruit	Mexico, Brazil, Central America, Florida	GI
<i>Jatropha curcas</i>	Barbados nut, curcas bean	Curcin	Seeds, fruit	India, Central America, South America	GI
<i>Hura crepitans</i>	Sandbox tree, monkey's dinner bell	Hurin	Bark juice, seeds	South America, Central America	GI, blindness

Adapted from Refs. [1–7]

CNS central nervous system, GI gastrointestinal



Fig. 1 *Ricinus communis* seeds (From New Leaf Graphics, Port St. Lucie, FL)

Stillmark, who found that the seed extract caused red blood cell agglutination, originally identified ricin in 1888. Ricin toxin gained notoriety in 1978, when a Bulgarian journalist for the British Broadcasting Company and political dissident, Georgi Markov, was stabbed in the thigh with the point of an umbrella at a bus stop near Waterloo Bridge. Days later he succumbed to multisystem organ failure and on autopsy, in Markov's leg, a small, perforated, metallic pellet was found that was presumed to contain ricin [11]. Also that year, a second Bulgarian émigré is said to have experienced a similar attack with a

similar pellet removed from his skin [12]. Ricin was also presumed to be involved in the second incident based on pellet's internal diameter and the clinical manifestations, but it was never confirmed due to limitations of laboratory testing at the time.

R. communis is grown in ornamental gardens and as a houseplant, but it is cultivated primarily for the production of castor oil, with more than one million tons of seeds harvested each year. Its seeds, as well as those of *Abrus precatorius*, are also incorporated into necklaces, rosaries, and other decorative items imported from South America and Africa. Many cases of ricin poisoning result from children unintentionally ingesting these colorful seeds [3, 6, 7, 13–15].

Castor seeds have been used for centuries in the treatment of various medical conditions. Some cultures have used this seed to treat leprosy and syphilis or as a cathartic. Modern medicine has experimented with ricin in pain control and in the prevention of graft-versus-host disease and as a cancer chemotherapeutic agent [8, 16–19].

Because ricin is one of the most potent poisons in the plant kingdom, it has been produced by governments for use in biologic weapons [12, 13, 20–25]. It has been tested since the 1940s by the United States, but in 1989, 10 L of concentrated weapons-grade, aerosolizable ricin was

made in Iraq for payload in artillery shells [13, 25]. Owing to this threat, the United States Army Medical Research Institute of Infectious Disease, congressional hearings, and government warnings have implicated ricin as a potential biologic warfare agent, and it is now designated as a select agent [26].

Abrus precatorius

A. precatorius is a green vine native to India, South America, Florida, and the Caribbean. This vine produces light purple or white flowers and 3 cm long pods each containing three to five oval, hard, glossy seeds approximately 5 mm in diameter. The seeds may be red with a black center, black with a white center, or white with a black center (Fig. 2). Abrus seeds, also called jequirity pea, Indian bean, crab's eye, rosary pea, and Buddhist's rosary, are used primarily in ornaments, jewelry, and other decor. The seed contains *N*-methyltryptophan, abric acid, and the toxin abrin [3, 6, 7]. Like ricin, *A. precatorius* seeds contain two types of toxins, abrin, a toxalbumin that is a RIP, and a heterotetrameric protein agglutinin, APA-1. The LD₅₀ for abrin by injection in humans is estimated to be approximately 20 mcg/kg and by inhalation is 3–4 mcg/kg. APA-1 has been studied in animals by intraperitoneal injection and has an estimated human LD₅₀ of 5 mg/kg.



Fig. 2 *Abrus precatorius* seeds (From New Leaf Graphics, Port St. Lucie, FL)

***Robinia pseudoacacia* (Black Locust Tree)**

R. pseudoacacia, commonly known as the black locust tree, grows to 30 m tall and 3 m in diameter and has deeply furrowed bark that is gray on the outside and creamy yellow on the inside. This tree is native to North American and found primarily in the United States, Appalachian and Ozark Mountains, as well as in areas of Canada, and Northern Mexico. The genus *Robinia* originally was named after Jean Robin, the herbalist to the kings of France during the sixteenth century who introduced this hardwood to Europe. Because of the strong bark, these trees are used primarily for furniture, mine timbers, boat ribs, fencing, and strip mine reclamation. The Cherokee Indians used this plant as a purgative, as a laxative, and for toothaches. The bark and roots contain five major flavonoids, including the toxalbumin robin [4, 7].

Biochemistry and Pharmacology

The toxalbumins ricin, abrin, and robin destroy cells by inactivating eukaryotic ribosomes. They are classified as RIPs or ribosome-inactivating proteins. Their structure, similar to those of botulinum, tetanus, diphtheria, and cholera toxins, consists of two subunits that, in the case of ricin and abrin, are joined by a disulfide bond. Ricin has a total weight of 60–66 kDa, depending on the isoform, and is divided into a B subunit and an A subunit [10, 27, 28]. The B subunit binds to glycoproteins on the surface of the cell, enabling the toxin to enter, then the A subunit, which is an *N*-glycosidase, removes single adenine residues on the 28S ribosomal RNA loop within the 60S subunit. This adenine depurination prevents polypeptide chain elongation, ultimately inhibits protein synthesis, and finally leads to cell death [8, 10, 18, 27, 29]. One molecule of ricin can deactivate up to 1,500 ribosomes/min ($K_{CAT} = 1,500 \text{ min}^{-1}$) [18].

Although apoptosis is one mechanism by which ricin causes its toxicity, there is evidence of direct necrosis from ricin by unknown mechanisms. Animal studies demonstrate concomitant systemic tissue injury from the resulting

Table 2 Comparative median lethal dose of toxins in laboratory mice

Toxin	Median lethal dose (μg/kg, IV)
Botulinum	0.001
Tetanus	0.002
Abrin	0.04
Ricin	5
Ricin (inhaled)	3–10
Sarin	100

Adapted from Refs. [13, 24]
IV intravenous

inflammatory cascade with activation of a myriad of pro-inflammatory cytokines including tumor-necrosis α , interleukin 1 β , IL-1, c-FOS, c-JUN, NF- κ B, and mitogen-activated protein kinase, among others [30–32]. The inflammatory response can lead to overproduction of oxidative species that can cause gaps in the endothelial tight junctions and poor membrane integrity. The subsequent migration of leukocytes to the site of injury can result in further tissue damage. This inflammatory process can also contribute to poor tissue repair mechanisms and excessive fibrosis in the survival phase, which, particularly if there was inhalational exposure, can subsequently lead to fibrosis and increased morbidity [32–34].

R. communis has two toxins in the fibrous portion of its seed: *R. communis* agglutinin (RCA I, RCA120) and ricin (RCA II, RCA60), each with a 60–66 kDa domain [8, 9]. In contrast to ricin, *R. communis* agglutinin is a weak cytotoxin but a powerful hemagglutinin. This ricin agglutinin is not absorbed enterally, but intravenous administration can result in red blood cell agglutination and hemolysis [8, 9].

Table 2 lists the LD₅₀ of selected toxalbumins.

Clinical Presentation

The clinical presentation of abrin and ricin toxicity depends on the route and magnitude of exposure. The most common route is oral, by unintentional ingestion of ornamental or jewelry seeds or eating the seeds whether intentionally or not. Inhalational or injection exposures are possible, particularly in the setting of biologic warfare or secondary to

Table 3 Frequency of clinical manifestations after ricin ingestion, 1900–1985

Clinical manifestations	Cases (%)
Vomiting	84
Diarrhea	83
Dehydration	35
Shock	27
Abdominal pain	13
Diarrhea with bleeding	3
Abnormal kidney function	9
Abnormal liver function tests	5
Hemolysis	3

Adapted from Ref. [39]
Total number of cases = 103

homicidal or suicidal actions. Hypersensitivity reactions can occur by either inhaled or dermal exposure to the seed’s pomace remaining after the castor oil is pressed from the seeds [35, 36].

Oral ingestion of abrin and ricin can produce biphasic toxicity. The first, or local, phase can present with mucosal irritation in the oropharynx; however, lack of this finding does not rule out an ingestion. Rarely, more severe corrosive-type lesions can be present within the GI tract. The castor seeds are reportedly quite bitter in taste; however, purified ricin has little to no taste. Clinical manifestations usually present within 6 h of ingestion but it can be delayed up to 12 h, and rare cases exist with onset outwards of 24 h after exposure, with most patients developing nausea, vomiting, diarrhea with or without hematochezia, and colicky abdominal pain [37, 38]. Challoner and McCarron [39] reviewed documented ricin ingestions and found that most patients experienced primarily gastrointestinal complaints (Table 3). Patients typically experience significant GI fluid losses leading to dehydration, electrolyte imbalances, and eventually, if not adequately addressed, hypotension, shock, and circulatory collapse. Hypovolemic shock and multiorgan involvement represent the second, or systemic, phase of toxicity. In a study of 424 cases of castor seed ingestion, 14 developed fatal hypovolemic shock from intestinal fluid losses [38]. Liver failure can result from direct hepatotoxicity and shock liver [3, 37, 38]. Hemolysis, kidney failure, splenic necrosis, seizures, and cardiac

dysrhythmias have been described [3, 15, 37–39]. On autopsy, diffuse intestinal hemorrhage has been reported. Involvement of lymph nodes and lymphatic tissues is usually noted. Histology after ricin exposure in both animals and humans is consistent with both direct cellular necrosis as well as apoptotic cell death [3, 33, 34].

Variations of this biphasic presentation have occurred, with cases of only mild gastroenteritis and one case of an infant developing fulminant liver failure without previous gastrointestinal manifestations [15, 37, 38, 40]. Which patients progress to the second phase of toxicity is difficult to predict on the basis of the number of seeds ingested; however, patients who have 3–4 days of progressive diarrhea and large fluid losses are likely to develop shock [37, 38]. Aggressive symptomatic and supportive care is the mainstay of treatment. There has been only one known reported death from ricin ingestion in the United States in almost 50 years because of excellent intensive supportive care. Unlike the ingestion of ricin, the exposure to ricin by inhalation or injection is expected to cause severe toxicity and increased mortality.

Inhalational exposures, primarily in settings of biologic warfare, produce a different presentation from oral exposure. Based on data collected during a sublethal unintentional aerosol exposure in the 1940s, fever, cough, dyspnea, chest tightness, and arthralgias develop after 4–8 h. Development of profuse sweating is usually the hallmark of resolution [13]. In animals exposed to large doses, they developed diffuse necrotizing bronchiolitis, alveolitis, and fibropurulent infiltrative disease with noncardiogenic pulmonary edema and died from hypoxia in 36–72 h [32–34]. Monkeys exposed to sublethal doses of aerosolized ricin still developed multifocal interstitial pneumonia, fibroplasia and fibrosis, interstitial pneumonitis with hyperplasia, and some patchy pulmonary edema. Of note, the monkeys also developed extrapulmonary involvement of their lymphatic tissues [33, 34].

Injection of crystalline or liquid abrin and ricin can produce local pain, mild dyspnea, and cough or wheeze. Progression to multiorgan failure and death can occur [3, 11, 12, 37, 38, 40]. In animal

models, IV or IP administration invariably leads to widespread necrosis of lymphoid organs and involvement of liver, kidneys, heart, and GI tract. Most animals die of multisystem organ failure, which is consistent with findings from the scattered case reports of people exposed to ricin by the intravenous or intramuscular route [3, 37–40]. Ingestion of *R. pseudoacacia* bark results primarily in gastroenteritis, similar to that described for ricin and abrin. Some reports of central nervous system involvement have been described. In unintentional ingestion by two horses, one showed alternating phases of somnolence and excitation, mydriasis, and decreased sensation to the head [4]. Vertigo, muscle twitches, cardiac dysrhythmia, and weakness also have been described [4, 37].

Hypersensitivity reactions to *R. communis* seeds have been well described in response to dermal and inhalational exposures. Garcia-Gonzalez and colleagues [41] showed the role of *R. communis* as a pneumoallergen, causing primarily respiratory and nasal symptoms. In sensitized industrial castor seed workers, allergic dermatitis, rhinitis, asthma, and anaphylaxis have been recognized [3, 14, 35, 36]. One representative case report described facial itching, periorbital edema with complete eyelid closure, and urticarial wheals after touching the powder in a broken ricin seed from a necklace [14]. Residents of neighborhoods surrounding castor oil plants exposed to high levels of castor seed pomace dust in the air have higher than average number of reports of allergic rhinitis and levels of ricin antibodies [35, 36]. Diagnosis depends primarily on history of exposure and is important for the avoidance of subsequent, more severe anaphylactic reactions.

Pathophysiology

The effects of ricin and abrin exposure can vary from mild gastroenteritis to multiorgan failure and death. The type and severity of a patient's response depend on the amount and route of exposure: ingestion, inhalation, or injection. Each route can evoke specific and early manifestations, but all can result in multisystem failure.

When ricin is injected intramuscularly, local necrosis of the soft tissue or regional lymph nodes can occur. If the toxin is absorbed systemically or injected intravenously, multiorgan failure can ensue. *R. communis* agglutinin causes hemagglutination and intravascular hemolysis by binding to glycoproteins on red blood cells [8, 9, 36]. The by-products of hemolysis can occlude the renal tubules, resulting in acute tubular necrosis and subsequent renal failure. Ricin can bind and damage the lung's vascular endothelium, resulting in noncardiogenic pulmonary edema and hypoxia. Fulminant liver failure may result from direct hepatotoxicity as well as indirectly from hypovolemic shock [34, 37–41]. In vitro experiments with mice have shown that peritoneal injection of ricin at low doses results in multifocal necrosis in parenchymal organs, and larger doses produce hemorrhage in visceral and serous cavities with subsequent death from organ failure and shock [40].

Ingestion of ricin, abrin, or robin can cause mild to moderate corrosive-type injuries and gut endothelial damage, resulting in ulceration and loss of fluid and blood [3, 37–39]. The ensuing bowel wall edema and decreased intestinal absorption can lead to diarrhea, dehydration, and hypovolemic shock. With systemic absorption, these toxins can cause cytotoxicity via both direct cellular necrosis and induction of apoptosis to any organ, such as the pancreas, spleen, liver, heart, and kidney [3, 37–40].

Inhalation of ricin is another method of exposure that is potentially dangerous. The airways can develop necrotizing lesions resulting in tracheitis, bronchitis, bronchiolitis, or interstitial pneumonia. These conditions can progress to perivascular and alveolar edema, damaging infiltrative and necrotizing bronchiolitis and pneumonitis, and subsequent hypoxia requiring mechanical ventilation [13, 32–34, 41].

Clinical Effects and Life-Threatening Complications

The modern case fatality rate is estimated at less than 2% with the availability of excellent supportive care. Worbs et al. [38] report a summary of

worldwide cases from the available literature with a summary of 875 ingestions and only 13 reported fatalities from 1900 to 2011 resulting in a case fatality rate of 1.5%. However, the fatality rate for injections is considerably higher at 45.5% [38]. Intravenous administration can produce death more quickly and at lower doses than can ingestion; inhalation can also be quite toxic if the particle is of sufficient size to reach the lower airways and the amount sufficient to cause toxicity and injury. Nearly all of case fatalities reported in the modern literature are from injection of the toxin [37, 38].

For oral administration, data have been variable on the number of seeds required for serious sequelae. Eight to 20 ricin seeds in adults and as few as three in children have been reported to produce death; however, mastication of the seeds is required to cause toxicity [3, 37–39]. In one case report, a patient swallowed more than 30 ricin seeds and survived, whereas other authors have reported ingestions of three seeds that resulted in only a mild gastroenteritis [3, 38, 39]. This variability in toxicity likely depends on how well masticated the seed is or plant to plant variation in seed toxicity because the concentration or the type (isoform) of the toxin can vary due to factors such as growing conditions, plant maturity, and plant variety or cultivar [9].

Ricin toxin can be inhaled as a lyophilized powder, although creating a “weaponized” size particle is extremely difficult to achieve. The aerosolized dose that was fatal in 50% of exposed mice (LD₅₀) is 3–5 µg/kg [3]. Based on this finding, approximately 8 t of toxin would have to be produced and deployed to significantly affect a human population living in an area of 100 km². Based on extrapolated data from studies in monkeys and other animals as well as human case reports, the estimated LD₅₀ in humans is 5–10 mcg/kg by inhalation and 1–20 mg/kg by ingestion [3, 13, 33, 34].

Experiments with mice show that the LD₅₀ for intraperitoneal administration of ricin and abrin varies from 2–20 mcg/kg, producing death within days [42]. Subcutaneous administration of 0.1–0.2 mg of abrin extracts into mice resulted in death within 24–48 h, and 0.2 mcg can induce

Table 4 Analytical methods and target analytes used in presumptive and confirmatory testing to detect ricin in selected matrices

Matrix	Presumptive	Confirmatory
Environmental		
Powder	PCR ^a (DNA), TRF IMA (protein), LC-MRM-IDMS(<i>N</i> -glycosidase activity) [9]	LC-MRM-IDMS (selected peptides) [9]
Liquid	PCR (DNA), TRF IMA (protein), MALDI-TOF/TOF MS (<i>N</i> -glycosidase activity) [49]	LC-LTQ/FT-ICR MS (selected peptides) [49]
Clinical		
Blood (serum)	MALDI-TOF/TOF MS (<i>N</i> -glycosidase activity) [49]	LC-LTQ/FT-ICR MS (selected peptides) [49]
Urine	LC-MRM-IDMS (ricinine, abrine) [47, 48]	

^aAbbreviations: *LC-LTQ/FT-ICR MS* liquid chromatography – linear quadrupole ion trap/Fourier transform ion cyclotron resonance mass spectrometry, *LC-MRM-IDMS* liquid chromatography – multiple reaction monitoring – isotopic dilution mass spectrometry, *PCR* polymerase chain reaction, *MALDI-TOF/TOF MS* matrix assisted laser desorption ionization – tandem time of flight mass spectrometry, *TRF IMA* time-resolved fluorescence immunoassay

red blood cell agglutination in vitro [6]. Because a lethal dose of these toxins can be delivered in a small concentration, there is concern for their potential use to commit suicide or homicide.

Diagnosis and Detection

Diagnosis of toxalbumin poisoning depends primarily on the history of illness. If the patient presents with the seeds for identification, protective gloves should be used when handling to avoid possible contact dermatitis. Because there are many causes of diarrhea and the exposure to a toxalbumin might not be apparent upon presentation, the diagnosis is often delayed or made incorrectly.

There are various strategies to detect ricin in environmental samples and clinical specimens that can aid the diagnosis of ricin poisoning. These approaches are detection of proteins, DNA, enzymatic activity (*N*-glycosidase), and amino acids (peptides) that are characteristic of ricin. The level of confidence that the test result is specific for ricin (*Ricinus communis* agglutinin II (RCA II, RCA60)) depends on the analytical method and test analyte (Table 4) [43–54].

For example, a positive test result from an immunoassay method is considered presumptive evidence for the presence of ricin (RCA60) because it can also

detect the less toxic protein *Ricinus communis* agglutinin I (RCA I, RCA120). Similarly, the detection of certain peptides or *N*-glycosidase activity is considered presumptive evidence for the presence of ricin because the same peptide sequence can be found in ricin and RCA120, and *N*-glycosidase activity is common among ricin, RCA120, and ribosome-inactivating proteins [9, 49].

The detection of ricinine is also presumptive evidence for the presence of ricin from a natural source [47]. The lack of detection of ricin DNA or ricinine does not exclude the presence of purified or protein isolates of ricin in the sample. The presence of ricin is confirmed when peptides specific to ricin are detected in the sample [9, 49]. The confirmation of a positive test result for ricin is made at a reference laboratory.

Virtually no testing will be available without involvement of law enforcement and public health agencies. It is advised to consult with these agencies early regarding patients with suspected poisonings from ricin or other toxalbumins. Depending on the circumstances, environmental testing may be needed and testing of close contacts of the patient as well, if they are symptomatic and under treatment. Healthcare providers are advised to contact their local public health department or Centers for Disease Control and Prevention when they anticipate the need to test for the presence of ricin or abrin [20, 21].

Treatment

If only one or two castor seeds were ingested and the exposure was unintentional, the patient can be discharged after remaining without signs or symptoms for 6 h while under observation. If more than two seeds were eaten or if clinical manifestations have developed, the patient should be admitted. Because of abrin's higher potency than ricin, any amount of oral exposure to this seed is potentially lethal, and patients should be admitted.

If a patient presents within 2 h of oral ingestion, gastric decontamination with activated charcoal can be considered, although it has not been studied in this setting, and it is unknown whether activated charcoal alters the clinical course or affects outcome in these ingestions. Precautions, such as a protected airway, need to be observed when administering activated charcoal to patients [55]. There is no role for cathartics. Whole-bowel irrigation after toxalbumin ingestion cannot be recommended at this time because it has not been shown to be helpful, although this has not been studied extensively.

Supportive measures are the mainstay of treatment of abrin, robin, or ricin toxicity. Aggressive fluid resuscitation should be started early for treatment of dehydration and prevention of hypovolemic shock and acute tubular necrosis. Admitted patients should be observed for 24–48 h for evidence of hypovolemia, hepatotoxicity, renal failure, and hemolysis with daily or twice-daily laboratory evaluation.

For inhalational exposure, the patient's respiratory status and pulse oximetry should be monitored. Patients with diarrhea persisting for more than 3–4 days, hepatotoxicity, or respiratory compromise should be monitored in an intensive care unit. Patients who have been injected with ricin or abrin have a high risk for systemic toxicity and should be monitored in an intensive care unit. Hypovolemic shock should be treated with intravenous crystalloid fluids and vasopressor support, if necessary. Pulmonary edema may require intubation and mechanical ventilation. Owing to toxin-induced dysrhythmias, continuous cardiac monitoring should be employed. Brisk urine output should

be maintained to prevent acute tubular necrosis; however, forced diuresis should not be performed.

In the setting of massive intravascular hemolysis, we recommend maintaining a rapid urine flow (150 mL per hour) and avoiding aciduria to limit hemoglobin precipitation and schistocyte-mediated renal tubular damage. Patients with inhalational exposure and those in multisystem organ failure are at increased risk for pulmonary edema, so their respiratory status needs to be monitored closely during large volume fluid resuscitation. There are no data to support the use of loop diuretics, atrial natriuretic peptide, or mannitol in the treatment of acute tubular necrosis caused by heme compounds. Dialysis may be required if uremia or refractory metabolic acidemia ensues.

Indications for ICU Admission in Toxalbumin Poisoning

Significant hepatotoxicity or other evidence of end organ failure

Diarrhea for >3–4 days with dehydration

Respiratory distress, failure, or significant hypoxia

Exposure by injection

Systemic inflammatory response syndrome/shock

Massive hemolysis

Ricin and abrin are water soluble and metabolized by the liver; consequently, hemodialysis or forced diuresis does not enhance their elimination. In a case series from China, seven children with clinical manifestations from unintentional ingestion of castor seeds appeared to improve with plasma exchange (plasmapheresis) [56].

An antidote for ricin toxicity is not currently available. Some novel treatments under investigation include use of *N*-acetylcysteine (NAC) and liposome-encapsulated NAC. An animal study with NAC showed some promise in mitigating the hepatotoxicity of the ricin A subunit (chain). NAC's potential benefit in this setting might be mediated through its anti-inflammatory effects and inhibition of lipopolysaccharide-induced activation of NF- κ B, which mitigates

downstream inflammatory cascade [57]. No human trials have been performed with NAC for ricin toxicity. Other novel therapies that have been studied in mice include dexamethasone and the antioxidant vitamin E. Although neither agent prevented death, both extended survival time in pretreatment trials [58]. An in vitro study demonstrated milk, lactose, and galactose inhibited binding of the ricin B subunit (chain) to cell surfaces and prevented entry of the toxin into cells [59].

Vaccines for ricin and specific antibody therapy have been in development for several years and they have had some significant successes; however, none of them are commercially available at this time [60–62]. People at high risk for exposure to ricin, such as military personnel and first responders, might benefit from vaccine therapy when it becomes available. Directed antibody therapy, with humanized animal derived Fab and recombinant antibodies, has been very promising in in vitro and in vivo studies [63–65]. For example, animals have excellent protection from ricin exposure when they received such treatment in a timely fashion even after inhalational exposure [61–64]. Other non-antibody small molecules and other cellular protein inhibitors are currently under investigation to identify alternative mechanisms to inhibit the protein-mediated effects of ricin [66].

Special Populations

Pediatric Patients

- Incidence of toxalbumin exposure is high in children, given their attraction to the decorative, colorful seeds.
- Oral mucosal irritation and GI mucosal lesions seen with ricin exposure can resemble viral exanthems and be misdiagnosed easily.
- As a result of the high respiratory rate in children, an aerosolized ricin exposure can deliver a high dose of the toxin and increase the risk of pulmonary manifestations.

- Children can progress to hypovolemic shock more readily than adults after gastrointestinal fluid losses.

Key Points in Toxalbumin Poisoning

The most common route of toxicity is unintentional ingestion; intravenous and inhalational delivery can produce death quickly and at low doses.

Diagnosis of toxalbumin toxicity is primarily by history.

Hypersensitivity reactions have been described for dermal and inhalational exposures.

Gastroenteritis, after seed ingestion, is the most common and usually the first manifestation; multiorgan failure can ensue.

Supportive measures are the mainstay of treatment.

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Water hemlock belongs to the family Apiaceae (Umbelliferae). The genus *Cicuta* includes the species spotted water hemlock (*C. maculata*), Western water hemlock (*C. douglasii*), and northern water hemlock also known as European water hemlock (*C. virosa*), *C. bolanderi*, *C. bulbifera*, *C. californica*, *C. curtissii*, *C. mackenziana*, *C. occidentalis*, and *C. vagans* (Figs. 1, 2, and 3). The active toxic compound in water hemlock is cicutoxin. The hemlock water dropwort (*Oenanthe crocata*) belongs to the family Apiaceae (Umbelliferae), genus *Oenanthe*. It is native to Europe but has been introduced to some parts of the United States. It lacks the chambered root of the *Cicuta* spp. and produces oenantheotoxin, a constitutional isomer (a compound that has the same molecular formula but a different structural formula) of cicutoxin.

The various species of *Cicuta* and *Oenanthe* have approximately equivalent clinical toxicity at similar stages of plant growth, producing virtually identical clinical manifestations in poisoning, and, therefore, will be discussed as a single group. Common names of these plants include cowbane, children's bane, poison parsnip, five-fingered root, dead men's fingers, death-of-man, wild parsnip, snakeweed, beaver poison, muskrat weed, spotted hemlock, spotted cowbane, musquash root, false parsley, poison hemlock, wild carrot, fever root, mock-eel root, spotted parsley, cique vireuse, and carotte à moreau.

Water hemlock species are biennial or perennial plants that grow to a height of 6–8 ft with

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Fig. 1 *Cicuta virosa* (Original book source: Prof. Dr. Otto Wilhelm Thomé *Flora von Deutschland, Österreich und der Schweiz* 1885, Gera, Germany. This image is in the public domain. Accessed at: http://biolib.mpiiz.mpg.de/thome/band3/tafel_056.html)



Fig. 3 Western water hemlock (*C. douglasii*) in natural habitat (Photo courtesy of Gerald D. Carr[®]. Used with permission)



Fig. 2 Western water hemlock (*C. douglasii*) Umbel (Photo courtesy of Gerald D. Carr[®]. Used with permission)

narrow, compound leaves that have serrated edges. Purple spots (“macules”) may be visible on the hollow and chambered stalk. Small fragrant white flowers develop as compound umbrellalike formations (umbels) that typically blossom in June or July. *Cicuta* and *Oenanthe* species grow only in habitats with continuous water, such as swamps, lakesides, stream banks, drainage ditches, and marshes. *Cicuta* spp. have thick, tuberous roots, which are often bundled with as many as five or six roots. When cut, they yield an oily yellow sap that has an odor of parsnips and rapidly turns brown on contact with air. When the thickened underground portion of the stem and roots are sectioned sagittally, characteristic multi-layered air chambers separated by pith diaphragms are seen [1] (Fig. 4). These chambers are not as distinct in the spring as they are later in the season [2]. All parts of the plant are



Fig. 4 Western water hemlock (*C. douglasii*). Note chambered root and hollow stalk (Photo: William Follette (Lagunitas Creek, Marin County, CA). Accessed at: <http://plantid.net/Slideshow/ShowPhotos.aspx>)

considered poisonous. The tuberous roots are the most toxic part, especially in the spring, prior to flowering, when they are typically the most developed. *Oenanthe crocata* roots are usually more bulbous than those of the *Cicuta* spp. and are solid rather than chambered. They also produce a sticky yellow, oily sap when cut [3, 4].

It is important not to confuse water hemlock with the closely related poison hemlock (*Conium maculatum*), which has a similar appearance. Poison hemlock also belongs to the family Apiaceae (Umbelliferae) and has small white flowers in umbellate clusters similar to those of water hemlock. However, poison hemlock has wider leaves that have three to five divisions and a single tap root that is non-chambered. The root of poison hemlock also yields an oily, yellow sap when cut. *Conium maculatum* was imported to North America from Europe and is now found in the same geographic range as water hemlock, throughout the United States and southern Canada. Poison hemlock occurs globally due to introduction into new areas, with reports from North and South America, Europe, Africa, Asia, Australia, and New Zealand, but appears native to Europe, Western Asia, and North Africa. In contrast, water hemlock appears to be restricted to the Northern Hemisphere, notably Europe and North America. The habitat for poison hemlock differs from water hemlock in that it is typically drier (e.g., roadsides, fields, and ditches). The active toxic principles in poison hemlock, including coniine,

N-methyl coniine, conhydrine, λ -coniceine, and pseudoconhydrine, produce a different spectrum of clinical effects than the toxins found in water hemlock. Poisoning from water hemlock manifests primarily as vomiting and seizures that occur within an hour of ingestion, whereas poison hemlock presents with initial gastrointestinal upset, then autonomic and somatic stimulatory features that are followed by central nervous system (CNS) depression, ascending paralysis, and bradycardia. A complete discussion of poison hemlock poisoning is given in ► [Chap. 113, “Poison Hemlock.”](#)

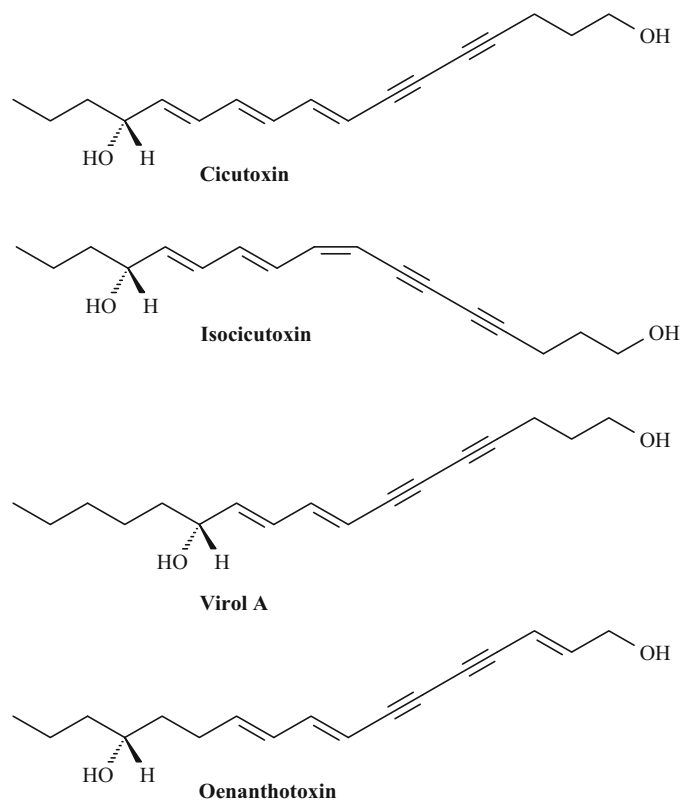
Water hemlock has also been mistaken for other members of the Apiaceae (Umbelliferae) family that are edible, such as *Daucus carota* (carrots), *Pastinaca sativa* (parsnip), “wild parsnips,” and many other wild tuberous plants that are objects of human foraging including artichokes, celery, sweet potatoes, and sweet anise [2–16]. Fatal poisonings have resulted from the ingestion of *C. maculata* that was mistakenly identified as American ginseng [17, 18]. Livestock poisoning also occurs, frequently in the spring, as water hemlock is usually located near water sources where animals graze and emerges early in the season before other forage becomes available.

Human ingestion of water hemlock roots is most often the result of ill-advised wild plant foraging by adults and/or children. Some reviews of water hemlock poisoning dating back over 100 years note that there are more cases of pediatric poisoning than adult, likely due to the fact that this population is more given to experimental ingestion of foraged plants than adults [7, 15, 19].

Biochemistry of Active Compounds

The compounds responsible for the water hemlock’s toxicity vary depending upon the species, but all belong to a class of conjugated C_{17} -polyacetylenes. These are highly unsaturated, polyacetylenic alcohols that are isomers or analogues of a 17-carbon skeleton that all include a conjugated polyacetylene system, a terminal hydroxyl group at C_1 , and an allylic hydroxyl

Fig. 5 Chemical structures of C_{17} -polyacetylenes from water hemlock



group at C_{14} [20]. Cicutoxin, isocicutoxin, cicutol, oenanthotoxin, oenanthetol, oenanthetone, and virols A, B, and C have been isolated from *Cicuta* and *Oenanthe* species. Cicutoxin was first described by Boehm in 1876 [21] and has since been extensively characterized in multiple subsequent works. The principle toxic members of this group are **cicutoxin** ($C_{17}H_{22}O_2$, *trans*-heptadeca-8:10:12-triene-4:6-diyne-1:14-diol); its isomer, **oenanthotoxin** ($C_{17}H_{22}O_2$, *trans*-heptadeca-2:8:10-triene-4:6-diyne-1:14-diol); and **virol A** (*trans*-heptadeca-8:10-diene-4:6-diyne-1:11-diol) [20, 22, 25, 26, 39] (Fig. 5). Cicutoxin and oenanthotoxin are structurally very similar and are equally toxic. Similarly, the alcohols cicutol and oenanthetol are structurally similar and are relatively nontoxic [22].

These C_{17} -polyacetylenes are found in all parts of the plants. However, the tuberous roots contain the highest concentration of toxins and are also the portion of the plant most commonly ingested. As is typical with most naturally occurring toxins, the

concentration and variety of active compounds in a given plant varies with season, geographical location, environmental conditions such as water supply and soil conditions, as well as which plant species or plant part being considered. Roots from *C. maculata* and *O. crocata* retain their toxicity long after harvesting and/or drying [25, 26]. Although cicutoxin and oenanthotoxin are relatively unstable compounds on exposure to air, light, and heat, poisonings after ingestion of dried and/or cooked roots of both *O. crocata* and *C. maculata* have been reported [3, 4, 27, 28]. Pharmacological studies by Grundy and Howarth have demonstrated marked toxicity with dried and powdered tubers of *O. crocata* [29].

The C_{17} -polyacetylenes are water soluble but can be readily extracted with organic polar solvents such as methanol, ethanol, and ethers. They can be studied in both biological and environmental samples using high-performance liquid chromatography, thin-layer chromatography, and mass spectroscopy [20, 22, 28, 29].

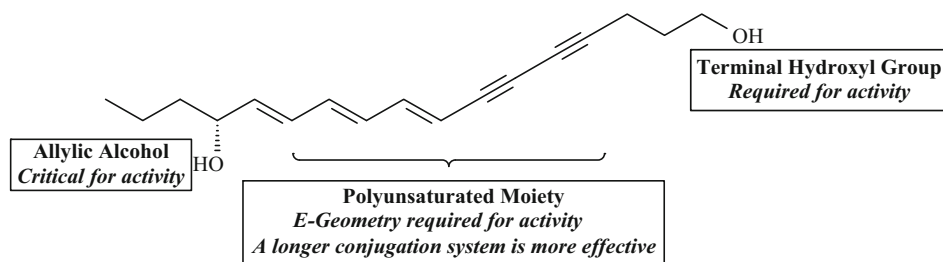


Fig. 6 General structure activity relationship of C_{17} -polyacetylenes from hemlock. Cicutoxin is the *trans*-isomer and isocicutoxin is the *cis*-isomer (After Uwai et al. [38], with permission)

The structure-activity relationship between C_{17} -polyacetylenes found in *C. virosa* and gamma-amino butyric acid A ($GABA_A$) receptors in rat brain cortex has been studied. Eleven C_{17} -polyacetylenes have been isolated from water hemlock root, including cicutoxin, isocicutoxin, and virols A, B, and C [20, 23, 24]. By synthesizing more chemically stable structural analogues, the structural requirements for toxicity have been determined. The length of the π -bond conjugation system and the geometry of the double bonds are critical for toxicity. This is exemplified by comparing the LD_{50} of cicutoxin, with all *trans* double bonds, and that of isocicutoxin, which has a *cis* configuration at its C_8 - C_9 double bond (Fig. 6). The LD_{50} values of cicutoxin, isocicutoxin, virol A, and picrotoxin in a mouse model (intra-peritoneal) are 2.8, 38.5, 9.5, and 9.8 mg/kg, respectively [20, 23, 24]. Other C_{17} -polyacetylene analogue studies showed that the terminal *O*-functional group and the allylic alcohol were also essential for toxicity [20].

Pathophysiology

The primary toxic effects of water hemlock, namely, severe and recurrent seizures, result from its $GABA$ antagonist action in the CNS. Normally, agonism of $GABA_A$ receptor-linked ion channels results in the influx of chloride into the neuron. This hyperpolarizes the neuron thereby inhibiting depolarization. Cicutoxin and the other toxic C_{17} -polyacetylenes are believed to inhibit this hyperpolarization, thus allowing depolarization of neurons to go unchecked, leading to

seizures. This effect is dose dependent, as the severity of poisoning has been found to be directly related to the amount of the plant (usually the root) ingested.

Grundy and Howarth noted that seizures produced by oenanthotoxin were indistinguishable from those produced by picrotoxin [29]. Picrotoxin is a noncompetitive indirect $GABA$ antagonist and binds to a specific site, distinct from the $GABA$ itself, on the $GABA_A$ chloride channel [30]. Pretreatment with one-tenth the convulsive dose of an extract of *C. douglasii* decreased the convulsive dose of picrotoxin in a dose-dependent manner, but did not significantly decrease the convulsive dose of pentylenetetrazol, supporting a picrotoxin-like mechanism for cicutoxin's proconvulsant activity [31].

The potency of each C_{17} -polyacetylene compound as a $GABA_A$ antagonist was determined by comparing their ability to inhibit the specific binding of [3H]EBOB (ethynylbicycloorthobenzoate, a specific noncompetitive inhibitor of $GABA_A$ -gated chloride channels that binds to the antagonist picrotoxin-binding site of the $GABA_A$ receptor) to the $GABA_A$ receptor complex in rat brain cortex [20]. Binding studies showed that virol A reversibly reduced $GABA$ -induced chloride current in a noncompetitive, concentration-dependent manner. The [3H]EBOB 50% inhibitory concentration (IC_{50}) values (μM) for cicutoxin, virol A, and picrotoxin were 0.54, 1.15, and 1.81, respectively. In addition, there was a correlation between the potency of the compounds in inhibiting the specific binding of [3H]EBOB to $GABA$ -gated chloride channels of $GABA_A$ receptors in rat brain cortex and their

LD₅₀ values [20]. These observations provide evidence that cicutoxin and related C₁₇-polyacetylenes act as noncompetitive antagonists of the GABA_A receptor by binding to the picrotoxin-binding site within the chloride channel to block ion flow through the channel [32–35].

In an in vitro model, Green et al. [36] incubated human embryonic kidney cells transfected with a plasmid containing cDNA encoding rat GABA_A receptors (which were expressed on the cell surface) with GABA with and without an aqueous extract of *C. douglasii* (containing cicutoxin and other cicutoxin-type compounds). The change in cell membrane potential was then determined for GABA alone (i.e., control or maximal response) and GABA combined with incremental concentrations of the extract (1%, 5%, 10%, 20%). They demonstrated that the extract depressed the maximal GABA response in a concentration-dependent manner (characteristic of noncompetitive antagonism). Pretreatment of 10 mM midazolam was found to reduce the action of the extract.

Binding studies have been performed to measure virol A's effect on the GABA-induced inhibitory chloride current (I_{GABA}). Virol A reversibly reduced I_{GABA} and muscimol-induced chloride current (I_{MUS}) (muscimol is a GABA_A receptor agonist) in rat brain hippocampal CA1 neurons in a concentration-dependent manner. However, it inhibited I_{GABA} in a competitive manner at lower concentrations and in a noncompetitive manner at high concentrations [37]. Other studies showed that virol A further reduced the I_{GABA} already reduced by lower doses of picrotoxin, but not at high doses of picrotoxin, indicating that picrotoxin and virol A may recognize a common binding site [37]. Virol A did not decrease the glycine-induced (glycine is an inhibitory neurotransmitter) current, indicating that it selectively inhibits the GABA response [37]. Virol A was not displaced by [³H]muscimol or by [³H]flunitrazepam in rat brain membrane preparations. Therefore, Virol A apparently binds to a site that is distinct from GABA agonist and benzodiazepine-binding sites [37]. Mice pretreated with subconvulsive doses of cicutoxin had a lower convulsive threshold to picrotoxin, further

suggesting a common, and possibly synergistic, mode of action [31]. Neuroanatomical studies in animals in which the CNS was either destroyed, or severed at different levels, suggest a GABA-antagonism-induced seizure origin in the brain stem [29].

Cardiovascular effects including hypotension, hypertension, bradycardia, tachycardia, ventricular fibrillation, and cardiac arrest have been reported in water hemlock poisoning [6, 7, 11, 12, 18, 26]. However, it is unclear from these case reports whether these cardiovascular effects are secondary to severe seizures or are due to a primary cardiotoxic effect of cicutoxin and/or related toxins found in water hemlock. Studies in anesthetized non-seizing animals have shown that these toxins can cause marked hypotension, usually followed by a hypertensive phase [29, 38]. Bilateral vagotomy, or destruction of the CNS, prevented the bradycardia seen in one of these experiments, but did not affect blood pressure, suggesting a centrally mediated mechanism for bradycardia [38]. However, in both human case reports and animal experiments, these cardiovascular effects have been quite variable, and a mechanism of action has yet to be elucidated.

Parts of *C. maculata* have been used as herbal remedies for scirrhous mammary cancer and cirrhou tumors [39]. Cicutoxin itself has even been studied as a potential chemotherapeutic agent. An extract of *C. maculata* was found to have significant in vitro cytotoxic effects against a human nasopharyngeal cancer cell culture line. Interestingly, structure-activity relationship studies have shown that the same structural moieties responsible for cicutoxin's toxicity (the conjugated double and triple bonds and the two hydroxyl groups) are also responsible for its cytotoxic antileukemic activity [39].

Cicutoxin has also been shown to have activity at voltage-gated potassium channels in stimulated T lymphocytes. Cicutoxin reversibly, and in a potent manner, blocked n-type potassium current in a dose-dependent fashion, thereby inhibiting potassium current-dependent T cell proliferation [40].

In summary, the toxic C₁₇-polyacetylenes responsible for water hemlock's neurological

toxicity inhibit the GABAergic inhibitory chloride current, resulting in decreased inhibitory tone, leading to seizures. They apparently do not have effects at the benzodiazepine and glycine receptors, may share a common binding site with picrotoxin, and may act primarily in the brainstem to cause seizures. They have variable effects on the cardiovascular system. They block voltage-gated potassium channels, are cytotoxic in vitro, and inhibit T cell proliferation. However, it is unclear how each of these effects may contribute to their clinical toxicity.

Clinical Presentation

Water hemlock poisoning typically occurs in persons, often in groups, foraging for edible wild plants. The clinical presentation of water hemlock poisoning was first reported by J.J. Wepfer in 1679 when he described five children who were poisoned after they ingested the plant [41]. The first report of poisoning in North America is attributed to John Stockbridge who published a case of fatal water hemlock poisoning in 1814 [42]. It has since been reported in adults as well as children, and often occurs in the spring when the plants have not yet developed to their full size, and are more likely to resemble other edible wild plants such as ginseng, or wild parsnips, carrots, and turnips. Fatal poisoning in a young woman who ingested water hemlock dropwort roots in the hope that they would be hallucinogenic has also been reported [28]. Egdahl reported a case of water hemlock poisoning as the means of a murder attempt [7]. Egdahl also cites Chevallier in reporting five cases, including two fatalities, of dermal water hemlock poisoning when a family rubbed their skin with the roots of *Cicuta aquatica* in an effort to treat pruritis [7]. It has even been reported that placing slices of *C. virosa* root on the backs of frogs can induce seizures [7]. Frazer [43] reported the deaths of two boys who used the hollow stalk of a hemlock who developed “severe muscular spasms” and died after “blowing the haws (small unripened false fruit) through the stem” for about 3 h. It is unclear from this account whether the hemlock was *Conium maculata*

(poison hemlock) as mentioned by the author or water hemlock (which would be more consistent with the clinical description of “severe muscular spasms” suggesting seizures). As mentioned above, poison hemlock would be associated with flaccid muscle paralysis and death due to respiratory failure, while water hemlock would be associated with seizures (i.e., muscular spasms) and death. However, these cases suggest that fatal poisoning can follow the use of the stalk as a “blow gun,” which would likely involve placing one’s lips on the stalk itself, allowing for absorption of sufficient amount of toxin to cause fatal poisoning [43]. Multiple poisonings can occur when water hemlock is erroneously collected as a presumably edible root and cooked in a meal shared by more than one person. The onset of clinical effects may be delayed and may vary widely in severity among victims. If the meal is not identified as the cause of an index patient’s effects (i.e., seizures), others may actually ingest the meal well after the first patient’s presentation resulting in additional cases of poisoning [44].

The clinical presentation of water hemlock poisoning is essentially identical for either *Cicuta* spp. or *Oenanthe* spp. Initial symptoms are generally gastrointestinal complaints including nausea, vomiting, and abdominal cramping. The onset of symptoms is often within a few minutes, and nearly always within 30–45 min, of ingesting the root but may be delayed several hours [11–13, 15, 16, 18, 26]. Typically, as the amount of the root ingested increases, the time to onset of symptoms decreases, and their severity increases. Vomiting may be significant and repetitive. Other early signs and symptoms include diaphoresis, mydriasis, increased salivation, confusion, dizziness, diarrhea, weakness, ataxia, and hypotension [11–13, 15, 16, 18, 26, 27]. Although mydriasis is typical, miosis has also been reported [26]. Respiratory distress is common, and rales and wheezing have also been reported [6, 7]. The initial symptoms of nausea, vomiting, diarrhea, abdominal cramping, diaphoresis, altered mental status, increased salivation, and weakness are suggestive of a cholinergic toxidrome. Conversely, the mydriasis and seizures are consistent with an anticholinergic toxidrome. There are a number of

poisonous plants that produce cholinergic or anticholinergic toxidromes. Therefore, a careful and complete physical examination is important to avoid mistaking water hemlock poisoning for either cholinergic or anticholinergic poisoning from another cause. The typical presentation is abrupt onset of seizures accompanied by cholinergic-like signs with the notable exception of mydriasis.

The hallmark of water hemlock poisoning is severe, recurrent, and often refractory, generalized seizures. Seizures may occur before or after the vomiting and may even be the initial sign of poisoning. They are most often described as *grand mal*, tonic, tonic-clonic, or status epilepticus. Opisthotonus and hemiballismus have also been reported [6, 12, 45]. Coma, hypotonia, and decreased deep tendon reflexes usually follow seizures [3, 4, 15]. If seizures persist, cyanosis and acidosis develop, and cardiac and/or respiratory arrest may follow. Other reported neurological symptoms include amnesia [2, 12, 26], parathesias [27], neuropsychological abnormalities [6], and hallucinations [12, 44]. Electroencephalograms show diffuse abnormalities that may be persistent [6, 12, 13, 26, 27]. Coagulopathy has been reported on multiple occasions [9, 26].

This author consulted on a group of five boys who ingested varying amounts of the root from a water hemlock plant. They were removing winter overgrowth from a drainage ditch in the springtime. All five developed gastrointestinal symptoms and two suffered seizures. One patient reported visual hallucinations and an “out-of-body” experience en route to the hospital. All patients survived, including the most severely poisoned patient who suffered multiple seizures over approximately 45 min prior to arrival at hospital. He was treated with benzodiazepines, phenobarbital, intubation, and mechanical ventilation and eventually recovered.

Rhabdomyolysis is common in water hemlock poisoning [5, 6, 27]. Patients may complain of muscle pain and tenderness, and creatinine phosphokinase (CPK) values are elevated. This has been noted many times in patients with recurrent seizures and has also been seen in patients in the

absence of seizures, although to a much lesser degree. The etiology of the rhabdomyolysis has not yet been clearly determined. It is likely multifactorial, resulting from seizure-induced muscle activity and breakdown and possibly direct myotoxicity. Therefore, CPK and renal function monitoring is recommended in all patients with water hemlock poisoning. Acute renal failure has also been reported following water hemlock poisoning [5].

Case fatality rates have been reported between 30% and 70%. Cardiopulmonary arrest during status epilepticus is the primary cause of death. This wide mortality range likely reflects, in part, publication bias and that many cases reported in the literature occurred prior to the development of effective anticonvulsant therapy and before the use of modern critical care techniques and advanced life support protocols [7, 9, 10, 22]. However, despite such advances in treatment, water hemlock is still considered the most toxic plant in North America and can be rapidly fatal if not diagnosed early and treated aggressively [11, 13, 28].

Diagnosis

The diagnosis of water hemlock poisoning must be made on the basis of history and clinical presentation. There are no easily available diagnostic tests. Table 1 lists critical features that should be elucidated in the history of possible water hemlock ingestion.

Table 1 Historical features of importance in the diagnosis of water hemlock poisoning

Detailed description of the ingested plant, including the locale in which it was found (if possible, the plant itself should be obtained for identification)
The part and amount of the plant ingested
Time of ingestion
History of any coingestants
History of all signs and symptoms since ingestion (<i>N.B.</i> patient may present obtunded and unable to provide history)
Other possible victims

The cholinergic-like manifestations, such as emesis, abdominal cramping, excessive salivation and lacrimation, diaphoresis, and seizures, may lead some to suspect poisoning by grayanotoxin-containing plants such as death camas (*Zigadenus* spp.), mountain-laurel (*Kalmia latifolia*), azalea, or *Rhododendron* (*Rhododendron* spp.). Death camas has been mistaken for wild onion by people foraging for edible wild plants. Identification of the ingested plant should help differentiate water hemlock from these species. Other poisonous plants found in the United States that cause seizures include black cherry (*Prunus serotina*), jimson weed (*Datura stramonium*), black nightshade (*Solanum nigrum*), and sneeze weed (*Helenium autumnale*) [7]. Jimson weed and nightshade present with an anticholinergic syndrome, including marked mydriasis, but should not have the cholinergic manifestations reported with water hemlock poisoning. Black cherry is a cyanogenic plant and produces significantly delayed effects, including vomiting, abdominal pain, coma, and seizures, whereas water hemlock poisoning typically develops soon after ingestion of the plant.

Water hemlock often grows in drainage ditches, which may contain irrigation runoff contaminated with organophosphate (OP) pesticides. Organophosphate (or, similarly, carbamate) pesticide poisoning also produces a cholinergic toxidrome similar to the symptoms seen in water hemlock poisoning. Therefore, OP poisoning should be considered in the differential diagnosis of the poisoned patient with cholinergic symptoms in an agricultural setting. However, the marked mydriasis seen in water hemlock poisoning would be inconsistent with a cholinergic agent. Also, these pesticides produce profuse *atropine-responsive* bronchorrhea, a feature that is not seen in water hemlock poisoning.

As discussed earlier, it is important not to confuse the water hemlock plant with the closely related poison hemlock (*Conium maculatum*), which has a similar appearance. The active toxins in poison hemlock, coniine, N-methyl coniine, conhydrine, λ -coniceine, and pseudoconhydrine, are structurally similar to nicotine and bind to nicotinic receptors. Toxicity from water hemlock

manifests primarily as vomiting and seizures within an hour of ingestion. Although poison hemlock poisoning may initially present with nausea, vomiting, and abdominal cramping, like water hemlock, this initial stimulatory phase is followed by an ascending paralysis, CNS depression, and bradycardia and death from respiratory paralysis. ► [Chapter 113, “Poison Hemlock”](#) provides a complete discussion of poisoning by that plant.

In summary, the diagnosis of water hemlock poisoning is based upon the identification of the plant ingested, a clinical presentation that includes signs and symptoms suggestive of cholinergic poisoning, mydriasis, and abrupt onset of severe seizures. The differential toxicologic diagnosis should include other toxic plants that produce similar manifestations, and OP/carbamate pesticide poisoning if the ingestion occurs in an agricultural setting, or other conditions that suggest such a pesticide exposure.

Treatment

There is no specific antidote for water hemlock poisoning. Management should focus on cardiopulmonary stabilization, control of seizures, and gastrointestinal decontamination. Aggressive airway management, if indicated, is the initial treatment priority as these seizing patients are at high risk for aspiration, hypoxia, and anoxia. Stability and security of the airway should be assured.

Patients will often theoretically partially self-decontaminate with repeated bouts of vomiting that may occur following water hemlock ingestions. However, given the extremely high toxicity of even a small amount of ingested plant material, if the patient presents for treatment early, prompt attempts at decontamination by the administration of activated charcoal should be performed without delay if the patient presents within the first hour or 2 after ingestion. However, these measures have not been shown to alter the outcome, or clinical course, of water hemlock-poisoned patients or even poisoned patients in general. The usual dose of activated charcoal is 50 g orally in adults and 1 g per kilogram in children. Since these

patients are prone to develop diarrhea, cathartics should not be administered with the activated charcoal. If charcoal is to be administered, due to the risk of seizures, the patient's mental status and ability to protect their airway must be assessed prior to the administration of activated charcoal. If the patient is unable to protect their airway, then intubation is indicated.

Although not studied in clinical trials, benzodiazepines, barbiturates, and propofol are the appropriate treatment of water hemlock-induced seizures based on cicutoxin's stimulatory effect on GABA_A receptors. The seizures seen in water hemlock poisoning are often refractory to treatment. Therefore, these anticonvulsants should be administered aggressively and as promptly as possible after onset of seizures. Anticonvulsant dose should be titrated to effect with the end point of seizure control. Intubation should also be considered early with the use of high or repeat doses of benzodiazepines and/or barbiturates and/or decreased mental status. Phenytoin has been shown to be less effective than phenobarbital in controlling cicutoxin-induced seizures in an animal model and should not be used [31]. Although water hemlock poisoning has many features of a cholinergic toxidrome, an animal study found that water hemlock-induced seizures were not suppressed by pretreatment with anticholinergic agents benztropine or biperiden, nor worsened by the cholinergic agonist physostigmine, but were well controlled with diazepam [46, 47]. In an animal study, Panter et al. [48] found that in sheep given 1.5–2.5 times the lethal dose of water hemlock (*C. douglasii*) by gavage, intravenous administration of sodium pentobarbital at the onset of the first seizure prevented further seizures and skeletal and cardiac muscle degeneration and resulted in rapid and complete recovery [48].

Rhabdomyolysis may be severe and may be treated with intravenous fluids and/or urine alkalization to maintain good urine output and minimize the risk of myoglobin-induced renal failure. If so chosen, urine alkalization (pH > 6.5) can be achieved by adding 50–100 mEq of sodium bicarbonate to 1 l of dextrose in water (D5W), or up to 0.5 normal saline, and administering this intravenously at approximately 1.5 to two times

the maintenance rate. Acute oliguric renal failure due to water hemlock poisoning with rhabdomyolysis has been treated with short-term hemodialysis [5].

Extracorporeal Elimination

The use of hemodialysis and hemoperfusion as treatment for water hemlock poisoning has been reported in a 30-year-old man who was also treated with gastric lavage, oral activated charcoal, urine alkalization, forced diuresis, paralysis, mechanical ventilation, and physostigmine [12]. The patient recovered, although it is unclear as to what impact, if any, the use of extracorporeal elimination techniques had on his outcome. Therefore, except for the supportive treatment of acute renal failure, there are insufficient data to recommend hemodialysis and/or hemoperfusion in the treatment of water hemlock poisoning.

Special Populations

Water hemlock poisoning should be suspected in patients with vomiting and recurrent seizures with a history of wild plant ingestion, camping, or foraging. No populations have been reported either as more, or less, susceptible to water hemlock poisoning.

Indications for ICU Admission

- Any clinically affected patient with a history of water hemlock ingestion
- Any patient requiring anticonvulsants for treatment of seizures after water hemlock ingestion

Common Pitfalls

- Misdiagnosis as either anticholinergic poisoning (due to mydriasis) or cholinergic poisoning (due to increased secretions,

(continued)

nausea, vomiting, diarrhea, abdominal cramping, and seizures)

- Failure to aggressively manage the patient's airway and cardiorespiratory status
- Failure to use benzodiazepine and/or barbiturate anticonvulsant medications aggressively (e.g., lorazepam, phenobarbital)

Criteria for ICU Discharge

- Resolution of seizure activity without ongoing anticonvulsant administration
- Resolution of acidosis (if previously present)
- Normal mental status

Key Points

- Rapid identification of ingested plant (if possible)
- Early and aggressive management of airway and cardiopulmonary status
- Early and aggressive management of seizures
- Monitoring for rhabdomyolysis

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Part XXII

Natural Toxins: Scorpions

Julian White

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Scorpions are the second most globally important cause of envenoming, after snakebite and in some regions are more important than snakebite. Estimates have been made of the incidence of medically significant scorpion stings (Table 1) [1]. Scorpion sting is a significant problem principally in regions within the two tropics, notably in more arid areas (Fig. 1) [1]. All scorpions are venomous, with a sting structure in the “tail” (telson) [1–4]. However, only a minority of scorpion species are known to cause medically significant envenoming in humans, and virtually all of these are found in a single family, Buthidae, and cause systemic envenoming that can prove lethal, particularly in children [1–4]. There is an important outlier, the Iranian species *Hemiscorpius lepturus*, family Hemiscorpidae (formerly in family Scorpionidae), which has a very different clinical envenoming profile [5–7]. At least two other genera of scorpions have occasionally been reported as causing medically significant stings: *Heterometrus* spp. and *Nebo* spp., family Scorpionidae (*Nebo* is placed within family Diplocentridae by some taxonomists) [8–11]. With the exception of *Hemiscorpius* and a few other species, scorpion stings cause immediate pain, often severe, occasionally nonspecific systemic symptoms, and, in the case of medically important species, a variable syndrome of neuroexcitatory systemic envenoming. This latter group has generally been considered homogenous in clinical presentation, but as more detail is collected on the effect of stings by individual species, it is

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Table 1 Epidemiology of scorpion stings globally according to Chippaux and Goyffon [1]

Region	Estimated total stings	Estimated total deaths	Incidence per 100,000	Mortality per 100/000
North Africa	350,000	810	222.93	0.52
Sub-Saharan Africa	61,500	570	37.96	0.35
East/South Africa	79,000	245	94.05	0.29
Near and Middle East	146,500	796	77.15	0.42
Asia	250,000	645	19.76	0.05
Mexico	250,000	75	233.64	0.07
Amazonian basin	17,500	20	22.15	0.03
South America	36,000	110	16.36	0.05
Total	1.19 million	3271	52.59	0.14



Fig. 1 Map of approximate range of “scorpionism,” those areas where scorpion stings represent a significant problem, modified from Chippaux and Goyffon [1]. Those areas highlighted in light red represent regions where the

approximate incidence of stings is 1 to 100/100,000 population. Those areas in dark red approximate incidence of stings >100/100,000 population (Figure copyright © Julian White 2016)

becoming apparent that there are distinct envenoming syndromes associated with each group, sometimes even species, of scorpion.

Taxonomy

Scorpions are invertebrates, arthropods, with four pairs of legs, the distinctive chelicerae (front “pin-cers” or “claws”), multiple eyes, and the defining “tail” with the terminal segment containing the venom gland and sting [4]. As a general rule,

scorpions with bulky pincers (chelicerae) use these to help capture and subdue prey and rely less on potent venom, so that for humans, their sting, though generally painful, is less likely to result in significant envenoming [12]. Conversely, those scorpions with comparatively delicate pin-cers often rely more on potent venom, so are more commonly associated with significant en-venoming in humans [12].

There are approximately 18 families of scor-pions (Table 2), with approximately 2,000 described species at last count, with numerous

new species being described each year, reflecting a concerted effort by scorpion taxonomists to catch up with the backlog of undescribed, but known, species, although there is significant controversy surrounding scorpion taxonomy [13]. All medically important species fall within just four families, Buthidae, Hemiscorpiidae (Scorpionidae), Diplocentridae (subsumed within Scorpionidae by some taxonomists), and Scorpionidae, though many other species of scorpion can deliver distressing locally painful stings, but without significant systemic effects.

The Anatomy of Scorpions is Distinctive

Family Buthidae

While the vast majority of medically important scorpions are in family Buthidae, they are found in only some genera (Table 2), and there are numerous Buthid scorpions which have not been reported as causing medically significant stings (Fig. 2) [1, 2]. Some of the most medically important genera include:

Genus *Androctonus*

These scorpions, found predominantly in North Africa through to the Middle East, include several species of known medical significance (*A. australis*, *A. bicolor*, *A. crassicauda*, *A. mauritanicus*), and it is possible other *Androctonus* spp. may cause medically significant stings [1, 2]. Recent taxonomic studies have indicated that even within currently defined species, such as *A. australis* (Fig. 3), there may be several distinct populations, and the implications of this for venom toxicity and clinical profile are unclear [14]. In Morocco it appears *Androctonus* spp. are responsible for many, possibly a majority of medically significant stings, with 30–50,000 cases reported to the Moroccan Poison Information Center (PIC) annually, of which about 1,000 are severe, with 10–100 fatalities/year [1]. However, the Moroccan PIC data includes stings by other species, and among these, *Buthus occitanus* is of major significance. It should be noted that appropriate anti-scorpion antivenom is generally not available in Morocco, so it is unclear if ready availability of antivenom might reduce the number of fatalities. Past studies in Morocco reported that *A. mauritanicus* was the principal species involved and clinical

Table 2 An approximate higher-level taxonomy for scorpions

Family	Subfamily	Medically significant genera
Bothriuridae		–
Buthidae		<i>Androctonus</i> , <i>Buthus</i> , <i>Centruroides</i> , <i>Hottentotta</i> , <i>Leiurus</i> , <i>Mesobuthus</i> , <i>Odontobuthus</i> , <i>Parabuthus</i> , <i>Tityus</i>
Chactidae		–
Chaerilidae		–
Diplocentridae	Diplocentrinae	–
	Nebinae	<i>Nebo</i>
Euscorpiidae		–
Hemiscorpiidae		<i>Hemiscorpius</i>
Heteroscorpionidae		–
Iuridae		–
Liochelidae		–
Microcharmidae		–
Pseudochactidae		–
Scorpionidae		<i>Heterometrus</i>
Scorpiopidae		–
Superstitioniidae		–
Urodacidae		–
Vaejovidae		–

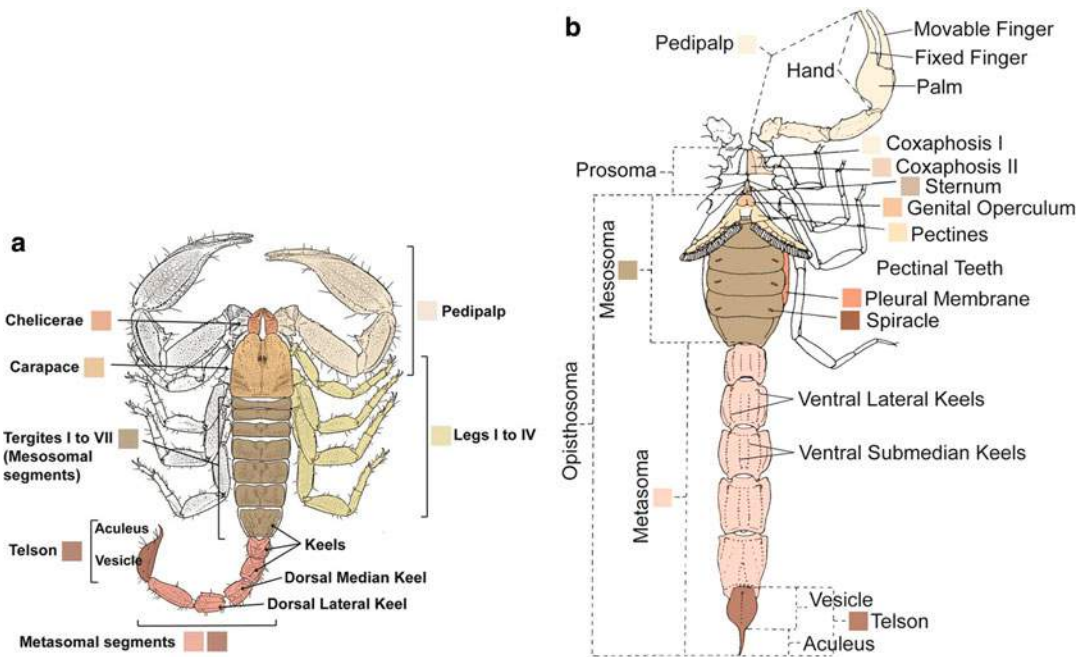


Fig. 2 Diagrammatic representation of some principal morphological features of scorpions of taxonomic relevance. (a) shows the dorsal (*upper*) side of the scorpion. (b) shows the ventral (*underside*) of the scorpion (Figures copyright © Julian White 2016)

Fig. 3 *Androctonus australis* from North Africa (Figure copyright © Julian White 2016)



improvement was noted with specific antivenom treatment, compared to patients not given antivenom, but in a nonclinical trial study [15, 16]. In Algeria *A. australis* is reported to cause 70% of medically significant stings [17]. In Libya *A. australis*, *A. bicolor*, and *A. amoreuxi* all occur, but it is unclear if all cause medically significant stings [18]. In Saudi Arabia *A. crassicauda*,

together with *Leiurus quinquestriatus*, is considered the most medically important scorpion [19]. In Turkey *A. crassicauda* is responsible for most medically significant scorpion stings, >50% in one series [20]. In Iran *A. crassicauda* is considered of major medical significance, second only to *Hemiscorpius lepturus* in severity and lethal potential [21].

Genus *Buthus*

At least *Buthus (occitanus) tunetatus* and *B. occitanus* (Fig. 4) may cause medically significant stings [15, 16, 22, 23]. The latter species, widely distributed in parts of Mediterranean Europe and North Africa, appears to have distinct differences in venom and clinical severity within the geographic range [1, 24]. While most stings may be painful, significant or severe systemic envenoming appears largely restricted to some North African populations such as those in Morocco.

Genus *Centruroides*

It is likely many species of *Centruroides* scorpions may cause medically significant stings, particularly in children, though only a limited range

of species are clearly hazardous (*C. sculpturatus* (Fig. 5), *C. noxius*, *C. suffusus*, *C. infamatus*, *C. limpidus*) [1–3, 25–27].

Genus *Hottentotta*

These scorpions range from Africa to the Indian subcontinent and include at least several species of major medical significance (*H. alticola*, *H. hottentotta*, *H. tamulus* (note *H. tamulus* was previously named *Mesobuthus tamulus*)) [1, 2, 28]. The taxonomy of this group of scorpions has been the subject of revision [29]. While the medical importance of stings in Africa appears to be minor, in the Indian subcontinent *H. tamulus* is arguably the most medically important Indian scorpion [1, 28, 30].

Genus *Leiurus*

Possibly all *Leiurus* spp. scorpions are medically important, not just the well-recognized and feared *L. quinquestriatus* (Fig. 6) [1, 2, 31]. While principally recognized from North Africa through to the Middle East, it is also reported as present and causing major envenoming in sub-Saharan Africa [31]. While the majority of stings are non-life threatening, in children severe and potentially fatal envenoming can occur and is occasionally reported in adults [1, 31–34]. In at least part of the range of *L. quinquestriatus*, it is reported to commonly cause acute pancreatitis in children [35].

Genus *Mesobuthus*

The medical importance of *Mesobuthus* spp. scorpions is less clear since the known important



Fig. 4 *Buthus occitanus* from North Africa (Figure copyright © Julian White 2016)

Fig. 5 *Centruroides sculpturatus* from Arizona, North America (Figure copyright © Julian White 2016)



Fig. 6 *Leiurus quinquestriatus* from the Middle East
(Figure copyright © Julian White 2016)



species, *M. tamulus*, was shifted to genus *Hottentotta*, as *H. tamulus* [1, 28–30].

Genus *Odontobuthus*

The medical importance of this genus and specifically *O. doriae* remains unclear, but limited clinical case experience in Iran indicates this species can cause, in addition to moderate to marked local pain, some systemic effects including tachycardia and pulmonary edema [21].

Genus *Parabuthus*

These sub-Saharan African scorpions include several species of medical significance (*P. transvaalicus*, *P. granulatus*, possibly *P. liosoma*, *P. mossambicensis*) (Fig. 7) [1, 2, 36–39].



Fig. 7 *Parabuthus transvaalicus* from Southern Africa
(Figure copyright © Julian White 2016)

Genus *Tityus*

Arguably the most medically important genus of South American scorpions, *Tityus*, includes a number of species causing major envenoming frequently in parts on the continent, notably, but not exclusively, Brazil (*Tityus serrulatus*, *T. bahiensis*, *T. pachyurus*, *T. zulianus*, *T. confluens*, *T. asthenes*, *T. breweri*, *T. stigmurus*, *T. obscurus*, *T. trivittatus*, *T. neoespartanus*, *T. trinitatis*) [1, 2, 40–54]. At least one species, *T. serrulatus*, is parthenogenetic (Fig. 8) [55].

Family Hemiscorpiidae

Genus *Hemiscorpius*

H. lepturus is clearly associated with medically important stings in southwestern Iran, where it is a leading cause of severe and lethal envenoming [1, 5–7, 21, 56–63]. It is also reported from Iraq, Yemen, and Pakistan, but it is unclear if it causes significant human envenoming in these locations. As mentioned earlier, the envenoming profile is



Fig. 8 *Tityus serrulatus* from Brazil, South America (Figure copyright © Julian White 2016)

very distinct from that caused by Buthid scorpions and is more closely clinically aligned with the necrotic arachnidism resulting from bites by brown recluse spiders, *Loxosceles* spp. [64].

Family Scorpionidae

Genus *Nebo*

Nebo hierichonticus has been reported to cause medically significant envenoming, more closely related to *Hemiscorpius lepturus* envenoming than Buthid-type envenoming, but few case reports are available to properly define the envenoming syndrome, and the epidemiologic importance of these scorpions remains uncertain [8]. A single case report documented intracranial and retinal hemorrhages in a child, which resolved without residual deficit [11].

The medical significance of stings by the widely distributed Asian scorpion genus *Heterometrus* remains unclear [8], though venom studies indicate at least some species have neurotoxic venoms (*H. longimanus*, *H. spinifer*; direct agonist actions on postjunctional muscarinic M3 cholinergic receptors and alpha-adrenoceptors) [65]. However, there is no clear evidence to verify any species causing medically significant stings.

Scorpion Venoms

Venom research into scorpions has concentrated on Buthid venoms which have proved a rich source of highly potent and often very specific ion channel toxins, particularly potassium channel toxins [3, 4]. These diverse small peptide toxins can target just a few, sometimes just one type of ion channel and so have proven instrumental in understanding the molecular basis of neural signaling pathways [4, 66, 67]. Scorpion toxins are divided into two broad classes of short chain peptides by some authors [4]:

1. The “long toxins,” with about 60 AA, target principally Na^+ channels and are considered as dominant in causing clinical envenoming in humans and divided into two subgroups. Alpha-type toxins found principally in Paleotropical species inhibit the inactivation phase of the nerve action potential, binding to site 3 on the Na^+ channel. Beta-type toxins are found in Neotropical species and reduce the excitability threshold of excitable cell membranes acting at site 4 of the Na^+ channel. For the most medically important scorpions of family Buthidae, usually only one type of long toxin is found, alpha or beta.
2. The “short toxins,” with about 30–40 AA, target principally K^+ or Cl^+ channels and are often present in only small quantities in scorpion venom. They occur across all types of scorpions. The K^+ channel short toxins can be subdivided into voltage-dependent and ligand-dependent types, and all have 3–4 disulfide bridges with a CSab motif and are of most importance as pharmacologic tools. They are generally nontoxic in mammals, except if injected intracerebrally.

In contrast to snake venoms, most scorpion venoms and specifically Buthid venoms are richly endowed with polypeptide toxins, but generally have few or no enzymatic toxins [4].

The toxins involved in the local necrotic and systemic hemolytic and organ destructive effects

of *Hemiscorpius lepturus* venom have been less well defined, in part because this species has a very limited geographic range, mostly in western Iran, and venom may be less easy to obtain for study. In vivo studies of whole venom in mice indicated it is highly cytotoxic, damaging the myocardium and renal tubules by 3 h postinjection, followed by intestinal damage by 6 h, with elevated creatine kinase and lactate dehydrogenase, but no observed effects on the lungs or liver [68]. The venom can induce the immune system to produce interleukin-12 [69]. Envenoming is associated with ADAMTS13 deficiency and ADAMTS13 autoantibody in human cases, and it has been suggested that this may play a role in venom-induced coagulopathy and development of both DIC- and an HUS-like syndrome [70]. The role of a sphingomyelinase-D-like toxin, Heminecrolysin, has been emphasized in some studies, interestingly given a similar toxin that is considered a major factor in recluse spider, *Loxosceles* spp., venom-induced local necrosis. Indeed there are significant similarities between *Hemiscorpius lepturus* envenoming and *Loxosceles* envenoming (loxoscelism) [71, 72]. Heminecrolysin has potent lysophospholipase-D activity, and this may play an important role in intravascular hemolysis in envenomed patients [73].

Scorpionidae scorpion toxins have also been examined for a limited range of species, notably from the two genera of possibly medically significant scorpions, *Nebo* and *Heterometrus* [65, 74–76]. The latter, in at least some species, contains a variety of components including peripheral muscarinic agonist toxins, ion channel toxins, phospholipase A₂ toxins, antibacterial toxins, and anti-osteoporosis agents [65, 76].

Clinical Presentation

Some key groups of scorpions will be covered in detail in subsequent chapters. As discussed earlier, most medically important scorpions cause predominantly neuroexcitatory envenoming, in addition to local pain [3, 4]. A summary of clinical features is listed in Table 2.

There are two broad types of clinical syndromes associated with scorpion envenoming:

1. Neuroexcitatory envenoming characterized by an initially painful sting, often severely painful, followed by development of systemic envenoming in patients where sufficient venom has been injected. Because of smaller body mass, children are more likely to develop severe or life-threatening envenoming. As with any other type of envenoming, not all patients will suffer significant envenoming, and in adults, for most scorpion species, envenoming is an unpleasant but time-limited and survivable illness. Neuroexcitatory envenoming by scorpions is predominantly a feature of selected Buthid (family Buthidae) scorpions. Many other scorpion species may cause significant, usually short-lived local pain, but without specific neuroexcitatory envenoming. Within this broad group there are clinical features specific for particular species groups, though delineation of such syndromes is generally rudimentary or incomplete in most cases at this time. Features common across many Buthid species groups include autonomic stimulation (a catecholamine-storm-like effect; hypertension, tachycardia, piloerection, sweating, salivation, etc.), cardiac dysfunction (reduced output, cardiac failure, raised troponins, cardiogenic pulmonary edema), neurologic effects (collapse, in some cases convulsions, coma, or athetoid movements of limbs or nystagmus), and nonspecific effects such as abdominal pain, headache, nausea, and vomiting [3, 4].
2. Dermonecrotic envenoming with systemic cytotoxic effects. This type of envenoming is rare for scorpion stings and is mostly seen with Iranian *Hemiscorpius lepturus* envenoming, particularly in the Khuzestan region of SW Iran [5–7, 21, 56–63]. The sting may not be painful and can go unnoticed, with later development of local skin necrosis and a systemic illness which, in severe cases, includes intravascular hemolysis, anemia, thrombocytopenia, disseminated intravascular coagulation, acute kidney injury (AKI) and renal failure, multi-organ failure, and death [5–7]. As for

neuroexcitatory scorpion envenoming, children are at highest risk [6]. In a study of envenomed children with hemolysis and hematuria, 23% had AKI, 6.7% developed DIC, and 10% developed a hemolytic uremic-like syndrome, and within this entire pediatric patient group, 98% had detectable anti-ADAMTS13 antibody, and 92% had decreased levels of ADAMTS13 [70]. *H. acanthocercus* has recently been reported as causing similar envenoming in Iran, with a confirmed fatality. It is unclear how many other *Hemiscorpius* spp. may be medically significant [63].

A group named the Scorpion Consensus Expert Group has proposed a unified clinical classification of scorpion envenoming, although this classification ignores dermonecrotic envenoming, concentrating on just neuroexcitatory envenoming, and the group is dominated by members from Morocco and France [77]. The “final proposed classification” of severity of scorpion stings, essentially a grading system, is presented in Table 3.

Treatment

The treatment of scorpion stings and of cases with significant envenoming remains controversial globally, with two distinctly different approaches advocated by groups of clinicians.

The intensive care and pharmacologic approach:

This approach is based on the assumption that antivenom, as a specific antidote, is ineffective in scorpion envenoming and that supportive care and standard pharmaceuticals are more effective. This view has been prominent across parts of North Africa, the Middle East, and the Indian subcontinent and is applicable only to classic neuroexcitatory scorpion envenoming; it has not been proposed for dermonecrotic envenoming [78–87].

The use of ICU and life-supportive measures such as inotropes, IV fluids, intubation, and ventilation, all where indicated, has been reported as effective in treating severe scorpion stings in both Israel and India and more

recently in parts of North Africa including Morocco, Algeria, and Tunisia [78–87]. The latter three countries, at least, had previously relied on use of antivenom, and it is unclear the validity of studies suggesting antivenom was less effective [84–86]. In India the advent of a specific scorpion antivenom has seemingly modified this approach, so that antivenom is now the preferred treatment in most centers [88–93].

The antivenom-centric approach:

Globally this is the predominant preferred treatment. There is ample published evidence that when used appropriately it results in better outcomes for patients and reduced mortality [17, 22, 23, 88–110]. In Mexico alone, with about 300,000 hospitalizations per year for scorpion sting, the advent of antivenom has dramatically reduced mortality in the prime risk group, children [95, 97].

The dose of antivenom will depend on the type of antivenom and the degree of envenoming, not the size of the patient. Scorpion venoms can rapidly distribute throughout the body, and systemic envenoming can develop rapidly; therefore antivenom should be given very early to have maximum benefit, with significant decreasing value as the time from sting to administration increases [17, 23, 101, 104]. (Grade IIa recommendation) It is unclear at what point giving antivenom is no longer appropriate, but certainly after 24 h it is likely to be much less effective. Nevertheless, in a patient with life-threatening envenoming, where other treatment modalities are also proving of limited effectiveness, active consideration to giving appropriate antivenom at a high dose is appropriate.

As in any other situation where antivenom is used, there is a risk of adverse reactions, and appropriate precautions should be taken, including having adrenaline (epinephrine) drawn up ready to give, if required, plus having resuscitation equipment immediately to hand.

It is important to note that for dermonecrotic scorpion envenoming by *Hemiscorpius lepturus*,

Table 3 A grading system for neuroexcitatory scorpion envenoming proposed by the “Scorpion Consensus Expert Group” [77]

Class I: local manifestations	Class II: minor manifestations (non-life threatening)	Class III: severe manifestations (life threatening). Presence of at least one of the following signs
Bullous eruption Burning sensation Ecchymosis Erythema Hyperesthesia Itching Necrosis paresthesia Pain Purpura/petechia Swelling Tingling	Abdominal distension Agitation/restlessness/excitement Anisocoria Arthralgia Ataxia Confusion Convulsion Diarrhea Dry mouth Dystonia Encephalopathy Fasciculation Gastrointestinal hemorrhage Hematuria Headache Hypertension Hyperthermia Hypothermia Lacrimation Local muscular cramps Miosis Mydriasis Myoclonia Nausea Nystagmus Odynophagia Pallor Pancreatitis General paresthesia Priapism Prostration Ptosis Rhinorrhea Salivation Somnolence/lethargy/drowsiness Stridor Sweating Tachycardia Thirst Urinary retention Vomiting Wheezing	Cardiogenic failure Hypotension Ventricular arrhythmia Bradycardia Cardiovascular collapse Respiratory failure Cyanosis Dyspnea Pulmonary edema Neurological failure Glasgow score ≤ 6 (in absence of sedation) Paralysis

antivenom is the current cornerstone of treatment, and there is no apparent dissent from its use in patients with this form of envenoming [21, 56–60]. The previously discussed non-antivenom approach to treatment of scorpion stings is entirely inappropriate for this form of envenoming. Studies have

demonstrated effectiveness of the antivenom in an in vivo rat model, even when administered 2 h post-venom [56]. Experimentally, a camelid nanobody antibody fragment-based antidote has been successfully developed against *Hemiscorpius* venom, but the role of this in future clinical use is untested [111].

Scorpion Antivenoms

A number of antivenoms against particular scorpion venoms are produced in South and Central America, Africa, the Middle East, Europe, and India [112]. In a number of regions/countries, Mexico being a good example, the introduction of scorpion antivenom has been associated with a dramatic improvement in outcomes [3, 27]. However, in certain regions and countries, there has been a move away from antivenom as a treatment choice, and the literature is replete with arguments in favor, or against, the use of antivenom, as noted earlier [17, 22, 78–80, 84–86, 98, 101, 103–105].

However, the availability of an effective antivenom may not equate with advocacy for routine use in envenomed patients because other factors, notably cost, may negatively influence the cost/benefit equation, a situation recently discussed in relation to treating scorpion envenoming in the USA [110].

Non-antivenom treatments

As noted earlier, non-antivenom treatment of scorpion stings has been advocated by a number of groups, mainly in North Africa, through the Middle East, to India, but in at least some of these places, notably India, now antivenom is available, the same authors who earlier advocated non-antivenom treatment now advocate use of antivenom [78–93]. This needs to be considered when perusing the often confusing literature on management of scorpion envenoming.

However, it is clear that treatments such as the use of prazosin can be effective in managing scorpion envenoming and should be considered when antivenom is not readily available [87–92]. Equally, such pharmacologic approaches may have a useful adjunctive role in treatment.

Conclusion

Scorpion stings are an important cause of injury from venomous animals globally and represent the second most important impact, after snakebite.

In some regions scorpion sting is more important than snakebite in impact on the health system. Only a small minority of scorpions can cause significant envenoming, and most of these are Buthid scorpions causing systemic and potentially lethal neuroexcitatory envenoming, in addition to marked local pain. An important outlier is the Iranian scorpion, *Hemiscorpius lepturus*, which causes delayed local necrosis and a potentially fatal cellulolytic systemic syndrome of hemolysis, DIC, and multi-organ failure, similar to loxoscelism caused by recluse spiders. Despite ongoing controversy, the available evidence, globally, favors the use of specific antivenom as the most effective treatment for systemic scorpion envenoming, but this is most effective when given early.

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Scorpions are arthropods with a hard exoskeleton, two anterior pinching claws, and a tail ending with a bulbous enlargement. The poison gland and the stinger are located at the distal part of the tail. The tail is long and able to arch over the head, allowing the stinger to hit the prey grasped between the claws [1]. Scorpions are among the oldest creatures on earth. Their habitat is warm and arid areas, as reflected in their first mentioning in the Bible: “He led you through the vast and dreadful desert, that thirsty and waterless land, with venomous snakes and scorpions” [2]. The scorpion is a nocturnal animal that hibernates in winter and is active in the warm seasons [3].

Epidemiology

Scorpion sting is common and endemic in various regions. Because most envenomations occur in developing countries, where regular reporting systems often are lacking, data on scorpion stings in several countries are based on estimates. High fatality rates were reported from scorpion envenomation from Saudi Arabia, Israel, Tunisia, Egypt, and Iran in the 1960s and 1970s. In recent years, there has been a marked reduction in mortality, however, owing to the improvement in supportive care and increased availability of antivenom therapy.

In a report by Chippaux and Goyffon from 2008, the estimated annual number of scorpion stings exceeded 1.2 million globally, with more

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Table 1 Scorpion envenomation by species, regions, and characteristic toxicity

Scorpion species	Geographic region	Cardio-toxicity	Neuro-toxicity	Hemolysis DIC, renal failure cytotoxicity	Reference
<i>Leiurus quinquestriatus</i>	Middle East, Turkey	+++	++		[14–20]
<i>Androctonus crassicauda</i> , <i>A. australis</i> , <i>A. mauretanicus</i>	Middle East and North Africa, Turkey, Iran	+++	++		[5–11, 20, 24, 27]
<i>Buthus occitanus</i>	North Africa	+++	+		[6]
<i>Hemiscorpius lepturus</i>	Iran, Iraq	+	+	++	[23, 25–29]

Fig. 1 The scorpion *Leiurus quinquestriatus*



than 3,250 deaths (0.27%). Middle Eastern and North African scorpion stings accounted for 42% of the global sting burden and a half of the fatalities. The number of scorpion stings in the Middle East and North Africa was estimated at 146,500 and 350,000, respectively [4]. The case-fatality rates were estimated at 0.42% and 0.52%, respectively, but these estimates are imprecise due to incomplete information.

Scorpion species of medical importance in the Middle East and Africa have been mainly reported from Tunisia, Morocco, Egypt, Israel, Saudi Arabia, Turkey, and Iran, though likely occur across all countries in North Africa and the Middle East [4–28]. Some of the main venomous scorpions, their geographic distribution, and target organ toxicities are listed in Table 1.

The main offending toxic scorpion in the Middle East, *Leiurus quinquestriatus* is illustrated in Fig. 1.

Some of the major clinical series of scorpion envenomations reported from Middle East and North African countries are listed in Table 2.

Biochemistry and Pathophysiology of Scorpion Envenomation

Scorpion venom is a complex mixture of mucopolysaccharides, hyaluronidase, serotonin, histamine, protease inhibitors, histamine releasers, neurotoxins, and approximately 70 polypeptides. Despite species differences, there are some similarities in venom composition; this explains some similarities among clinical manifestations in envenomation sustained from scorpion stings from different geographic locations [30].

Scorpion venom increases neuronal Na^+ influx by blocking inactivation of the Na^+ channel, resulting in increased duration and amplitude of the neuron action potential (Fig. 2). Consequently, a voltage-gated channel opening is enhanced by increased Ca^{2+} conductance at presynaptic nerve fibers, with increased release of neurotransmitters, including acetylcholine [31, 32]. The clinical effects of this enhanced neural impulse

Table 2 Reports on scorpion envenomation by regions, study population, setting, and case fatality rates

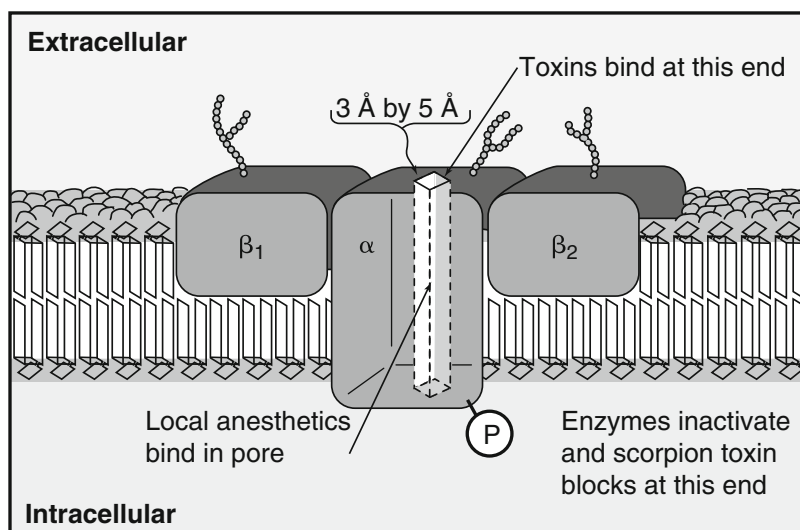
First author; region; reference; years	Setting and sample size	Case fatality rate	Comment
Goyffon [5], Tunisia 1977	Hospital, a few were admitted; $n = 717$	0.35%	All fatalities <15 year old
Abroug [7], Tunisia 1994–1995	Hospital, controlled study $n = 825$; age > 10 year old	0.24%	Only 18% had systemic envenomation
Bouaziz [9], Tunisia 1990–2002	ICU, $n = 951$; 72% < 16 year old	7.5%	81% had severe envenomation
Ghalim [11], Morocco 1997	Prospective, hospitals $n = 275$;	Not reported	10% has systemic envenomation
Farghly [12], Egypt 1994–1995	Prospective, hospital $n = 302$; 78% < 18 year old	8%	19% with congestive heart failure
Mohamad [13], Egypt 2012	Retrospective, hospital: $n = 111$; <16 year	18%	53% had severe systemic envenomation
Amitai [14], Israel 1977–1982	Retrospective, hospital; $n = 51$; <13 year	3.9%	29% had severe systemic envenomation
Sofer [15], Israel; 1985–1992	Retrospective, historical control; 104 children in PICU, 52 with AV	1.9%	Treatment group 1985–9 controls in 1989–92 Time of AV $M = 1.56$ h after sting
el-Amin [17] Saudi Arabia; 1988–1994	Retrospective; hospitalized children; $n = 780$	Mortality reduced from 4.8% to 0%	Antivenom was very effective
Bosnak [20], Turkey 2004–2007	Retrospective hospitalized PICU; <15 years; $n = 45$	4.4%	All patients received antivenom and prazosin
Konca [22], Turkey 2015	Retrospective; hospitalized <17 years; $n = 80$	1.2%	57% with severe envenomation
Pipelzadeh [23], Iran 1993–1997	Retrospective, hospitalized $N = 354$; 40% < 10 years	8.4%	90% of the fatalities got antivenom >12 h after the sting. Most of severe cases due to <i>H. lepturus</i> .
Shahbazzadeh [24], Iran 2003	Retrospective; emergency departments; $n = 12,150$	0.02%	74.5% were mild
Dehghani [27], Iran 2001–2009	Review; retrospective $n = 42,500$	0.46%	

transmission include muscle fasciculations, respiratory, gastric, and pancreatic hypersecretion, and, occasionally, bradycardia [33, 34]. Parasympathetic stimulation also may cause vascular dilation of the penile arterioles supplying the corpus cavernosus, resulting in priapism.

Scorpion venom also induces sympathetic stimulation with excessive adrenergic discharge [35]. The clinical effects of scorpion envenomation may include parasympathetic and sympathetic stimulation. The nonspecific signs of tachycardia, tachypnea, hypothermia or hyperthermia, and leukocytosis are explained by

cytokine release (particularly, interleukin-6 [64] and interleukin-1) and increased autonomic neurotransmission. In a canine model, injection of venom from the yellow scorpion (*Leiurus quinquestriatus*) resulted in an early stage of increased cardiac output and hypertension, followed by a second stage of reduction in cardiac output [37]. These two stages may reflect an initial catecholamine discharge with a subsequent stage of catecholamine depletion. The mechanism of cardiotoxicity in scorpion envenomation is multifactorial, beginning with catecholamine overstimulation, causing hypertension and a

Fig. 2 Schematic representation of the voltage-gated channel in a neuron showing the site of scorpion toxin binding. The channel is roughly a $0.3 \text{ nm} \times 0.5 \text{ nm}$ rectangular hole formed by four of the transmembrane helices within this subunit (From Brody TM, Garrison JC: Sites of action: Receptors. In Brody TM, Larner J, Minneman KP (eds): Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, p 18. With permission)



transient phase of increased contractility. There is a diminished systolic performance in addition to the catecholamine effect. The combination of myocardial ischemia, excessive catecholamine effect, cardiac arrhythmia, and increased oxygen demand may result in acute myocardial infarction [38].

Respiratory failure, caused by pulmonary edema, is a common complication of severe scorpion envenomation. The pulmonary edema has a cardiogenic and noncardiogenic component. The latter is thought to occur as a result of increased vascular permeability induced by release of vasoactive substances [38]. Central nervous system involvement is more frequent in children with severe envenomation. In the case of *L. quinquestriatus* sting, central nervous system effects are explained partially on the basis of hypertension, causing hypertensive encephalopathy, and may respond to antihypertensive therapy (prazosin) [39]. Central nervous system manifestations, such as agitation, hyperthermia, hypertonus, seizures, and coma [14, 38, 40], also occur, however, in the presence of normal blood pressure, suggesting a more direct central mechanism of toxicity [38]. Intraventricular injection of extremely small doses of toxic *L. quinquestriatus* venom to rabbits (1/500 to 1/100 of the intravenous lethal dose) caused complex neurotoxicity with restlessness, tremors, and convulsions [38].

Clinical Manifestations

The severity of scorpion envenomation varies with the scorpion's species, age, and size, but clinical severity tends to be greater in children. As a general rule, venomous scorpions with thin claws are more toxic than scorpions with thick claws. Clinical severity ranges from local pain to encephalopathy and potentially fatal cardiotoxicity.

In most cases, adults stung by scorpions experience only local symptoms and signs consisting of pain, erythema, pruritus, edema, and paresthesias [34, 41], occasionally involving the extremities and the perioral area [41]. Local skin necrosis has been documented only from stings of *Hemiscorpius lepturus* in Iran and may occasionally be severe and accompanied by hemolysis and complicated by renal failure and disseminated intravascular coagulopathy [23, 29]. This is a unique and quite atypical form of scorpion envenoming, not seen following stings by other medically important scorpions, which can broadly be characterized as neuroexcitatory, as opposed to the dermonecrotic and hemolytic venom of *Hemiscorpius lepturus*.

For the numerous neuroexcitatory scorpion species, systemic envenoming reflects stimulation or depression of the central nervous system and stimulation of the sympathetic, parasympathetic, and

skeletal motor nervous systems. Skeletal motor and parasympathetic stimulation is manifest mainly as tongue and muscle fasciculation, gastric and pancreatic hypersecretion, and occasionally bradycardia [14, 33, 42]. Salivation, abdominal pain, nausea, and vomiting are common and may be attributed to stimulation of salivary glands and to pancreatitis [42]. Parasympathetic stimulation also may cause priapism, even in young boys [14, 43].

In the cardiovascular system, the increased sympathetic tone prevails, as reflected by the high incidence of tachycardia and hypertension (72% and 58%) and the much lower incidence of bradycardia and hypotension (14% and 5%) in victims of scorpion envenomation [34]. In a report of 386 children with scorpion stings from Saudi Arabia, tachycardia occurred in 32% of children and bradycardia in 0.77% [43].

Most scorpions with the potential to cause human envenomation in the Middle East and North Africa exert cardiotoxicity and neuroexcitatory neurotoxicity (see Table 1). A grading system for scorpion envenomation has been developed in Tunisia, consisting of three classes. This grading system has been further developed by a Consensus Group of experts in 2011, for the purpose of facilitating development of international clinical studies.

The three classes are: Class 1—local manifestations; Class 2—minor manifestations (non-life-threatening), and Class 3—severe manifestations (life-threatening) [44]. The details of this classification with the specific symptoms are specified in Table 3.

A simplified grading system, based on clinical grade and focused on treatment, has been published by Isbister and Bawaskar (Table 4), though presumably largely based on experience with scorpion sting in India [45].

Envenomation by the main venomous scorpion species in North Africa and the Middle East (*L. quinquestriatus* and *Androctonus crassicauda*) and India (*Hottentotta tamulus*) has a similar clinical course. Effects of mild envenomation are agitation, tachycardia, and sweating. In more severe cases, particularly in young children, additional symptoms include vomiting, abdominal

pain, salivation, dehydration, priapism, extreme agitation, generalized erythema, muscle rigidity and twitching, tremor, seizures, coma, pupillary changes (miosis, mydriasis, or anisocoria), hyperthermia, tachyarrhythmia or occasionally bradyarrhythmia and A-V Block, hypertension (less often hypotension), cardiac and respiratory failure, and death [14, 34, 43]. Idiopathic dilated cardiomyopathy was found to be eight times more frequent in patients with a past history of scorpion sting in India, despite apparent complete recovery from the acute envenomation [46].

Diagnosis and Laboratory Findings

The diagnosis of scorpion envenomation is made by the characteristic clinical presentation of the patient in an area in which scorpions are endemic. Occasionally the scorpion is seen, or the sting may be witnessed, though in nearly all cases the initial pain of the sting helps assure the diagnosis. The exception is dermonecrotic envenoming by *Hemiscorpius lepturus* in Iran and adjacent countries, where the sting may be initially painless and unnoticed, with later development of local skin damage and, in more severe cases, systemic envenoming characterized by intravascular hemolysis, DIC, shock, and sometimes multiorgan failure.

Laboratory abnormalities have been reported mainly from scorpion stings from the Middle East, North Africa, and India. Hyperglycemia and leukocytosis are nonspecific but common [14, 20, 47]. Cardiac ischemia is expressed by transient elevation of cardiac enzymes [38, 48] and electrocardiograms with depressed or elevated ST segment, Q waves in leads I and aVL, prolonged QT_c intervals, and peaked T waves [38]. Cardiac dysfunction is evidenced on echocardiography as diminished global wall motion with decreased systolic left ventricular performance and diminished ejection fraction [49–51]. Left ventricular dysfunction also has been shown by cardiac radionuclide scan [50]. Transient elevation of pancreatic enzymes has been reported [42]. For *Hemiscorpius lepturus* stings in Iran there may be laboratory evidence of hemolysis, coagulopathy, renal failure, and other secondary effects.

Table 3 Modified proposed classification of scorpion stings

Local manifestations	Minor manifestations (non-life-threatening)		Severe manifestations (life threatening) Presence of at least one of the following signs
Pain	Agitation/restlessness/excitement	Priapism	Cardiogenic failure
Local paresthesia	Altered mental status	Pupillary abnormalities	GCS score ≥ 6 (in absence of sedation)
Rash	Arthralgia	Rhinorrhea	Paralysis
	Ataxia	Salivation	Respiratory failure
	Dry mouth	Seizures	Paralysis
	Dystonia	Stridor	
	Fasciculation	Sweating	
	Gastrointestinal symptoms	Tachycardia	
	Generalized paresthesias	Temperature abnormalities	
	Hematuria	Urinary retention	
	Headache	Wheezing	
	Hypertension		
	Lacrimation		
	Muscular cramps		
	Myoclonia		
	Odynophagia		
	Pallor		
	Pancreatitis		

Modified from Khattabi et al. [44]

Treatment

Numerous treatments have been recommended for scorpion envenomation, including antivenom, prazosin, inotropic agents, atropine, vasodilators, and benzodiazepines (Table 4). However, the evidence for the effectiveness of most treatments is variable, and types of treatment appear to vary according to region [45].

As a general approach, the following recommendations can be made:

First aid and prehospital treatment:

1. Cleansing the sting site with alcohol or soap.
2. Reducing the spread of the venom before arriving at a medical facility is crucial. Several reports emphasize the critical effect on the outcome of delay in time of arrival of the victim to medical facilities [11, 15, 38]. This is explained by the rapid spread of the venom [52]. To reduce

lymphatic spread of the venom, immobilize the stung limb (Grade III recommendation).

3. Application of an elastic bandage or gauze bandage with light pressure on the sting site may reduce the spread of the venom. This “pressure-immobilization technique” is endorsed by the National Health and Medical Research Council of Australia to reduce lymphatic spread in toxic snake bites [53]. It is logical to also use such technique for venomous scorpions. Increased venom concentration at the sting site should not be a problem in envenomation by most scorpion species as local necrosis is rare with scorpion stings by most scorpion species. Applying this technique is not recommended in stings by *Hemiscorpius lepturus* in Iran and Iraq, which tends to cause local necrosis [23, 29]. Application of tourniquet, cauterization, or incision and drainage are contraindicated for all scorpion stings. An Australian study of

Table 4 Clinical grade and treatment of scorpion stings

Grade	Effects	Treatment
1	Local effects only	Analgesia, local anesthesia
2	Autonomic excitation	Antivenom, prazosin
	Agitation and anxiety	Benzodiazepines
3	Pulmonary edema	Admission to intensive care unit, noninvasive or mechanical ventilation, antivenom
	Hypotension and cardiogenic shock	Antivenom, dobutamine
	Severe neuromuscular excitation (associated with <i>Centruroides</i> species)	Antivenom, benzodiazepines
4	Multiorgan failure, including coma, seizures, and end-organ damage caused by hypotension	Supportive care, mechanical ventilation, inotropes (e.g., dobutamine), benzodiazepines

Adapted from Isbister and Bawaskar [45]

venomous snake bites without local necrosis in a rat model showed that local application of nifedipine, lidocaine, and NO releasing ointments markedly reduced the spread of venom from the sting site [53]. However, there are no published data for such treatments in humans.

4. Transport the victim to a medical facility as soon as possible, particularly when the victim is an infant or small child. If it is known or suspected that the scorpion is capable of envenoming humans, all victims of sting should be transported to a hospital or clinic.
5. When an elastic bandage has been applied, it should be removed under observation when the victim has arrived at a medical facility.
6. Analgesics (acetaminophen, ibuprofen) are recommended for pain relief [45]. Topical application of lidocaine may also be helpful.
7. In most cases, adults stung by scorpions do not develop a systemic envenomation syndrome. Close observation outside of a health care facility for 2–6 h is sufficient in these cases. In

regions where cardiotoxic scorpions are endemic (see Table 1), an electrocardiogram should be performed.

Hospital admission and in-hospital treatment:

1. A clinical score predicting the need for hospitalization in scorpion envenomation was developed by Nouria et al., from Tunisia, based on a prospective study in 868 patients with scorpion envenomation with a validation group of 435 patients. The following variables were strong predictors for admission: priapism, vomiting, hypertension (>160 mmHg), administration of corticosteroids before arrival to emergency department, delay (>30 min) to emergency department arrival, hyperthermia, and tachycardia [8].
2. In cases of systemic envenomation, the principles of management are observation, cardiac monitoring, supportive treatment with intravenous fluids and electrolytes, sedatives and analgesics, and cautious use of cardiovascular agents, including vasodilators, adrenergic antagonists, or calcium channel blockers, in the hypertensive phase. Sofer and colleagues [15] advocated the use of hydralazine or nifedipine. Bawaskar and Bawaskar [36] found prazosin to be safer and more effective than nifedipine in their patients stung by the Indian scorpion, *Hottentotta tamulus* and recommended using prazosin alone in patients with hypertension and tachycardia from scorpion sting. In a controlled study, these authors reported lower complication rates (no fatalities) in patients treated with prazosin compared with patients treated with nifedipine or supportive care alone (fatality rates of 35% and 25%, respectively). However, subsequent studies by these authors have indicated that antivenom is the most effective treatment.
3. Elatrous and coworkers from Tunisia reported the efficacy of dobutamine infusion at 7–20 µg/kg/min in 19 patients with severe scorpion envenomation and acute pulmonary edema, of whom ten also had severe hypotension. In these patients, cardiac output, blood pressure, tissue oxygenation, and clinical outcome improved

significantly, but there were two fatalities [54]. Antiarrhythmics, such as lidocaine, may be required [38]. In an experimental envenomation by *L. quinquestriatus* in rabbits, lidocaine infusion significantly attenuated venom-invoked effects and reduced mortality [55].

Use of sedatives to reduce anxiety and agitation has an important role in the treatment of symptomatic patients. Benzodiazepines are used for sedation [45]. At the Hadassah University Hospital, Mt. Scopus, Jerusalem, we have used diazepam or midazolam at doses titrated to control agitation and anxiety in children with scorpion envenomation with good response. Steroids have no role in the treatment of scorpion envenomation [56].

Antivenom Therapy

Specific antivenom therapy has been used for several decades. Most antivenom preparations consist of animal serum (mainly equine) and are immunoglobulin F(ab)₂ fragments. The types of scorpion antivenom used in each country were summarized by Bahloul et al. in 2013 [47]. Those relevant to Middle Eastern and North African appear in Table 5.

The antivenom currently used in Israel is SCORPIFAV, a polyvalent scorpion antivenom against *A. australis*, *B. occitanus*, and *L. quinquestriatus*, produced by Sanofi-Pasteur (France).

Numerous reports exist on the clinical use of specific antivenom preparations from Middle Eastern and North African countries [7, 11, 15–17, 38, 43, 57].

Due to ethical limitations, most studies are retrospective, observational, or historical controls. There are only a few prospective, randomized, controlled studies [6, 7]. Reports on antivenom therapy are summarized in Table 6. Of the seven reports summarized there, five concluded that antivenom is effective [11, 16, 17, 38, 57], two concluded that antivenom is not effective [7, 15], and one gave data only on safety and did not report efficacy [43]. The two studies reporting a

Table 5 The types of scorpion antivenom used in Middle Eastern and North African countries (Adapted from Bahloul et al. [47])

Antivenom	Species	Country
Polyvalent scorpion antivenom	<i>Androctonus australis garzonii</i> , <i>B. occitanus tunetanus</i> , and <i>Tityus serrulatus</i>	Morocco
Purified polyvalent anti-scorpion serum (equine)	<i>Leiurus quinquestriatus</i> <i>Androctonus amoreuxi</i> <i>Androctonus crassicauda</i> <i>Androctonus aeneas</i> <i>Androctonus australis</i> <i>Scorpio marus palmatus</i> <i>Buthus occitanus</i>	Egypt
Scorpion antivenom (Pasteur Institute of Algeria)	<i>Androctonus australis</i>	Algeria
Bivalent scorpion antivenom (Institut Pasteur, Tunis, Tunisia)	<i>A. australis</i> and <i>B. occitanus</i>	Tunisia
Polyvalent scorpion antivenom	<i>Leiurus quinquestriatus</i> , <i>Androctonus crassicauda</i> , <i>Buthus arenicola</i> , <i>Butus mimax</i> , <i>Buthus occitanus</i> , <i>Leiurus quinquestriatus hebreus</i> , and <i>A. amoreuxi</i>	Saudi Arabia
Monovalent scorpion antivenom	<i>Leiurus quinquestriatus</i>	Israel

lack of antivenom efficacy were controlled, and one was randomized controlled. However, the main limitation was that 82% of the patients had only local signs of envenomation (grade 1) and only 1% of patients in both groups had life-threatening envenomation [7, 57]. A meta-analysis of controlled studies by Abroug et al. concluded that antivenom for scorpion envenomation is ineffective [58]. However, the main weight of randomized controlled studies in this study was given to the original study of these authors, which had the largest number of patients

Table 6 Published studies on antivenom efficacy in scorpion envenomation in the Middle East and North Africa

Study; region; years; scorpion species	Study design; sample size	Antivenom type; dose; and route	Results and conclusion	Comment
Sofer et al. [15]; Israel; 1985–1992; <i>Leiurus quinquestriatus</i>	Retrospective, historical control; 104 children in PICU, 52 with AV	Specific AV, donkey's serum; 5–15 mL; IV	No effect; emphasis on supportive therapy	Treatment group in 1985–9; Controls in 1989–92 Time of AV $M = 1.56$ h after sting
Ismail [16, 38]; Saudi Arabia; 1991–1992; <i>Androctonus</i> , <i>Leiurus quinquestriatus</i>	Statewide, multicenter; 24,000 patients	Specific AV; ≥ 5 mL; IV	Mortality reduced from 4–6.8% to $<0.05\%$	Efficacy requires prompt IV infusion and large dose
el-Amin et al. [17]; Saudi Arabia; 1988–1994; <i>Leiurus quinquestriatus</i> , <i>Androctonus</i>	780 hospitalized children and children treated as outpatients	Specific AV; ≥ 5 mL; IV	Mortality reduced from 4.8% to 0%	Very effective
Gajre and Dammas [43]; Saudi Arabia; 1991–1995; <i>Leiurus quinquestriatus</i> , <i>Androctonus</i>	182 children treated, 90% symptomatic	Specific AV; 5 mL (10–20 mL for severe patients); IV	Efficacy not reported; adverse reactions in 13.7%, severe in 1%	Restrict AV use to patients with systemic envenomation
Abroug et al. [7]; Tunisia; 1994–1995; <i>Androctonus australis</i> , <i>Buthus occitanus</i>	Randomized, controlled; 825 patients >10 year old, 412 treated	Specific bivalent AV; 20 mL; IV	No effect; four (1%) developed anaphylactic reversible shock	The antivenom was not highly specific [57] 82% of patients had only local signs and only 1% of patients had life-threatening envenomation
Krifi et al. [6]; Tunisia; 1993–1997; <i>Androctonus australis</i> , <i>Buthus occitanus</i>	Randomized, controlled; 147 severely envenomed children, 1–2 doses IV or IM or no AV	Specific bivalent AV, Pasteur Institute, Tunisia; 5–30 mL; IV	AV given IV – effective; IM – not effective	
Ghalim et al. [11]; Morocco; 1997; <i>Androctonus mauretanicus</i> , <i>Buthus occitanus</i>	Retrospective; 275 patients	Specific bivalent AV, Pasteur Institute, Tunisia; 2–10 mL; IV ^a	Effective	Prompt use and large dose important

AV antivenom, PICU pediatric intensive care unit

^aSome patients received 2–5 mL of antivenom, and some received 1 mL. In those who received the higher dose, there was a higher degree of circulating venom depth

[7] and affected the overall result. In a recent review of scorpion envenomation by Isbister and Bawaskar, the authors conclude: “Although the evidence in favor of antivenom is heterogeneous, given the small sample size of the trials with positive results and the different scorpion species across studies, the reports, when taken together, suggest that administration of antivenom after a sting is of some benefit” [45].

Of note, antivenom for the scorpion *Centruroides sculpturatus* from Southern United States and for the Indian scorpion *Hottentotta tamalus* were shown to be effective in randomized controlled studies [45] (Grade I evidence).

Ismail [16, 38] from Saudi Arabia reported robust data on 24,000 patients with scorpion envenomation treated by a national protocol. Thousands of these patients were treated with

antivenom, with a reduction in the fatality rate from 4% to 6.8% to less than 0.05%. Among 780 children, the use of antivenom therapy resulted in reduction of mortality from 4.8% to 0% [17].

In Iran, there are trials to prepare a specific antivenom for envenomation by the scorpion *Hemiscorpius lepturus*, which so far were successful only in an animal model [59]. However, this antivenom is currently used in clinical practice in Iran.

Important points regarding the optimal use of antivenom can be inferred from these reports, as follows:

1. Because of regional variations in scorpion species and specific antivenom preparations, *always obtain the advice of local experts* (i.e., poison information centers, medical toxicologists, or treatment centers with expertise in the field of scorpion envenomation).
2. Reserve antivenom preparations for patients with systemic toxicity. A suggested guideline for treatment with antivenom is the appearance of two or more of the signs and symptoms of systemic envenomation listed in the box below or the occurrence of one of the following: arrhythmia, hypertension, hypotension, seizures, coma, and pulmonary edema (Grade II-2 evidence).
3. When indicated, give antivenom promptly after onset of systemic signs or symptoms. In the event of a rash appearing during antivenom administration, decrease the infusion rate, add intravenous antihistamine, and continue the antivenom infusion, with caution and standby intravenous epinephrine and airway management equipment.
4. Administer antivenom *intravenously only*. The intramuscular route is not effective, likely due to the slow absorption and distribution of the large antibody molecules from the intramuscular injection site [6].
5. The volume required depends on the preparation and the initial and subsequent responses to treatment but may vary from 6 to 10 mL in severe cases. Always consult with local experts about the proper preparation, dose, and precise instructions about how to administer the antivenom. The antivenom is diluted in 50 mL of normal saline and administered intravenously starting with a slow infusion rate and increasing gradually. Skin testing generally is not performed because when antivenom is deemed necessary, there should not be a further delay in its administration and there is no evidence indicating reliability of such testing but ample evidence of the potential hazard. The safety of specific scorpion antivenom (i.e., low likelihood of anaphylactic or anaphylactoid reaction) given in various geographic locations is considered to be generally satisfactory [14, 38]. This safety is related to the low protein content of the antivenom. Paradoxically, the theoretical likelihood of patients with severe envenomation developing an anaphylactoid reaction is lower than that of patients with mild envenomation because severe venom toxicity causes the release of massive amounts of catecholamines, inhibiting mast cell degranulation [60].
6. The dose should not vary with the age or weight of the patient because it should be directed at neutralizing a given amount of venom introduced by the scorpion into the patient's body. At the Hadassah Hospitals, we have used antivenom therapy to treat more than 50 children with systemic scorpion envenomation. In many instances, an impressive reversal of signs and symptoms was observed immediately after antivenom administration. This specific antivenom is the only one available in Israel; however, it has been reported also to be effective in the case of envenomation by another (nonhomologous) scorpion species, *A. crassicauda* [61]. The explanation of this effect is related to the similarity in venom composition between these two scorpion species.
7. Patients who receive antivenom should be followed at home for the next few days. If serum sickness occurs, antihistamines or a short course of oral steroids should be given according to the severity of symptoms [62].
8. Advances in supportive care and antivenom therapy have markedly improved the outcome of patients treated for scorpion envenomation.

Indications for ICU Admission in Neuroexcitatory Scorpion Envenomation

Infants and young children (<5 years old)

Anyone with systemic manifestations consisting of two or more of the following:

Cardiovascular: tachycardia/bradycardia, hypertension/hypotension, arrhythmia

Neurologic: agitation, lethargy, coma, tremor, hypertonicity, seizures, opisthoclonus, paresthesia (other than at the sting site)

Respiratory: tachypnea, respiratory distress, stridor, pulmonary edema

Dermatologic: sweating, flushed skin, “goose bumps”

Laboratory: electrocardiogram abnormalities, elevated myocardial enzymes, echocardiogram evidence of cardiac wall dysfunction (reduced contraction)

One of the following: arrhythmia, hypertension (new onset), hypotension, seizures, lethargy, coma, pulmonary edema, electrocardiogram or echocardiogram abnormalities, increased myocardial enzymes – CKMB, troponin

Criteria for ICU Discharge in Neuroexcitatory Scorpion Envenomation

Infants and young children (<5 years old) – lack of signs or symptoms of systemic envenomation for 6 h and normal electrocardiogram

Others – resolution of systemic manifestations of scorpion envenomation for 3 h and no new abnormalities on electrocardiogram

particularly compared to significant systemic envenoming, therefore pregnancy should not be considered a contraindication for antivenom treatment. As for poisoning by other toxins, indications for treatment should be guided by maternal clinical state.

Key Points in Scorpion Envenomation

1. Venomous scorpions exist in different regions, usually in warm climates, and are active in the warm season, particularly after dark.
2. Because of marked geographic variations in scorpion species and their toxicity, the clinician *always* must consult with local experts about treatment and administration of antivenom.
3. As a rule, venomous scorpions with thin claws are more toxic than scorpions with thick claws.
4. Young children are at greater risk for severe envenomation after a sting.
5. When antivenom is indicated, the dose should be similar in children and adults.
6. After being stung, it is helpful if the patient can catch or take a photo of the scorpion, for identification.
7. In contrast to bee stings, scorpions excrete only a small fraction of their venom in one sting and could cause severe toxicity immediately in repetitive stings [63].
8. After being stung, the patient should not run. Immobilization of the affected limb is important to slow venom distribution.
9. Incision and drainage at the site of the sting is contraindicated.

Special Populations

Pregnant Patients

Data are insufficient to make conclusions about the safety of antivenom administration in pregnant women. However, in general there is no evidence antivenom is harmful in pregnancy,

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Introduction

Scorpions are arthropods with a hard exoskeleton and eight legs. Cephalad to the body are two large pinchers, which the scorpion uses to grasp prey. Caudal to the body is the tail, which terminates in the telson. This last segment contains both a venom gland and a stinger (Fig. 1).

While there are hundreds of different species of scorpions, only a few are capable of causing clinically significant envenomations in humans. Most of the dangerous scorpions worldwide belong to the Buthidae family, which includes the genera *Leiurus* (the Middle East), *Buthus* and *Androctonus* (North Africa), *Mesobuthus* (Asia, especially India), and *Tityus* (South America). The genus *Centruroides* is found in parts of North and Central America [1]. In the United States, the only native scorpion capable of producing a severe or life-threatening envenomation is the bark scorpion (*Centruroides sculpturatus*), which was previously referred to as *C. exilicauda*, although more recent data suggests these are, in fact, two different species [2]. *Centruroides sculpturatus* is found almost exclusively in the American southwest and parts of Mexico. In the United States, it is mostly concentrated in Arizona, although the bark scorpion is also found in New Mexico and parts of Nevada, Texas, and California [3, 4]. Rarely, such scorpions have “hitchhiked” on airplanes, resulting in envenomations outside of their normal geographical distribution [5].

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Fig. 1 Bark scorpion, *Centruroides sculpturatus* (*exilicauda*). (a) Enlarged chela. (b) Enlarged vesicle showing a tubercle below the stinger. The body length including telson is 55 mm (From Ref. [37])

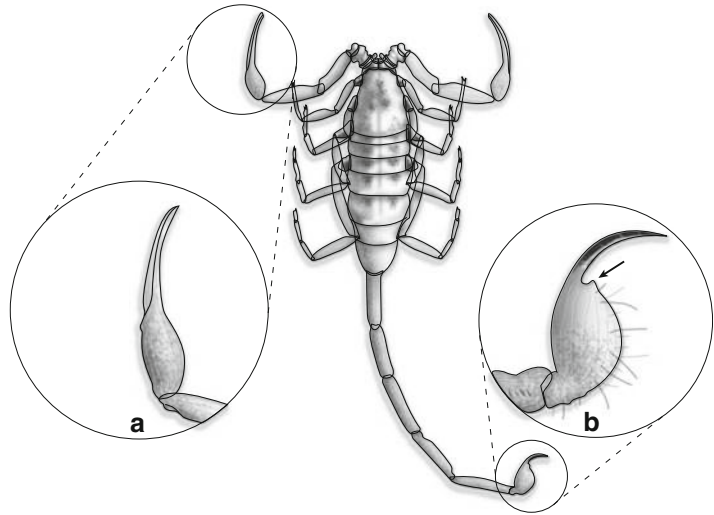


Fig. 2 Bark scorpion showing its long pedipalps and its unique tail

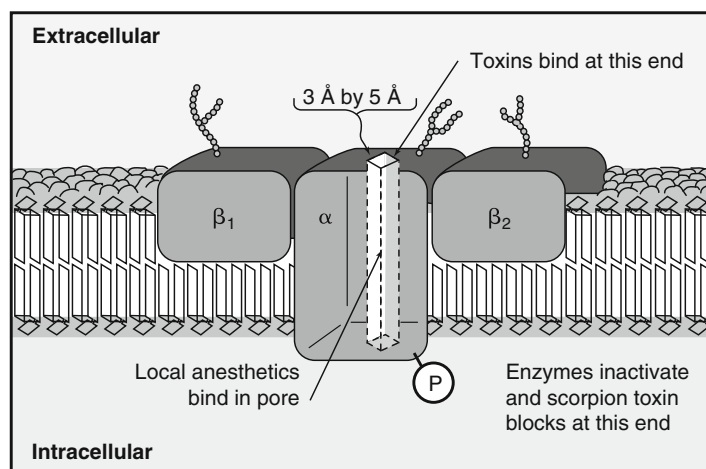


The bark scorpion is a small (mean length 6.5 cm with a range of 1–7 cm), tan/brown, nocturnal, non-burrowing animal which is capable of climbing vertically [3, 6, 7]. These animals reside both in rural and urban dwellings [7]. They prey on small lizards, insects, and arachnids. *Centruroides sculpturatus* can be distinguished from other scorpion species by its long pedipalps and its unique tail, whose terminal segment is rectangular, rather than square (Fig. 2).

While other species of *Centruroides* (e.g., *C. hentzi*, *C. gracilis*, *C. guanensis*, *C. vittatus*) and other genera (e.g., *Hadrurus* or *Vaejovis*) are present in the United States, stings by these scorpions are of little medical importance and rarely cause symptoms other than localized pain. Consequently, the rest of this chapter will focus exclusively on *C. sculpturatus*.

Historically, mortality following envenomations from *C. sculpturatus* was not uncommon.

Fig. 3 Schematic representation of the voltage-gated channel in a neuron showing the site of scorpion toxin binding. The channel is roughly a $0.3 \text{ nm} \times 0.5 \text{ nm}$ rectangular hole formed by four of the transmembrane helices within this subunit (From Ref. [38])



In the 1930s there were 40 deaths directly attributed to stings from the bark scorpion [8]. Deaths today, however, remain relatively rare. Despite accounting for more than 19,000 calls annually to US poison control centers, there were no reported fatalities in 2012 and only a single reported fatality in 2013. The declining mortality is largely attributed to both improved access to healthcare and improvements in supportive care [9].

The majority of envenomations occur in adults and require little intervention [4, 10]. Despite accounting for a smaller percentage of envenomated patients, pediatric patients are much more likely to become significantly ill and require critical care management [4].

Biochemistry and Clinical Pharmacology

Scorpion venom is a complex mixture of low molecular weight proteins, oligopeptidases, nucleotidases, lipids, mucoproteins, and amino acids [2, 11]. Among the various *Centruroides* species, there is a high degree of homology in the peptide sequence among the various toxins [12–14]. Mouse models demonstrate toxicity beginning at 1.12 mg/kg, with lethality consistently occurring at doses exceeding 3 mg/kg [2, 8]. Additional rodent studies have demonstrated

reduced time intervals between envenomation and mortality with subsequent envenomations. However, this time difference was not associated with changes in serum levels of antivenom antibodies [15].

Toxicokinetic studies have been performed utilizing the venom from *C. limpidus*, a scorpion indigenous to Mexico. Following subcutaneous injections in a rabbit model, the venom is distributed in a two-compartment model. The volume of distribution was 850 ml/kg, with the maximal plasma concentration occurring approximately 1 h postinjection. The toxic fraction of the venom had an α elimination half-life of 0.35 h and a terminal elimination half-life of 1.9 h [16]. Despite the relatively short half-life in animals, limited human data with *C. sculpturatus* venom indicates patients may remain symptomatic with detectable levels for at least 20 h post envenomation [17]. The venom is primarily renally eliminated.

Pathophysiology of Toxic Effects

In general, scorpion venom targets voltage-gated sodium or potassium channels [11, 18] (Figs. 3 and 4). *Centruroides sculpturatus* venom has been shown to inhibit ERG potassium channels [12, 19] and prevent inactivation of the voltage-gated sodium channels [20–24] (Fig. 5).

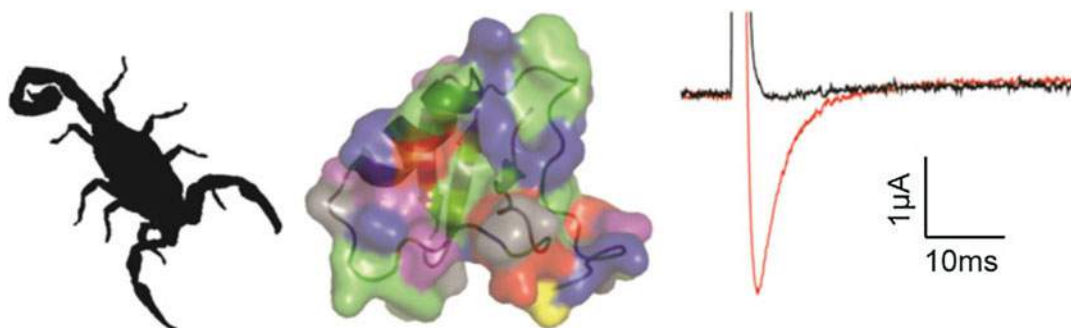


Fig. 4 β -scorpion toxins promote Nav channel opening. The β -scorpion toxin CssIV is found in the venom of the *Centruroides suffusus suffusus* scorpion (silhouette on the left), and amino acids important to toxin functionality have been identified in both the hydrophobic region and a ring of charged residues a (middle figure: protein backbone of the related β -scorpion toxin TsVII is shown together with the

electrostatic surface of the protein). At 1 μ M, CssIV opens rNav1.2a at voltages where the channel is normally closed. Current trace shown was evoked from a holding potential of -90 mV to a voltage of -40 mV when expressed in *Xenopus oocytes*. Black is control and red is after addition of 1 μ M CssIV (right) (From Ref. [39])

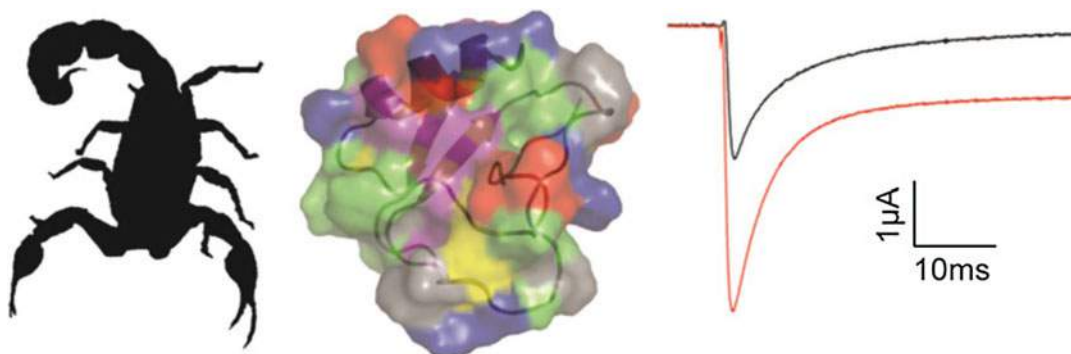


Fig. 5 α -scorpion toxins hamper Nav channel fast inactivation. The α -scorpion toxin AaHII is produced by the *Androctonus australis* Hector scorpion (silhouette on the left), and amino acids important to toxin functionality have been identified in both the hydrophobic patch as well as charged residues surrounding it (middle figure: protein

backbone is shown together with the electrostatic surface of the protein). At 100 nM, AaHII inhibits fast inactivation of rNav1.2a currents evoked from a holding potential of -90 mV to a voltage of -20 mV when expressed in *Xenopus oocytes*. Black is control and red is after addition of 100 nM AaHII (right) (From Ref. [39])

Consequently, there is an increase in neuronal sodium influx, resulting in prolonged duration and amplitude of the action potential. A study examining the effects of the venom of various species of *Centruroides*, although not specifically *C. sculpturatus*, demonstrated reduced sodium conductance, left shift in the voltage-dependent activation and induction or resurgent currents at negative voltages [25].

Clinical Presentation and Life-Threatening Complications

The most severe envenomations occur in young children, although high-grade envenomations occur in all ages [4]. Following an envenomation, symptoms generally develop within minutes to an hour and may progress rapidly [9, 10]. The clinical effects of scorpion envenomation form the

Table 1 Grading system for envenomations by *C. sculpturatus* (Adapted from Ref. [4])

Grade	Symptom
I	Local pain or paresthesias
II	Pain or paresthesias distal to the bite site
III	Either isolated cranial nerve dysfunction or diffuse somatic skeletal neuromuscular dysfunction
IV	Both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction

basis for our current grading system, which is shown in Table 1.

Most patients develop only minimal symptoms and are thereby classified as having a grade I or II envenomation. These symptoms include pain or paresthesias either at the sting site (grade I) or more diffusely throughout the envenomated extremity and body (grade II).

Most children with high-grade envenomations experience autonomic hyperactivity, including tachycardia, hypertension, and/or fever [9, 26]. Vomiting is relatively common, especially at the onset of toxicity [9]. Respiratory distress, including hypoxemia or stridor, is also frequently observed. The respiratory findings may result from the combination of asynchrony of the respiratory musculature, loss of tongue control, and increased salivation. This may be compounded by the respiratory depressant effects of opioid analgesics, especially with concurrent administration of benzodiazepines. Respiratory findings occur in approximately one-third of patients with severe envenomation [9, 10].

The presence of cranial nerve or neuromuscular dysfunction defines a high-grade (grade ≥ 3) envenomation. Cranial nerve findings can include opsoclonus, disconjugate gaze, hypersalivation, tongue fasciculations, slurred speech, and occasionally stridor. The somatic skeletal neuromuscular findings can include myoclonic jerking movements of the extremities, arching and twisting of the torso, general restlessness, agitation, and tremor. While the myoclonic jerks may resemble seizure-like activity, they are typically asymmetric, the patient is awake and alert, and epileptic findings are not present on EEG.

Cutaneous findings are notably absent from stings by *C. sculpturatus*, although a positive tap test, performed by tapping the examiner’s fingers over the sting site to elicit an increase in pain, may be noted. In addition, unlike other species of scorpions, direct cardiotoxicity is not expected following envenomation by *C. sculpturatus*.

Diagnosis

The diagnosis of bark scorpion envenomation is largely based on history and physical examination. Young children are often unable to provide the history of a sting, so details regarding the onset of effects (i.e., sudden inconsolable agitation in a previously well child) and recognition of characteristic clinical findings must be relied upon in diagnosing envenomation [27]. Because scorpions are nocturnal, patients may be awakened by the onset of symptoms. Cutaneous findings are usually absent. A positive tap test may help aid in the presumptive diagnosis; however in young children with severe agitation, it can be difficult to identify a positive response. While serum venom concentrations can be obtained [17], their use is limited to research settings and is not routinely available. Thus, the diagnosis remains clinical.

The differential diagnosis of scorpion envenomation includes both toxicologic (e.g., methamphetamine toxicity, black widow envenomation) [28, 29] and non-toxicologic etiologies (e.g., thyrotoxicosis, central nervous system infection).

Treatment

One of the primary reasons for the reduced mortality seen today is improved access to care, with supportive care being paramount [9].

Following envenomation, patients should be observed for progression of clinical effects. However, most patients with mild symptoms can be managed at home without referral to a medical facility [4, 10, 30, 31] (grade III recommendation).

Patients with a compromised airway, or those with ineffective ventilatory effort, should be intubated as per standard indications (grade III recommendation).

Patients with significant hypersalivation are sometimes treated with small doses of atropine; however, there is not sufficient evidence supporting this practice to recommend its routine use [9, 26, 32] (grade III evidence). Analgesics should be administered to those with significant pain (grade III recommendation). Most patients who have high-grade envenomations, and are thus unable to communicate verbally, should be assumed to have pain and can be treated with analgesics empirically. Due to its lack of significant histaminergic effects, fentanyl is the preferred analgesic [3] and should be administered with a starting dose of 1 mcg/kg intravenously (grade III recommendations). Additional doses can be titrated based on need. In addition to analgesics, benzodiazepines should be administered to assist in the control of neuromuscular excitation and agitation [9, 10] (grade III recommendation).

In August, 2011 the United States Food and Drug Administration approved *Centruroides* (scorpion) immune F(ab')₂ antivenom for the treatment of scorpion envenomation. While the approval is not based on grade of envenomation, because low-grade envenomations universally do well without therapy, and the expensive nature of the antivenom, its use is primarily reserved for those with grade III or IV envenomation. The use of this antivenom has been demonstrated to be highly safe and effective [33–35] (grade Ib evidence). The use of this antivenom in an emergency department may obviate the need for admission and/or transfer to a pediatric facility for admission [35]. The cost of such therapy can exceed \$10,000, and some data suggests its use may not be a cost-effective option [36]. If antivenom is not an option for patients with high-grade envenomations, admission to an intensive care unit, and possible mechanical ventilation, is indicated. During the approximately 2-year period between September 2004 through July 2006 when antivenom was not available in Arizona, nearly 25% of all grade III or IV scorpion envenomations required intubation with ventilatory support [9].

While antivenom is an option for patients with high-grade envenomations, supportive care is paramount. Antivenom should be considered an adjunctive agent for severe envenomations, but its use is not necessarily the standard.

Indications for ICU Admission

Grade III or IV envenomations not treated with antivenom

Hypoxia that does not resolve after antivenom administration, especially if concern for significant aspiration

Mechanical ventilation

Key Points

- Most patients will develop only minor symptoms and not require admission.
- Antivenom may be administered for high-grade symptoms.
- Clinicians should prepare for possible respiratory compromise and treat any impending respiratory failure with endotracheal intubation.

Criteria for ICU Discharge

- Resolution of significant respiratory compromise
- Resolution of symptoms

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Part XXIII

Natural Toxins: Snakes

Julian White

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Venomous snakes are undoubtedly the most significant cause of both major morbidity and mortality among all terrestrial venomous and poisonous animals. Although poisoning by marine animals may affect large numbers of people, mortality is comparatively rare, and thus venomous snakes are the leading cause of death from venomous and poisonous animals in all environments. In some parts of the rural tropics, snakebite is in the top 10–15 most important health problems, but in temperate “Western” countries, snakebite is often considered to be of negligible significance, a designation not necessarily in tune with reality.

Types of Venomous Snakes

Even though there are approximately 3000 species of snakes globally, only about 600 species are clearly venomous. The higher-level taxonomy of snakes has undergone significant change in recent years and the previous view that all of them are found in just four snake families: Colubridae, Elapidae (includes sea snakes, subfamily Hydrophiinae), Atractaspididae, and Viperidae is no longer valid. The current taxonomy places venomous snakes in families Colubridae, Natricidae, Elapidae, Lamprophiidae, and Viperidae (Table 1) [1].

Table 1 Current taxonomy of higher-level snakes, including all clearly venomous taxa. *NFFC* non-front-fanged venomous, *FFV* front-fanged venomous. Note all these snakes are classed as Colubroid, but the precise subclassification into several superfamilies remains contentious [1]

Superfamily	Family and subfamily	Relevant examples of included genera	Type of venomous snakes
Superfamily Colubroidea	Colubridae		
	Colubrinae	<i>Boiga, Dispholidus, Thelotornis</i> , etc.	NFFC
	Grayiinae		
	Calamariinae		
	Dipsadidae		
	Dipsadinae	<i>Leptodora, Sibynomorphus</i> , etc.	NFFC
	Heterodontinae	<i>Heterodon</i>	NFFC
	Xenodontinae	<i>Alsophis, Boiruna, Clelia, Hydrodynastes, Phalotris, Philodryas, Tachymenis</i> , etc.	
	Natricidae	<i>Natrix, Rhabdophis, Thamnophis</i> , etc.	NFFC
	Pseudoxenodontidae		
Superfamily Elapoidea	Elapidae	(Includes sea snakes, e.g., “Hydrophiinae”)	FFV
	Lamprophiidae		
	Atraspinae		FFV
	Lamprophiinae		
	Psammophiinae		
	Pseudoxyrhophiinae		
Superfamily Homalopsoidea	Homolopsidae	<i>Cerberus, Homalopsis</i> , etc.	
Superfamily Viperoidae	Viperidae		FFV
	Azemiopinae		
	Crotalinae		
	Viperinae		

Among those snakes considered venomous, there are two morphologic subgroups, based on the fang and toxin-producing gland. These subgroups do not precisely relate to taxonomic classification. Classic venomous snakes such as cobra-type snakes (family Elapidae) and vipers, including pit vipers (e.g., rattlesnakes, etc.) (family Viperidae), have fangs placed toward the front of the mouth (FFV). Other snakes considered as venomous either have fangs further back in the mouth (sometimes labeled as “back fanged”) or no clear fangs; this group are labeled as “non-front-fanged colubroids” (NFFC).

To add a further layer of complexity, there is an ongoing debate about what constitutes venomousness, with some toxinologists advocating a much broader definition that sees almost all snakes, many lizards, and other vertebrates as “venomous” (the Toxicofera hypothesis), a view rejected by others, including this author, and by the vast majority of toxinologists at a formal debate on this hypothesis held at Oxford University as part of the World Congress of the International Society on Toxinology, September 2015. The various hypotheses and definitions of venom and venomousness have recently been reviewed [2].

Medically Important Nonvenomous Snakes

When compared with the human toll from venomous species, nonvenomous snakes cause few problems, but it should not be forgotten that a few large nonvenomous species, notably the pythons

and boas (family Boidae), can cause significant bites and rarely may kill and more rarely still may eat humans.

Pythons and boas have many long, sharp, recurved teeth (Fig. 1) capable of penetrating deeply, even to bone in some areas such as the hand. These teeth, in addition to causing mechanical injury, may be expected to be coated with bacteria and thus may cause significant local infection. Besides the effects of the bite, large pythons and boas can potentially wrap around a human torso or neck and cause crush injuries. Such injuries may include significant internal organ damage in addition to the lethal effects of constriction of the cardiovascular and respiratory systems.

Some researchers have claimed that even the python/boa group can produce toxins from oral glands, thus are technically venomous. This view is controversial and, in practical terms for bites to humans, irrelevant, as there is no evidence indicating that bites by these snakes cause envenoming in humans [2].

NFFC Snakes

In the past most snakes were generally considered nonvenomous and distributed globally in a single family, Colubridae (Fig. 2). As noted earlier, a revised taxonomy has split this family into many distinct families and subfamilies (Table 1), and among these, a number of families and subfamilies contain at least some species considered as venomous [1]. These latter snakes, designated NFFC (see earlier), do not have fangs at the

Fig. 1 Boid skull showing large array of long, sharp recurved teeth (Copyright © Dr. Julian White)

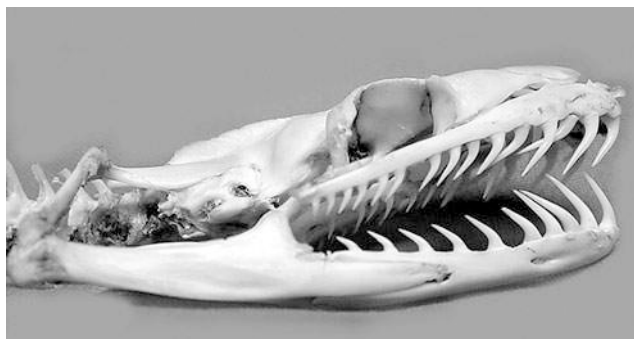




Fig. 2 Approximate global distribution of “colubrid” snakes, covering the following families: Colubridae, Dipsadidae, Natricidae, Pseudoxenodontidae,

Lamprophiidae (but excluding Atractaspinae), Homolopsidae (Copyright © Dr. Julian White)

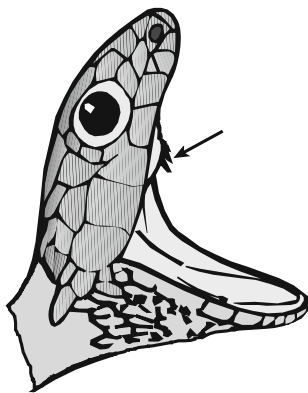


Fig. 3 Diagrammatic representation of a typical colubrid snake head and fang position (Copyright © Dr. Julian White)

front of the mouth, and some have no discernable fangs at all. Venom is generally produced in a low-pressure elongated gland, Duvernoy’s gland, but not all snakes possessing Duvernoy’s gland are necessarily “venomous.” However, a few of these species have evolved fangs toward the back of the mouth (Fig. 3) that deliver venom. Several

of these species have caused human fatalities or major envenoming (Table 2). A further group of NFFC snakes have evolved toxic oral secretions that are inoculated during the biting process, though not with fangs. There is increasing evidence that at least some of these species can cause significant injury to humans [1]. Some other NFFC snakes reported to cause effects in humans are listed in Table 3. This list is not exhaustive, and most NFFC snakes should be considered to have some potential of causing at least local envenoming, whether via fangs or inoculation of toxic oral secretions.

Family Elapidae

It is a large and diverse family of exclusively venomous snakes covering all continents (except Antarctica) and several major oceans (Fig. 4), these snakes have well-developed fangs toward the front of the mouth that can deliver often highly potent venom produced in paired venom glands (Fig. 5) [1, 4]. The archetypic elapid snake is the Indian cobra, but the typical cobra hood is present

Table 2 NFFC snakes reported to have caused major or lethal envenoming [1]

Scientific name	Common name	Effect
<i>Dispholidus typus</i>	Boomslang	Coagulopathy and hemorrhage
<i>Thelotornis</i> spp.	Vine snakes	Coagulopathy and hemorrhage
<i>Rhabdophis</i> spp.	Yamakagashi, red-necked keelback	Coagulopathy and hemorrhage
<i>Balanophis ceylonensis</i>	Sri Lankan keelback	Local swelling ± discoloration, bleeding, lymphangitis; coagulopathy and hemorrhage reported in single case [3]
<i>Malpolon monspessulanus</i>	Montpelier snake	Mild neurotoxicity (poorly defined)
<i>Philodryas olfersii</i>		
<i>Boiga irregularis</i>	Brown tree snake	Local swelling plus respiratory distress and possible mild paralysis in infants only

Table 3 Some NFFC snakes reported capable of causing mild envenoming^a [1]

Scientific name	Common name	Effect
<i>Ahaetulla nasuta</i>	Asian green whipsnake	Local swelling ± discoloration, lymphangitis
<i>Amplorhinus multimaculatus</i>	African many-spotted snake	Local swelling ± headache, nausea
<i>Boiga</i> spp. (e.g., <i>blandingii</i> , <i>ceylonensis</i> , <i>dendrophila</i> , <i>forsteni</i>)	Tree snakes from Africa and Asia	Local swelling ± discoloration, bleeding, lymphangitis, headache, nausea
<i>Cerberus rynchops</i>	Indian dog-faced water snake	Local swelling ± discoloration, lymphangitis
<i>Coluber</i> spp. (e.g., <i>ravergieri</i> , <i>rhodorachis</i>)	African racer	Local swelling ± discoloration, bleeding, lymphangitis
<i>Crotaphopeltis hotamboeia</i>	African herald snake	Local swelling
<i>Enhydrys enhydryis</i>	Asian rainbow water snake	Local swelling ± discoloration, lymphangitis
<i>Madagascarophis meridionalis</i>	Madagascan snake	Local swelling ± discoloration, bleeding, blistering, necrosis, lymphangitis, headache, nausea
<i>Malpolon moilensis</i>	African hooded malpolon	Local swelling ± discoloration, lymphangitis
<i>Psammophis sibilans</i>	African racer	Local swelling ± discoloration, bleeding, lymphangitis, headache, nausea
<i>Psammophylax</i> spp. (selected)	African skaapstekers	Local swelling ± discoloration, bleeding, lymphangitis, headache, nausea
<i>Telescopus semiannulatus</i>	African tiger snake	Local swelling ± discoloration, bleeding, lymphangitis, headache, nausea

^aThis list is not exhaustive

in only a few elapids. Some smaller species are unable or unlikely to successfully envenom humans; however, essentially all the larger species are capable of causing envenoming, and many are potentially lethal (Table 4). Elapids are a major cause of snakebite morbidity and mortality globally.

Family Lamprophiidae, Subfamily Atractaspinae

It is a small subfamily of venomous snakes found solely in Africa and the Middle East (Fig. 6); atractaspines are characterized by side-striking fangs (Fig. 7) and unique venom components



Fig. 4 Approximate global distribution of elapid snakes, including sea snakes (Copyright © Dr. Julian White)

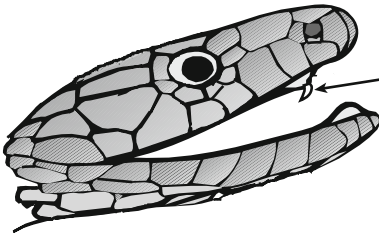


Fig. 5 Diagrammatic representation of a typical elapid snake head and fang position (Copyright © Dr. Julian White)

enables the fangs to fold away against the roof of the mouth and thus permits longer fangs in proportion to head size (Fig. 9). There are two major groups of vipers; the subfamily Viperinae contains the classic vipers of the “Old World” (Fig. 9; Table 6), and the pit vipers, subfamily Crotalinae, are characterized by their anteriorly placed heat-sensitive pit organs, which can detect prey by their heat signature (Figs. 10 and 11; Table 7). Vipers are probably the most important cause of global snakebite morbidity and mortality.

(sarafotoxins), but only a few species appear to be able to significantly envenom humans (Table 5) [1, 4].

Family Viperidae

It is a large and diverse family of exclusively venomous snakes covering most continents (except Australia, New Guinea, and Antarctica) (Fig. 8); viperids have a highly evolved fang structure [1, 4]. The fangs are at the front of the mouth, attached to a mobile maxilla, which

Epidemiology of Snakebite

No precise figures on the extent of global snakebite are available. One of the most recent estimates is 2.54 million venomous snakebites and at least 125,000 deaths per year [5]. A subsequent study, using different methodology, estimated venomous snakebite cases as 0.42–1.84 million/year, with 20–94,000/year fatalities [6]. However, subsequent detailed studies in India, as part of the “million deaths” research, determined that in India alone there were at least 45,500 snakebite deaths every year, which indicates the

Table 4 Major groups of elapid snakes and their principal clinical effects

Scientific name	Common name	Effect
<i>Acanthophis</i> spp.	Australian death adders	Neurotoxic paralysis
<i>Austrelaps</i> spp.	Australian copperheads	Neurotoxic paralysis
<i>Aspidelaps</i> spp.	African coral snakes	Neurotoxic paralysis
<i>Bungarus</i> spp.	Asian kraits	Neurotoxic paralysis, myolysis (only some species), hyponatremia (only some species)
<i>Calliophis</i> spp.	Asian coral snakes	Neurotoxic paralysis
<i>Dendroaspis</i> spp.	African mambas	Neurotoxic paralysis and muscle fasciculation
<i>Elapsoidea</i> spp.	African garter snakes	Local effects only
<i>Hemachatus haemachatus</i>	African rinkhals spitting cobra	Local tissue injury, paralysis
<i>Hoplocephalus</i> spp.	Australian broad-headed snakes	Coagulopathy and hemorrhage
<i>Micropechis ikaheka</i>	New Guinea small-eyed snake	Paralysis, coagulopathy, myolysis
<i>Micrurus</i> spp.	American coral snakes	Depending on species, paralysis and/or myolysis
<i>Micruroides euryxanthus</i>	Arizona coral snake	Neurotoxic paralysis (rarely severe)
<i>Naja</i> spp.	African and Asian cobras	Depending on species, severe local tissue injury and/or paralysis
<i>Notechis</i> spp.	Australian tiger snakes	Paralysis, coagulopathy, myolysis, renal damage, hyponatremia (rare)
<i>Ophiophagus hannah</i>	Asian king cobra	Paralysis, local tissue injury
<i>Oxyuranus</i> spp.	Australian taipans	Paralysis, coagulopathy, myolysis, renal damage
<i>Paranaja multifasciata</i>	African burrowing cobra	Local effects only
<i>Pseudechis</i> spp.	Australian mulga and black snakes	Depending on species, myolysis, coagulopathy (anticoagulant), renal damage
<i>Pseudohaje</i> spp.	African tree cobras	Local effects only
<i>Pseudonaja</i> spp.	Australian brown snakes	Coagulopathy, renal damage, rarely paralysis
<i>Tropidechis carinatus</i>	Australian rough-scaled snake	Paralysis, coagulopathy, myolysis, renal damage
<i>Walterinnesia aegyptia</i>	Middle East desert black snake	Neurotoxic paralysis
Various	Sea snakes	Paralysis and/or myolysis

Kasturiratne [6] estimates are significantly too low [7]. On this basis a global annual death toll from snakebite of at least 100,000 seems likely. Certain areas are at high risk, particularly the rural tropics. Unfortunately, these areas coincide with those that have the least medical and financial resources, and thus the fatality rate is higher than would occur if modern medical care and antivenoms were universally available. Certain species groups are responsible for very high numbers of cases and deaths. Of particular note are the saw-scaled or carpet vipers of the genus *Echis* (Fig. 12), which are found from West Africa to

the Indian subcontinent and are possibly responsible for more than 100,000 bites and 10,000 deaths annually. Also important are Russell's vipers (*Daboia russelii* and *D. siamensis*) (Fig. 13), found from Sri Lanka to Southeast Asia; the puff adder (*Bitis arietans*) (Fig. 14), related species in many parts of Africa; and numerous cobra (*Naja*) species (Fig. 15) in Africa and Asia. Additional important venomous snakes are the krait species (*Bungarus*) (Fig. 16), found from Sri Lanka to Southeast Asia; the Malayan pit viper (*Calloselasma rhodostoma*) (Fig. 17) in Southeast Asia; and pit vipers of the genera



Fig. 6 Approximate global distribution of atractaspine snakes (family Lamprophiidae, subfamily Atractaspinae) (Copyright © Dr. Julian White)

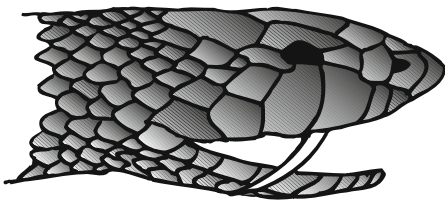


Fig. 7 Diagrammatic representation of a typical atractaspine snake head and fang position (Copyright © Dr. Julian White)

Trimeresurus (Fig. 18) and *Gloydius* (Fig. 19) in Asia and *Bothrops* (Fig. 20), *Crotalus* (Fig. 21), and *Agkistrodon* (Fig. 22) in the Americas. Although Australian elapids have a fearsome reputation, they cause relatively few bites and very few deaths and are thus comparatively unimportant.

Those most at risk for snakebite are rural workers, especially while toiling in fields or rice paddies. Some areas, particularly rice-growing regions such as Southeast Asia, have a major seasonal peak of bites during harvest time. Indeed, in much of the rural tropics globally, snakebite is predominantly an occupational disease. Although

Table 5 Atractaspine snakes and their principal clinical effects

Scientific name	Common name	Effect
<i>Atractaspis</i>	African mole or side-fanged vipers	Depending on species, may cause local effects, necrosis, cardiotoxicity

snakebite can occur at any time of the year in tropical regions, it tends to show a seasonal fluctuation, but in temperate climates, where venomous species may hibernate, legitimate snakebites (those not caused by deliberate handling or provocation of the snake) are a phenomenon of the summer or warmer months.

Particularly in Western countries, where keeping venomous snakes attracts hobbyists, some less careful than others, illegitimate snakebites (those caused by deliberate handling or provocation of the snake or by a captive snake) are an important problem that often involves severe bites from exotic species for which no appropriate anti-venom may be readily available. Such hobbyists have in the past enjoyed a reputation for



Fig. 8 Approximate global distribution of viperid (including crotaline) snakes

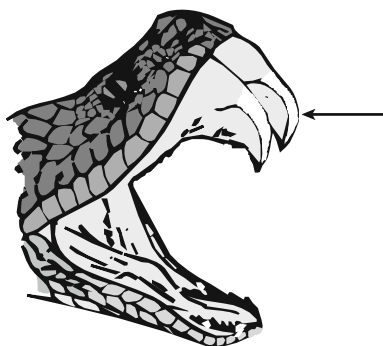


Fig. 9 Diagrammatic representation of a typical viperid snake head and fang position (Copyright © Dr. Julian White)

recklessness and almost an encouragement of bites, the numbers of which were sometimes “worn” as a badge of honor. It is often assumed by health professionals that this attitude is as inevitable as the numerous bites. It is my experience in South Australia that such need not be the case and that with correct education and encouragement, private keepers of venomous snakes can be very careful and responsible and can work with health authorities to minimize legitimate bites and

provide assistance in identifying snakes that have caused envenoming. This is therefore a plea to my medical colleagues to abandon the past, often hostile relationship between keepers and doctors and seek to establish a good, mutually respectful working relationship that reinforces an ethos among keepers that being bitten is something to be ashamed of and to be avoided at all cost.

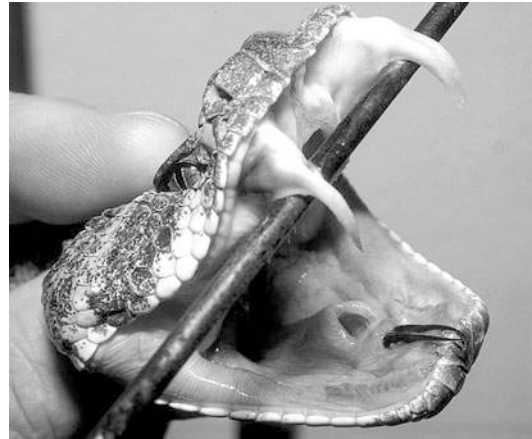
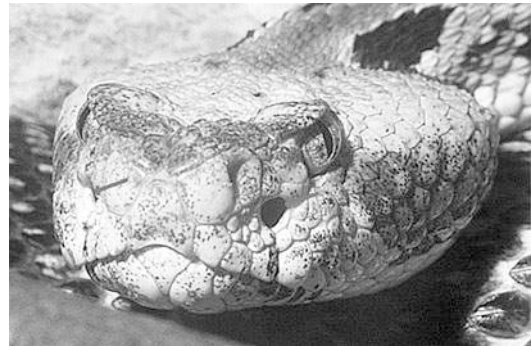
Snake Venoms

Snake venoms are generally produced in specific venom glands derived from the salivary glands, the exception being Duvernoy’s glands in some NFFC snakes [1, 4]. The venom, once produced, is delivered by a duct to the fang base, where it is transported into the victim either by a groove in the fang or through a fang duct. Production of intraglandular pressure by contraction of muscles around the gland is the usual mode of venom transport, and this mechanism often allows the snake to “fine-tune” how much venom is expended in a given bite. This may explain, in part, why many venomous snakes exhibit the “dry bite” phenomenon whereby a bite fails to inject

Table 6 Major groups of Viperid snakes and their principal clinical effects

Scientific name	Common name	Effect
<i>Atheris</i> spp.	African bush vipers	Nothing significant
<i>Bitis</i> spp.	African puff adders, Gaboon vipers, etc.	Depends on species, but some cause severe local tissue injury, coagulopathy and hemorrhage, shock, cardiotoxicity, a few cause at least mild neurotoxicity (<i>B. atropos</i>)
<i>Causus</i> spp.	African night adders	Local effects, paralysis
<i>Cerastes</i> spp.	African horned adders	Local effects, coagulopathy, hemorrhage, shock
<i>Daboia russelii</i> and <i>D. siamensis</i>	Russell's viper	Local effects, coagulopathy hemorrhage, and in specific populations/ regions, renal failure, paralysis, myolysis, Sheehan's syndrome, capillary leak syndrome
<i>Echis</i> spp.	African and West Asian saw-scaled vipers	Local effects, coagulopathy, hemorrhage, shock
<i>Macrovipera</i> spp.	Eurasian vipers	Local effects, coagulopathy, hemorrhage, shock
<i>Pseudocerastes</i> spp.	Middle East horned Vipers	Paralysis
<i>Vipera</i> spp.	European vipers	Local effects, necrosis, shock

enough venom to cause medically significant envenoming. Those NFFC snakes producing venom in Duvernoy's glands may have less fine control of venom ejection as these glands are low-pressure glands, unlike the high-pressure glands of FFV snakes (elapids, vipers, atractaspines) [1].

**Fig. 10** Crocrotaline snake head showing fangs in the erect position (Copyright © Dr. Julian White)**Fig. 11** Typical crocrotaline snake head showing the position of heat-sensing pit organs (Copyright © Dr. Julian White)

Snake venoms generally consist of a complex mixture of substances, each of which may exhibit one or more distinct toxic actions [4]. Many of the most potent snake toxins have evolved highly specific targets, such as the neuromuscular junction or components of the hemostatic system. It is likely that all snake venoms fulfill multiple functions for the snake, principally:

- Prey acquisition
- Defense against predators

A third possible function, predigestion of prey, though logical and possible, remains largely unproven.

Table 7 Major groups of Crotalid snakes and their principal clinical effects

Scientific name	Common name	Effect
<i>Agkistrodon</i> spp.	North American copperhead, cottonmouth, cantil	Local effects, necrosis, coagulopathy, hemorrhage, shock
<i>Atropoides</i> spp.	Central American jumping pit vipers	Local effects, necrosis
<i>Bothriechis</i> spp.	Central American palm pit vipers	Local effects, necrosis, shock
<i>Bothrops</i> spp.	South and Central American pit vipers	Depends on species, but may include local effects, necrosis, coagulopathy, hemorrhage, renal damage, myolysis, shock
<i>Calloselasma rhodostoma</i>	Malayan pit viper	Local effects, necrosis, coagulopathy, hemorrhage, renal damage, shock
<i>Cerrophidion</i> spp.	Central American montane pit vipers	Local effects, necrosis
<i>Crotalus</i> spp.	Rattlesnakes	Depends on species; in North America, local effects, necrosis, coagulopathy, shock + paralysis (in a few species); in South America, local effects, paralysis, coagulopathy, myolysis, renal damage
<i>Deinagkistrodon acutus</i>	Chinese hundred pace viper	Local effects, necrosis, coagulopathy, hemorrhage, shock
<i>Gloydus</i> spp.	Asian terrestrial pit vipers	Local effects, necrosis, coagulopathy, hemorrhage, shock

(continued)

Table 7 (continued)

Scientific name	Common name	Effect
<i>Hypnale</i> spp.	Sri Lankan hump-nosed vipers	Local effects
<i>Lachesis</i> spp.	Central and South American bushmasters	Local effects, necrosis, coagulopathy, shock
<i>Ophryacus</i> spp.	Central American horned pit vipers	Local effects, necrosis, shock
<i>Ovophis</i> spp.	Asian montane pit vipers	Local effects, coagulopathy, hemorrhage
<i>Porthidium</i> spp.	Central American montane pit vipers	Local effects, necrosis, shock
<i>Sistrurus</i> spp.	North American pygmy rattlesnakes and massasauga	Local effects, necrosis, rarely hemorrhage
<i>Trimeresurus</i> ^a spp.	Asian green pit vipers	Depends on species; local effects, rarely necrosis, coagulopathy, hemorrhage
<i>Tropidolaemus</i> spp.	Asian tree vipers	Local effects; rarely necrosis, coagulopathy, hemorrhage

^aThe pit viper genus *Trimeresurus*, from Asia, contains many species. Some taxonomists controversially split it up into seven separate genera (*Cryptelytrops*, *Himalayophis*, *Parias*, *Peltopelor*, *Popeia*, *Trimeresurus*, *Viridovipera*), but this split is increasingly considered invalid by taxonomists and so is not listed here. However, recent literature may list both venom research and clinical reports based on this contentious taxonomy

Venom variability among snakes is an important concept, with some medically important species showing marked regional variation in venom activity across their geographic range, and there are examples of variability of venom for a single specimen over time, sometimes seasonal, with ontogenetic variability documented for some species [8] (see later section in this chapter). Snake venoms may be classified in many ways, and some classifications still frequently used in

Fig. 12 Saw-scaled viper
(specimen from Africa)
(Copyright © Dr. Julian
White)

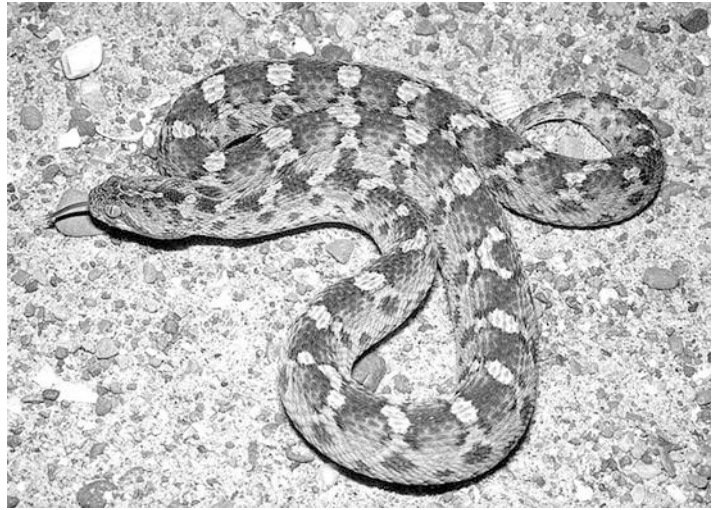


Fig. 13 Russell's viper
(specimen from Thailand)
(Copyright © Dr. Julian
White)



Fig. 14 Puff adder (specimen from Africa) (Copyright ©
Dr. Julian White)

medical texts are misleading or inaccurate. Foremost among these is the old aphorism that elapids are neurotoxic and viperids are hemorrhagic, a classification that is inaccurate and should be abandoned. Some of the most potent toxins active against human hemostasis are found in certain elapid venoms, whereas some other elapid species cause major local tissue injury at the bite site. Conversely, in a number of viperid species, the principal clinical effect is neurotoxic paralysis, with no or minimal effect on either local tissues at the bite site or the hemostatic system. From a medical perspective, a classification based on clinical effects is generally useful (Table 8) and



Fig. 15 Typical cobra with hood displayed (specimen from Thailand) (Copyright © Dr. Julian White)



Fig. 16 Asian krait (specimen from Thailand) (Copyright © Dr. Julian White)

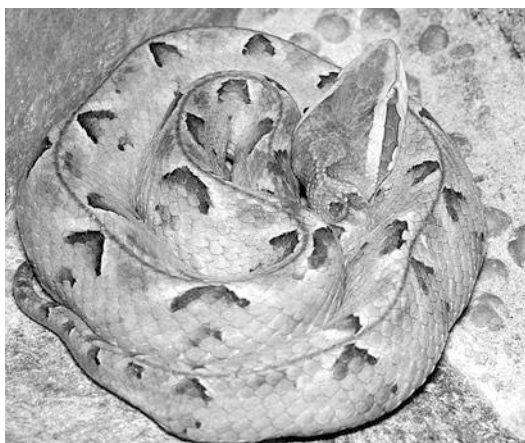


Fig. 17 Malayan pit viper (specimen from Thailand) (Copyright © Dr. Julian White)

will be adopted in this chapter, but the reader should be aware that more biochemically based classifications of venoms yield a quite different picture (Table 9) and that some medically important toxins from snake venoms have several physiologically distinct actions, each caused by separate regions in the structure of a single toxin.

Neurotoxins

Snake venom neurotoxins are a diverse group of toxins that clinically cause paralytic effects mediated at the neuromuscular junction (in most cases) (Fig. 23). A hundred years ago, snakebite paralysis usually condemned the victim to death from respiratory failure. In the current era of intensive care unit (ICU), management, intubation, ventilation, and other treatment modalities, such an outcome, should be rare; however, in many regions such facilities are unavailable, and thus many snakebite victims still die annually of neurotoxic paralysis.

Presynaptic neurotoxins are generally modified phospholipase A_2 toxins that specifically target the terminal axon of the neuromuscular junction, where they interact with and disrupt the axonal cell membrane, enter the cytoplasm, and then disrupt synaptosome production, causing significant intracellular damage. These toxins first cause release of neurotransmitter and then extensive damage to the axonal structure culminating in complete disruption of production of transmitter synaptic vesicles and thus cessation of transmitter release. Experimentally there is a latency period of about an hour, between the time the toxin binds to the axonal cell membrane and complete cessation of neurotransmitter release. Clinically, this causes a progressive flaccid paralysis, with the onset of signs usually 1+ hours after the bite and progressive paralysis thereafter. Full respiratory paralysis, including paralysis of the diaphragm, may take 3–24 h; once paralysis is complete, the recovery rate is determined by axonal repair and is not influenced by antivenom therapy. It is therefore critical in this type of envenoming to recognize the early signs of paralysis and institute effective antivenom therapy

Fig. 18 Green pit viper (specimen from Thailand) (Copyright © Dr. Julian White)



Fig. 19 Asian Gloydus pit viper (Copyright © Dr. Julian White)

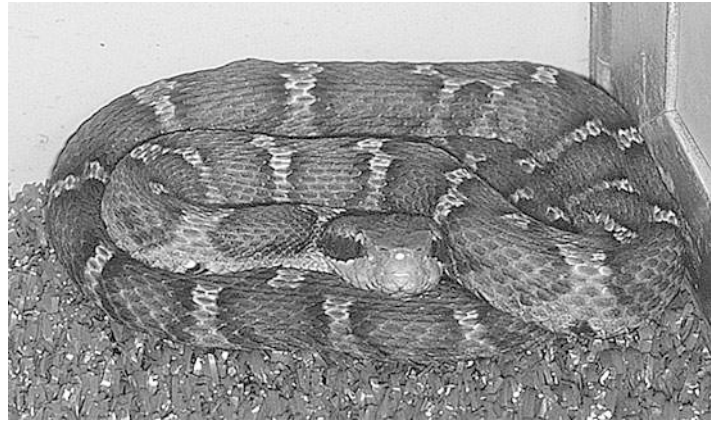


Fig. 20 South American Bothrops pit viper (specimen from Brazil) (Copyright © Dr. Julian White)

before more extensive paralysis becomes irreversibly established (Grade III recommendation). Complete paralysis may take days, weeks, or rarely months to resolve. During this period the victim is dependent on external ventilatory support and is at risk for a number of potentially severe complications. Presynaptic neurotoxins are found in selected elapid and viperid venoms (Table 10).

Postsynaptic neurotoxins are polypeptides of varying size, usually under 12 kd, and they also target the neuromuscular junction. They act extracellularly by binding to the acetylcholine receptor on the muscle end plate and blocking neurotransmitter binding, thus causing paralysis. The cell is not specifically damaged, and therefore this type

Fig. 21 North American *Crotalus* pit viper (specimen from the United States) (Copyright © Dr. Julian White)

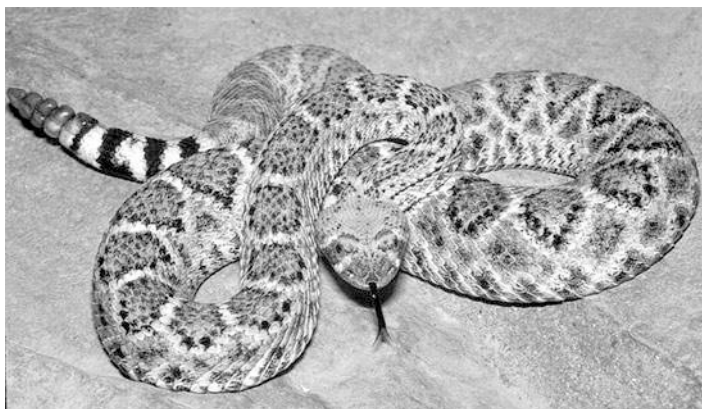


Fig. 22 North American *Agkistrodon* pit viper (specimen from Mexico) (Copyright © Dr. Julian White)



of flaccid paralysis is often reversible with anti-venom therapy, even if very extensive. The mode of action may also allow more rapid onset and progression of paralysis, although major paralysis is uncommon earlier than 1 h after the bite. Post-synaptic neurotoxins are present in many elapid and a few viperid venoms (Table 11).

Dendrotoxins and fasciculins are synergistic neurotoxins found in some African mamba venoms. Both toxins target the neuromuscular junction and cause paralysis and muscle spasms or fasciculation. Dendrotoxins target certain potassium channels in the terminal axon membrane, ultimately resulting in overrelease of neurotransmitter molecules that swamp and overstimulate the adjacent muscle end-plate receptors. Fasciculins inhibit or interfere with anticholinesterases in the junctional space, thereby significantly reducing the normal removal

of synaptic acetylcholine. This decreased removal of acetylcholine enhances the effect of dendrotoxins and results in gross overstimulation of the muscle manifested as spasm or fasciculation, thereby effectively paralyzing the victim. Both toxins may exert their effect rapidly, and thus the clinical effects may become apparent in less than an hour after a bite.

Other types of snake neurotoxins are produced, some targeting different areas, but they either are uncommon or have limited or no significant clinical effects, particularly when compared with the foregoing toxins.

Myotoxins

Most snake venom systemic myotoxins are based on phospholipase A₂ and cause systemic myolysis

Table 8 Broad medical classification of Snake Venom activities

Toxin activity type	Clinical effects
Neurotoxin	Flaccid paralysis
Presynaptic	Resistant to late antivenom therapy
Postsynaptic	Often reversed with antivenom therapy
Anticholinesterase	Fasciculation
Myotoxin	
Local	Local muscle damage in bite area
Systemic	Systemic skeletal muscle damage
Hemostatic system toxins	Interference with normal hemostasis causing either bleeding or thrombosis
Hemorrhagins	Vascular wall damage causing bleeding
Nephrotoxins	Direct renal damage
Cardiotoxins	Direct cardiotoxicity
Necrotoxins	Direct tissue injury at the bite site/bitten limb

of skeletal muscle but rarely affect cardiac or smooth muscle. The damage occurs to individual muscle cells with sparing of the basement membrane; thus, regeneration of muscle usually begins about 3 days after the bite and is complete after about 28 days. Experimentally, only slow-twitch fibers regenerate, but this is still unconfirmed in human cases. In the process of muscle destruction, massive release of myoglobin, creatine kinase, and potassium occurs. The former is associated with secondary renal damage and often gross myoglobinuria. Theoretically, antivenom therapy should have no effect if muscle breakdown is already established, but experience in Australia suggests that even late antivenom treatment may reduce the severity of muscle damage (Grade III recommendation). Myotoxins are found in both elapid and viperid species (Table 12).

Some snakes, particularly some of the pit vipers such as North American rattlesnakes, possess locally acting myotoxins that do not result in systemic myolysis, but are involved in local tissue injury around the bite site.

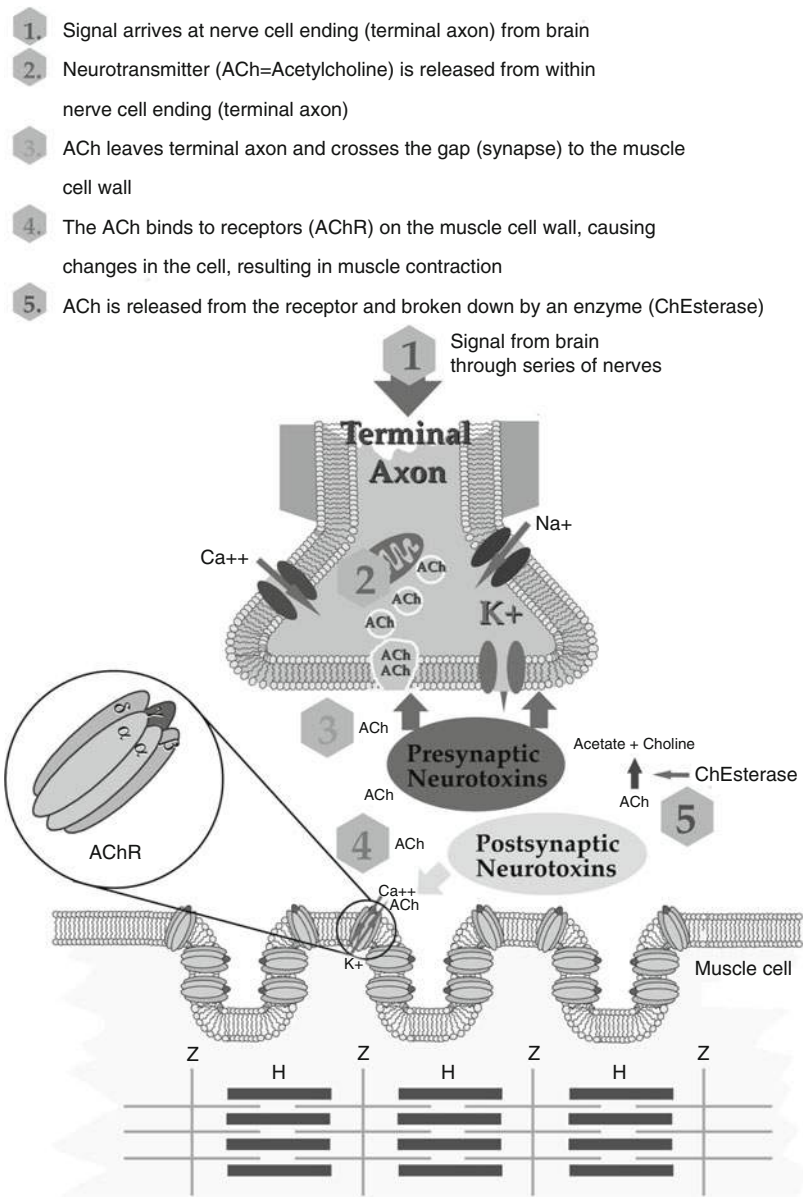
Table 9 Broad biochemical classification of snake venom activities

Toxin class	Clinical effects
Polypeptide toxins	Various; autonomic, neurotoxic, cardiotoxic, myotoxic
Phospholipase toxins	Various; presynaptic neurotoxic, myolytic, procoagulant, cardiotoxic, necrotic
Enzyme toxins	Various; interfere with hemostasis, necrotic, hemolytic
Oxidoreductases	
Transferases	
Hydrolases	
Carbon-nitrogen lyases	
Metalloproteinases	
Other toxins	Various; autonomic, etc.
Lectins	
Nerve growth factors	
Phospholipase inhibitors	
Proteinase inhibitors	
Complement inhibitors	
Other components	Various or ill-defined
Amino acids	
Biogenic amines	
Carbohydrates	
Lipids	
Nucleosides and nucleotides	
Riboflavin	
Organic acids	
Anions	
Cations	

Toxins Affecting Blood Coagulation

The human hemostatic system seems to be a favorite target of snake venoms. There are toxins targeting almost all parts of the system, as represented in several snake families (Colubridae, Natricidae, Lamprophiidae, Elapidae, Viperidae) [1, 9]. Major toxin groups include procoagulants, anticoagulants, and platelet aggregation inhibitors

Fig. 23 Diagrammatic representation of the neuromuscular junction as target site for snake neurotoxins (Copyright Dr. Julian White)



and promoters (Table 13). The net effect of most of these toxins is to increase bleeding, particularly when combined with hemorrhagins, but a few venoms cause clinical thrombosis with potential for embolic problems. The mechanisms of increased bleeding vary, but most components acting as procoagulants exert their effect by consumption of fibrinogen, which results in defibrination rather than classic disseminated intravascular coagulation (DIC), and thus the

thrombocytopenia associated with DIC may be absent. However, some venoms do cause thrombocytopenia via other mechanisms. Yet other venoms cause defibrination through direct action on fibrinogen by splitting fibrinopeptides inappropriately. The biochemical nature and structure of these diverse toxins vary from comparatively small molecules to large, complex multicomponent toxins that mimic normal clotting complexes such as the prothrombinase

Table 10 Snakes considered to have presynaptic neurotoxins of medical significance (Postsynaptic neurotoxins may also be present in these venoms) (Includes Mamba Dendrotoxins)

Scientific name	Common name	Effect
Elapidae		
<i>Acanthophis</i> spp.	Australian and New Guinea death adders	Presynaptic and postsynaptic
<i>Austrelaps</i> spp.	Australian copperheads	Presynaptic and postsynaptic
<i>Bungarus</i> spp.	Kraits	Presynaptic and postsynaptic
<i>Dendroaspis</i> spp.	Mambas	Dendrotoxins and fasciculins
<i>Notechis</i> spp.	Australian tiger snakes	Presynaptic and postsynaptic
<i>Oxyuranus</i> spp.	Australian taipans	Presynaptic and postsynaptic
<i>Pseudonaja</i> spp.	Australian brown snakes	Presynaptic and postsynaptic
<i>Tropidechis carinatus</i>	Rough-scaled snake	Presynaptic and postsynaptic
Viperidae		
<i>Crotalus</i> spp. (selected)	Selected rattlesnakes from South and Central America, plus one North American species	Presynaptic
<i>Vipera ammodytes</i>	European viper (Balkans)	Presynaptic

complex. The majority of viper species have toxins affecting coagulation, but only a few elapid species, notably those from Australia and New Guinea, cause similar effects (Table 14).

Hemorrhagins

In addition to the toxins acting on hemostasis, some venoms, notably those of certain viper species, also contain direct hemorrhagins (Table 15). These toxins damage the vascular endothelium,

Table 11 Snakes considered to have only postsynaptic neurotoxins of medical significance

Scientific name	Common name	Effect
Elapidae		
<i>Micropechis ikaheka</i>	New Guinea small-eyed snake	Postsynaptic only
<i>Micrurus</i> spp.	American coral snakes	Postsynaptic only (note some species may have presynaptic neurotoxins as well; e.g., <i>M. corallinus</i>)
<i>Naja</i> spp. (selected)	Some cobras from Africa and Asia	Postsynaptic only
<i>Ophiophagus hannah</i>	King cobra	Postsynaptic only
Various	Sea snakes	Postsynaptic only
Viperidae		
<i>Daboia russelii pulchella</i>	Sri Lankan Russell's viper	Postsynaptic only

thereby promoting bleeding, and are generally zinc metalloproteinases. They are potentially lethal.

Nephrotoxins

Secondary renal damage is common in envenoming by many venomous snake species, but a few species have direct nephrotoxins (Table 16).

Necrotoxins

Local tissue injury around the bite site is a common feature of viperid bites, although not all vipers cause local necrosis. However, certain elapids, notably some cobra species from Africa and Southeast Asia, routinely cause local necrosis (Table 17) [10, 11]. In most cases the venom components causing this damage are incompletely understood, although the ubiquitous phospholipase A₂ toxins are thought to have a major role. The misnamed “cobratoxins” also cause local tissue injury.

Table 12 Snakes known to have systemic myotoxins of medical significance

Scientific name	Common name	Effect
Elapidae		
<i>Micropechis ikaheka</i>	New Guinea small-eyed snake	Moderate systemic myolysis
<i>Micrurus</i> spp. (selected)	Selected South American coral snakes	Moderate systemic myolysis
<i>Notechis</i> spp.	Australian tiger snakes	Severe systemic myolysis
<i>Oxyuranus</i> spp.	Australian taipans	Moderate systemic myolysis
<i>Pseudechis</i> spp.	Australian mulga and black snakes	Moderate-to-severe systemic myolysis
<i>Tropidechis carinatus</i>	Rough-scaled snake	Severe systemic myolysis
Various	Sea snakes	Moderate-to-severe systemic myolysis
Viperidae		
<i>Bothrops</i> spp. (selected)	Selected species of South American pit vipers	Moderate systemic myolysis
<i>Crotalus</i> spp. (selected)	Selected species of South American rattlesnakes	Moderate systemic myolysis
<i>Daboia russelii pulchella</i>	Sri Lankan Russell's viper	Moderate systemic myolysis

Other Toxins

There are, of course, many other components found in snake venoms that are too numerous to list here. For many, the clinical consequences in humans are uncertain.

Venom Toxicodynamics

In recent years it has been possible to measure venom or individual toxins over time in both experimental animals and human snakebite victims. Although such measurement has thus far been performed for only a very limited range of species, there is greater understanding of the

Table 13 Principal types of toxin effects on the hemostatic system [9]

Toxin type	Effect
Procoagulants	Factor V activating
	Factor X activating
	Factor IX activating
	Prothrombin activating
	Fibrinogen clotting
Anticoagulant	Protein C activating
	Factor IX/X activating protein
	Thrombin inhibitor
	Phospholipase A ₂
Fibrinolytic	Fibrin(ogen) degradation
	Plasminogen activation
Vessel wall interactive	Hemorrhagins
Platelet activity	Platelet aggregation inducers
	Platelet aggregation inhibitors
Plasma protein activators	Serpin inhibitors

toxicodynamics of envenoming (Fig. 24). In most cases, venom is injected fairly superficially, usually subcutaneously. Locally acting toxins causing tissue injury are placed directly at their target site and will thus begin exerting their clinical effects immediately. A significant proportion of the venom, in some species perhaps most of the venom, will not be absorbed directly into the circulation. Instead, it will be transported first via the lymphatic system and then enter the circulation through the thoracic duct. This helps explain the common clinical finding of enlarged or tender lymph nodes draining the bite area and also the high concentration of venom in these nodes at autopsy. Transport via the lymphatic system may be rapid or sometimes delayed, and there is a potential for sequestration of venom locally with prolonged release over a period of hours or days. Once in the circulation, those components affecting hemostasis or acting as hemorrhagins will have reached their target site and will quickly exert their effect. Similarly, nephrotoxins will quickly damage the kidneys. However, toxins that seek extravascular targets, particularly the neurotoxins and myotoxins, will need to exit the circulation in sufficient concentration to exert

Table 14 Snakes considered to cause medically significant effects on the hemostatic system [1, 3, 9]

Scientific name	Common name	Effect
Colubridae		
<i>Dyspholidus typus</i>	Boomslang	Coagulopathy and hemorrhage
<i>Thelotornis</i> spp.	Vine snakes	Coagulopathy and hemorrhage
Natricidae		
<i>Rhabdophis</i> spp.	Yamakagashi, red-necked keelback	Coagulopathy and hemorrhage
<i>Balanophis ceylonensis</i>	Sri Lankan keelback	Coagulopathy and hemorrhage
Elapidae		
<i>Hoplocephalus</i> spp.	Australian broad-headed snakes	Coagulopathy and hemorrhage
<i>Micropechis ikaheka</i>	New Guinea small-eyed snake	Anticoagulant and hemorrhage
<i>Notechis</i> spp.	Australian tiger snakes	Coagulopathy and hemorrhage
<i>Oxyuranus</i> spp.	Australian taipans	Coagulopathy and hemorrhage
<i>Pseudechis</i> spp.	Australian mulga snakes	Anticoagulant and hemorrhage
<i>Pseudonaja</i> spp.	Australian brown snakes	Coagulopathy and hemorrhage
<i>Tropidechis carinatus</i>	Rough-scaled snake	Coagulopathy and hemorrhage
Viperidae		
<i>Agkistrodon</i> spp.	American copperheads	Coagulopathy and hemorrhage
<i>Bitis</i> spp.	African puff adders, Gaboon vipers, etc.	Coagulopathy and hemorrhage
<i>Bothrops</i> spp. Includes	Central and South American pit vipers	Coagulopathy and hemorrhage
<i>Bothriechis</i> ,		
<i>Cerrophidion</i> ,		
<i>Ophryacus</i>		
<i>Porthidium</i> spp.		
<i>Bothrops lanceolatus</i> , <i>B. caribbeus</i>	Martinique viper	Coagulopathy; thrombosis with DVT and pulmonary embolism

(continued)

Table 14 (continued)

Scientific name	Common name	Effect
<i>Calloselasma rhodostoma</i>	Malayan pit viper	Coagulopathy and hemorrhage
<i>Cerastes</i> spp.	North African horned vipers	Coagulopathy and hemorrhage
<i>Crotalus</i> spp. (selected)	North American rattlesnakes	Coagulopathy and hemorrhage
<i>Daboia russelii</i>	Russell's viper	Coagulopathy and hemorrhage
<i>Echis</i> spp.	Saw-scaled vipers	Coagulopathy and hemorrhage
<i>Lachesis</i> spp.	Bushmasters	Coagulopathy and hemorrhage
<i>Trimeresurus</i> spp.	Green pit vipers	Coagulopathy and hemorrhage
<i>Vipera</i> spp. (selected) Includes <i>Macrovipera</i> spp.	Selected European vipers	Coagulopathy and hemorrhage

DVT deep venous thrombosis

their effect clinically; thus, these toxins are most likely to have a delayed onset of clinically detectable action. Some of these latter toxins also have a significant delay between reaching their target site and causing clinically detectable effects, and thus clinical evidence of their effects may be significantly delayed, even though they may be causing irreversible damage prior to clinical manifestations. Some venoms are quickly cleared from the circulation, but others remain detectable for days or even weeks without antivenom therapy. Knowledge of such variation is clearly relevant in determining antivenom therapy, as will be discussed later.

Venom Variability

It is often assumed by those unfamiliar with clinical toxicology that a given species of snake will have a consistent venom. Though sometimes true, probably more often there is significant intraspecies and even intraindividual venom variability [8]. Some medically important species exhibit great variability in venom throughout their

Table 15 Snakes considered to have medically significant hemorrhagins [9]

Scientific name	Common name	Effect
Viperidae		
<i>Agkistrodon</i> spp.	American copperheads	Disintegrins and hemorrhagins
<i>Bitis</i> spp.	African puff adders, Gaboon vipers, etc.	Disintegrins and hemorrhagins
<i>Bothrops</i> spp.	Central and South American pit vipers	Disintegrins and hemorrhagins
<i>Calloselasma rhodostoma</i>	Malayan pit viper	Hemorrhagins
<i>Crotalus</i> spp. (selected)	North American rattlesnakes	Disintegrins and hemorrhagins
<i>Daboia russelii</i> , <i>D. siamensis</i>	Russell's viper	Hemorrhagins
<i>Echis</i> spp.	Saw-scaled vipers	Disintegrins and hemorrhagins
<i>Trimeresurus</i> spp.	Green pit vipers	Disintegrins and hemorrhagins
<i>Vipera</i> spp. (selected)	Selected European vipers	Disintegrins and hemorrhagins

Table 16 Snakes considered to potentially cause renal damage through direct nephrotoxins or related mechanisms (excluding those causing renal damage through the secondary mechanisms of shock, myolysis, or coagulopathy)

Scientific name	Common name	Effect
<i>Daboia russelii</i> , <i>D. siamensis</i>	Russell's viper	Direct nephrotoxin

geographic range, so significant that antivenom developed by using venom from one part of that range will be totally ineffective in treating bites by specimens from another part of the range. Classic examples are Russell's viper (*Daboia russelii*, *D. siamensis*) and the South American rattlesnake (*Crotalus durissus terrificus*). Even a single geographic location may have several distinct subpopulations of venom type. Equally, it is well established that some snake species show either

or both ontogenetic and seasonal venom variability.

Clinical Effects of Envenoming

The clinical effects of a snakebite will vary with the species of snake; the age, size, and geographic origin of the snake; the quantity of venom injected; the route of injection; the age, size, and previous health of the victim; and past exposure to venom. Thus, although there may be typical features of envenoming for a given snake species, there will usually be significant variation between cases [12].

Local Effects

Snakebite may result in very obvious bite marks and a prominent local tissue response, but equally, the bite marks may be indistinct or virtually undetectable and the local response negligible. The latter is particularly true for certain elapid species, but a few viperids also cause minimal local effects and similarly exert their major clinical effects systemically.

Bite marks vary from a single fang puncture (Fig. 25) to classic double punctures from paired fangs (Fig. 26), through numerous punctures from both fangs and nonfang teeth (Fig. 27), to scratches where fangs have dragged through the skin (Fig. 28). If two or more bites have been delivered to the same region, an even more complex pattern may be seen (Fig. 29). The distance between paired fang punctures may indicate the size of the snake but depends on the species; if the snake species is unknown, interfang distance is an unreliable method of predicting snake size.

The presence of associated effects may be of value in determining the most likely culprit. Thus, there may be local swelling (Fig. 30), erythema, ecchymosis (Fig. 31), hemorrhage (Fig. 32), blistering (Fig. 33), or frank necrosis (Fig. 34). In general, it should never be assumed that the lack of a local response to a bite indicates a trivial bite, unless the snake species responsible is already

Table 17 Snakes known to potentially cause significant local tissue injury and necrosis at the bite site [10, 11]

Scientific name	Common name	Effect
Elapidae		
<i>Naja</i> spp.	Selected cobras, especially spitting cobras	Local blistering to extensive deep necrosis
<i>Ophiophagus hannah</i>	King cobra	Occasional local necrosis
Atractaspinae		
<i>Atractaspis</i> spp.	Mole or side-fanged vipers	A few species cause only local tissue injury, occasionally necrosis
Viperidae		
<i>Agkistrodon</i> spp.	Cottonmouth, copperhead, cantil	Local blistering to necrosis
<i>Atropoides</i> spp.	Jumping pit vipers	Local blistering to necrosis
<i>Bitis</i> spp.	Puff adder, Gaboon viper, etc.	Local blistering to extensive deep necrosis
<i>Bothriechis</i> spp.	Palm pit vipers	Local blistering to extensive deep necrosis
<i>Bothrops</i> spp.	Lancehead vipers	Local blistering to extensive deep necrosis
<i>Calloselasma rhodostoma</i>	Malayan pit viper	Local blistering to extensive deep necrosis
<i>Causus</i> spp.	Night adders	Local blistering to necrosis
<i>Cerastes</i> spp.	Horned adders	Local blistering to necrosis
<i>Cerrophidion</i> spp.	Montane pit vipers	Local blistering to necrosis
<i>Crotalus</i> spp.	Rattlesnakes	North American spp.; local blistering to extensive deep necrosis
<i>Daboia russelii</i>	Russell's viper	Local blistering to extensive deep necrosis
<i>Deinagkistrodon acutus</i>	Hundred pace viper	Local blistering to extensive deep necrosis
<i>Hypnale</i> spp.	Hump-nosed vipers	Local blistering to necrosis

(continued)

Table 17 (continued)

Scientific name	Common name	Effect
<i>Echis</i> spp.	Saw-scaled vipers	Local blistering to extensive deep necrosis
<i>Lachesis</i> spp.	Bushmasters	Local blistering to extensive deep necrosis
<i>Ophryacus</i> spp.	Horned pit vipers	Local blistering to necrosis
<i>Porthidium</i> spp.	Montane pit vipers	Local blistering to necrosis
<i>Sistrurus</i> spp.	Massasauga, pygmy rattlesnake	Local blistering to necrosis (uncommon)
<i>Trimeresurus</i> spp.	Green tree pit vipers	Local blistering to necrosis (selected species only)

known and is clearly associated with significant local effects in all medically noteworthy cases.

Local pain is quite variable and not always reliable as an indicator of significant envenoming.

General Effects

General systemic symptoms vary among species and individuals but usually include some or all of the following: headache, nausea, vomiting, abdominal pain, diarrhea, dizziness, collapse, and convulsions. Particularly in children, collapse and convulsions may be the first evidence of envenoming, at least for certain species (e.g., Australian elapids). It is often assumed that hypotension will occur in response to envenoming, but hypertension is also common, and both tachycardia and bradycardia are reported.

Specific Effects

In addition to the nonspecific systemic symptoms, a variety of quite specific symptoms and signs is associated with particular venom actions. Recognition of these symptoms and signs in the early stages is important because it allows appropriate

Fig. 24 Diagrammatic representation of the toxicodynamics of envenoming (Copyright Dr. Julian White)

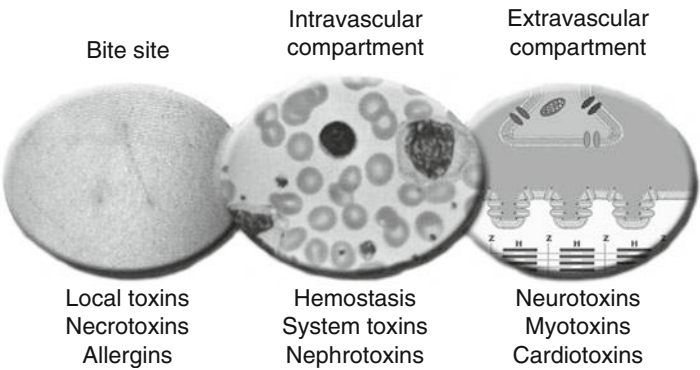


Fig. 25 Single fang puncture mark (Copyright © Dr. Julian White)

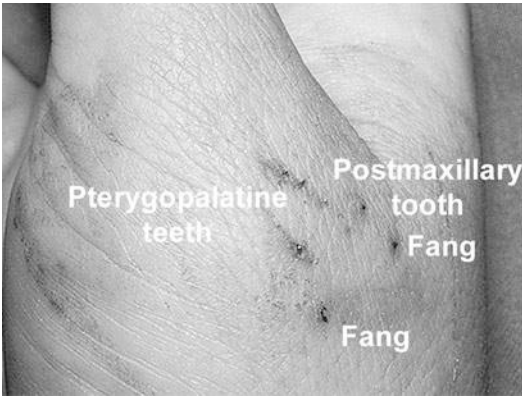


Fig. 27 Multiple punctures in a single bite from both fangs and nonfang teeth (Copyright © Dr. Julian White)



Fig. 26 Classic double puncture from paired fangs (Copyright © Dr. Julian White)



Fig. 28 Scratches where fangs have dragged through skin (Copyright © Dr. Julian White)



Fig. 29 Complex bite marks from multiple bites (Copyright © Dr. Julian White)



Fig. 30 Local swelling in the bitten limb (Copyright © Dr. Julian White)

remedial action, usually antivenom therapy, before major complications occur.

Paralysis

The flaccid paralysis caused by neurotoxins affects principally skeletal muscle and respiration, rather than cardiac or smooth muscle, and is a descending paralysis. For species with potent postsynaptic neurotoxins, paralytic symptoms can develop within 3–15 min of the bite and major paralysis within 15–30 min, but such cases are the exception. In most instances, clinically detectable paralysis will not be apparent



Fig. 32 Local hemorrhage at the bite site (Copyright © Dr. Julian White)

Fig. 31 Erythema and ecchymosis at the bite site (Copyright © Dr. Julian White)





Fig. 33 Blistering of a bitten limb (Copyright © Dr. Julian White)



Fig. 34 Necrosis of a bitten limb (Copyright © Dr. Julian White)

until at least 1 h after the bite and may be delayed up to 24 h. The cranial nerves are usually affected first, with ptosis often being the initial sign (Fig. 35). Other common initial signs are dysphonia, dysphagia, drooling, and diplopia, the latter caused by partial ophthalmoplegia (Fig. 36). As paralysis progresses, drooling may increase and ophthalmoplegia may become total, with fixed forward gaze often associated with fixed dilated pupils. Limb weakness becomes apparent, the victim usually first noticing an ataxic gait and then an inability to walk and subsequently an inability to stand or even sit up. The neck may

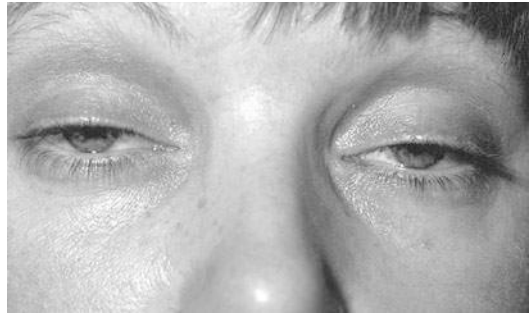


Fig. 35 Bilateral ptosis, usually the earliest sign of progressive flaccid neurotoxic paralysis (Copyright © Dr. Julian White)

become floppy (“broken neck” sign). Deep tendon reflexes will become reduced and then disappear. Respiratory distress develops, breathing may become shallow and rapid, and cyanosis may be apparent. Complete respiratory failure will ensue unless respiratory support is offered. The time from a bite to respiratory failure is highly variable, from as little as 30 min (rare) to more than 24 h, but commonly within 6–12 h. Without antivenom or anticholinesterase therapy, the period of respiratory failure may vary from less than 24 h to several days or even several weeks.

For species with potent presynaptic neurotoxins but low concentrations of postsynaptic neurotoxins, although the symptoms and signs are the same, the rapidity of onset is usually slower, with the first signs essentially never evident in less than 1 h after the bite. Unless paralysis is diagnosed and halted at an early stage with antivenom therapy, this type of paralysis is not reversible, and days, weeks, or months may elapse before axonal repair is sufficient for return of neuromuscular function.

In addition to the major features just noted, several other neurotoxic effects may occur. Of particular note are transient or permanent alterations in taste or smell, sometimes leaving the victim with permanent partial or complete anosmia.

Myolysis

Muscle damage may sometimes be purely local (some rattlesnake species) but is more commonly

systemic. Onset is likely to be at least 1 h after the bite, but symptoms and signs are mostly delayed considerably longer. Symptoms include muscle pain, tenderness, and weakness, the latter potentially mimicking paralysis. The onset of symptoms is usually associated with detectable, often frank myoglobinuria, with the urine varying from clear red (similar to hemoglobinuria) to deep muddy brown (Fig. 37).

Coagulopathy and Hemorrhagin Effects

The severity and clinical manifestations of coagulopathy will be determined, in part, by the species of snake. In general, the first clinical evidence of coagulopathy is often persistent oozing of blood from the bite site, any other areas of recent trauma, venipuncture sites, and often the

gums. The gums are particularly likely to bleed if hemorrhagins are present in the blood. The area around the bite site may show mild to gross and extensive ecchymosis (Fig. 38). Hematuria may be present; if myoglobinuria is also suspected, microscopic evidence of red cells or casts may assist in differentiation. The coagulopathy may be severe, yet the victim may be virtually symptom-free and thus the severity of envenoming masked. It is particularly because of this danger that at least baseline clotting tests should be routinely performed for most types of snakebite, the exception being regions where none of the culprit species cause coagulopathy. Although full laboratory tests of coagulation might be ideal, in most parts of the world, they are either unavailable or will take a long time. If detailed coagulation studies are unavailable, the 20-min whole-blood clotting test (20WBCT; discussed later) is an invaluable bedside test in snakebite victims. In the presence of major coagulopathy, any trauma has the potential to result in major or lethal hemorrhage, particularly with head injuries.

Fibrin degradation products are cleared through the kidneys, and secondary renal failure is a potential complication of coagulopathy. A few species can cause quite specific hemorrhages; most notably, Russell's viper (*Daboia siamensis*) in Myanmar (Burma) can cause anterior pituitary hemorrhage or Sheehan's syndrome, with long-term and potentially lethal consequences due to panhypopituitarism.



Fig. 36 Partial ophthalmoplegia with divergent squinting and diplopia, as well as ptosis, indicative of progressing paralysis (Copyright © Dr. Julian White)

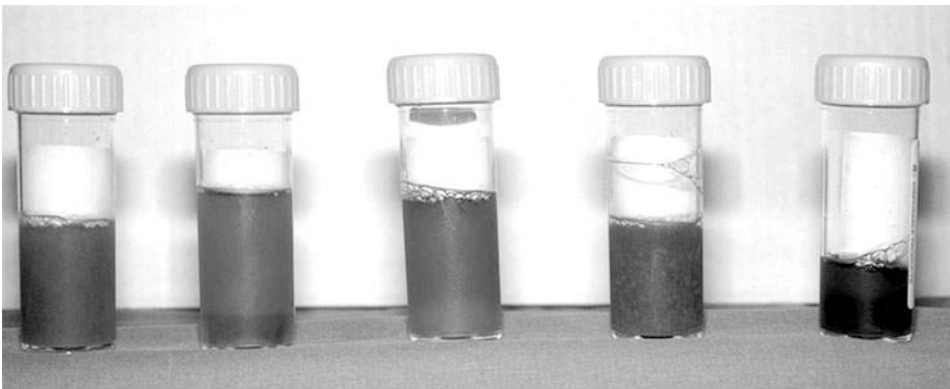


Fig. 37 Myoglobinuria secondary to systemic myolysis (Copyright © Dr. Julian White)

Fig. 38 Marked hemorrhagic effects in a bitten limb (Copyright © Dr. David Hardy)



Although the net effect of most hemostatically active venoms is functional anticoagulation, often through consumption of fibrinogen, thrombosis is sometimes the most prominent effect. Bites by vipers (*Bothrops lanceolatus*, *B. caribeus*) in Martinique, in particular, are associated with the development of deep venous thrombosis and a significant risk for pulmonary embolism, myocardial infarction, and stroke.

Thrombocytopenia, usually as a delayed onset finding after coagulopathic snakebite, can be severe and resistant to treatment, either further antivenom or platelet transfusion, though where clinically indicated both should be actively considered as therapy (Grade III recommendation). Inadequate doses of antivenom in the acute stage, or using antivenom with rapid clearance, can be associated with late-onset thrombocytopenia, such as with some North American rattlesnake bites.

Another clinical syndrome sometimes associated with coagulopathic snakebites is a microangiopathic hemolytic anemia, generally presenting with a classic triad of thrombocytopenia, intravascular hemolytic anemia, and secondary acute renal failure. This is similar to thrombotic thrombocytopenic purpura or hemolytic uremic syndrome, though the underlying causative pathology may be different. This syndrome has been seen following bites by a variety of Australian elapid snakes, as well as bites by some vipers such as the horned vipers (*Cerastes* spp.).

Nephrotoxicity

Renal damage is a common sequela of bites by many species of snakes and may be primary or secondary and varies from mild transient increases in creatinine and urea levels, detectable only by laboratory tests, through oliguric or anuric renal failure, to rare cases of permanent renal damage (renal cortical necrosis). Careful measurement of urine output is important to detect early evidence of functional renal problems, which are otherwise asymptomatic, at least in the critical early hours after a bite.

Cardiotoxicity

The cardiotoxic effects of a snakebite are primary in only a few species but may occur secondarily after bites by many species; these effects vary from mild arrhythmias to cardiac arrest. Severe myolysis, particularly when associated with secondary renal failure, may result in severe hyperkalemia, with consequent and sometimes lethal effects, as seen with other causes of hyperkalemia.

Management of Snakebite

First Aid

First aid for a snakebite is controversial. Many techniques are promoted or used around the world, but most have in common a complete

lack of objective evidence of efficacy and are often associated with significant adverse side effects varying from delay in obtaining appropriate care to directly related death.

The only universally approved first aid for a snakebite, applicable globally, is immobilizing the bitten area/limb and keeping the victim still, though it is an unproven technique [12, 13] (Grade III recommendation). For bites by nonnecrotic species, including many elapids (but not most cobras) and a few viperids, the Australian-developed pressure immobilization method (pressure bandage + immobilization; PBI) is both safe and effective [12, 14, 15] (Grade III recommendation). It is based on retarding venom transport in the lymphatics by applying moderate local and limb pressure sufficient to occlude the superficial lymphatics and inhibiting the muscle pump transport system by immobilizing the limb in a splint. Applied correctly, it may be safely left on for several hours and experimentally is as effective as a tourniquet in preventing venom movement, but far safer. This technique has not been subjected to clinical trials, although extensive anecdotal evidence from Australia suggests that it is safe and effective when used correctly [15]. More recently, a study has shown that using the originally recommended crepe bandages are unlikely to result in effective compression in humans, while use of an elasticized bandage is far more likely to be effective [16]. This study has not been tested in envenomed patients, so it remains unconfirmed, but logical. A modification of the technique using a local pressure pad over the bite site has been tested for viper bites in Myanmar, and the initial results suggest promise, with no increase in local tissue injury [17]. This method is now the recommended first aid for snakebite in Myanmar, and there is no evidence published indicating it is associated with increased local tissue damage. If these studies are extended to other necrotic bites without evidence of increased necrosis, the pressure immobilization method, or possibly the pressure pad method, may become the universally accepted first aid for all snakebites. That it is not presently accepted universally reflects concern that

immobilizing necrotic venom locally may worsen the extent of necrosis and thus be counterproductive in treating the victim. A further additional method to reduce local lymphatic flow has been proposed, based on experiments in a rat model, applying nifedipine or lignocaine topically, to be used in association with pressure bandaging and immobilization, though no human studies to confirm benefit have been published [18].

In general, the bite wound should be gently cleaned, except where bite site venom detection is available, as in Australia and New Guinea. Clear fluids may be given by mouth, but not food and certainly not alcohol.

Tourniquets are no longer recommended for snakebite (Grade III recommendation) because they are easily misused, are effective for too short a period, and have a high and proven potential for causing severe injury to the victim through ischemic necrosis [12]. The resulting gangrene may prove lethal, and the personal and social cost of amputated limbs is devastating. Suction applied to the bite site is inappropriate (Grade III recommendation) [12]. If mouth suction is used, active venom may be transferred to the oral cavity and bacteria instilled in the wound. Contrary to many positive claims, dedicated suction kits remove only small and often negligible quantities of venom and may disrupt local tissues and thereby promote spread and absorption of venom. Cutting the wound or, worse still, excision only adds further injury to the victim, increases the absorption of venom, and provides an avenue for major hemorrhage if a coagulopathy is present [12]. Application of local electric shock, as used in parts of the Americas and Africa, has never been shown in either experimental studies or clinical trials to be other than a charlatan treatment [12]. Similarly, the use of cryotherapy is without merit and associated with tissue damage [12]. Traditional healing, such as snake stones, has no rational basis, but it is possible that certain native plant extracts may ultimately prove beneficial. However, until their safety and effectiveness have been conclusively demonstrated, they cannot be recommended.

Hospital Treatment

In regions where effective hospital care is available, it should be the cornerstone of snakebite treatment. The hospital management of specific snakebites is discussed in considerable detail in the following chapters. Unfortunately, in many snakebite-prone areas, such treatment is not reliably available.

Some Basic Principles

Whenever possible, the first priority is to critically assess and stabilize the vital systems if imperiled. Thus, attention to the airway, breathing, and circulation should take priority. However, if there is a possibility of coagulopathy, attempts at cardiac compression should be circumspect and instituted only if absolutely indicated.

An intravenous (IV) line should be inserted and, in most cases, an initial IV fluid load given, especially in cases in which significant local reaction is occurring with consequent fluid shift and the potential for hypovolemic shock (Grade III recommendation). The choice of IV fluids will depend on the circumstances and availability.

Particularly in victims likely to have a coagulopathy necessitating repeated assessment of coagulation, insertion of a line suitable for repeat sampling, rather than performing repeated venipunctures, should be considered. The femoral, jugular, and especially the subclavian vessels should be avoided.

Diagnosis

As in other diseases, diagnosis is crucial in effective management of a snakebite [12]. Three principal diagnostic questions should be asked: is this a snakebite or some other condition? If it is a snakebite, is significant envenoming present and to what extent? And, finally, what type of snake was responsible?

The diagnosis of snakebite may be obvious, as in patients seen after being bitten by their pet snake, but such cases are the exception. Usually, however, it is likely that the identity of the snake is unknown. Also, there are numerous cases without a history of a bite, just a set of symptoms to be

explained, where snakebite may not even be thought of initially.

History. The key features required when taking a history from a suspected snakebite victim are as follows:

- Time and geographic location where the bite did or might have occurred (time since the bite is important, and geographic location may limit the number of possible snake species).
- If a snake was seen, its description, particularly its color, pattern, and length.
- If a bite was witnessed, was it a single or multiple bite? (A multiple bite is much more likely to be severe.)
- Was first aid applied, what type of first aid was it, how long after the bite was it applied, and what did the victim do between being bitten and application of first aid? (If the victim was actively chasing the snake or was escaping from the snake before application of appropriate first aid [e.g., immobilization or, for nonnecrotic species, pressure immobilization], first aid was unlikely to have been effective; thus, if the victim is not envenomed at initial hospital evaluation, it is more likely to be a dry bite. If, in contrast, the victim immediately lay still and had appropriate first aid applied, the lack of envenoming at initial hospital assessment may simply mean that the first aid was effective; in such cases, envenoming may rapidly ensue once first aid measures are removed.)
- Are there any nonspecific symptoms suggestive of envenoming, such as headache, nausea, vomiting, abdominal pain, fasciculations, collapse, or convulsions?
- Are there any symptoms suggestive of ongoing major envenoming, such as “tired/sleepy eyes (ptosis) and blurred or double vision; difficulty speaking, swallowing, walking, or breathing; bleeding from the bite site; or muscle pain?
- Is there any relevant past history, such as past exposure to antivenoms; preexisting cardiac, respiratory, renal, or allergic disease; or recent surgery or trauma?

- Is the patient taking any medications, particularly those that might interfere with key blood tests (especially anticoagulants)?

Examination. Careful examination can often be vital in determining the extent of envenoming.

Local Signs

- Examine the bite site and look particularly for evidence of multiple bites. Fang marks may be single or double punctures or scratches when fangs have dragged through the skin, and they are sometimes very small and difficult to see, particularly with colubrids and smaller elapids. Also look for local swelling, bruising, discoloration, blistering, and developing necrosis, typical of bites by certain species. For locally active venoms, such as bites by many viperid species, the rapidity and extent of swelling may indicate the probable severity of envenoming.

General Signs

- Check the draining lymph nodes for tenderness or swelling, which may indicate absorption of venom.
- Check the pulse and blood pressure (systemic envenoming often causes hypertension).

Specific Signs

- Check for evidence of paralysis, such as ptosis, partial or complete ophthalmoplegia, fixed dilated pupils, flat facies, poor tongue protrusion, dysarthria, drooling, limb weakness, poor grip strength, reduced or absent deep tendon reflexes, paralytic-type respiratory difficulties, and cyanosis.
- Check for evidence of coagulopathy and hemorrhagin activity, such as persistent oozing of blood (not serosanguineous) from the bite site, extensive local ecchymosis, hemorrhagic blistering, and persistent bleeding from venipuncture sites, gums, recent trauma, or elsewhere. When appropriate (e.g., viper bite in Martinique), check for evidence of developing deep venous thrombosis. When appropriate (e.g., Russell's viper bite in Myanmar), check for evidence of anterior pituitary hemorrhage and secondary panhypopituitarism (develops late).

- Check for evidence of myolysis, such as muscle tenderness or weakness and red or brown urine (myoglobinuria).
- Check for evidence of renal impairment, such as oliguria or anuria.
- Check for evidence of cardiac abnormalities, particularly arrhythmias or electrocardiographic changes associated with hyperkalemia.

Laboratory Investigations. Laboratory tests are often very helpful in determining the extent of envenoming, but this does not mean that only a large hospital with a well-equipped laboratory can manage a snakebite. It is also vital to repeat tests, even if the results are initially normal. If the patient's initial examination and test results are normal and thus indicative of no current envenoming, the tests should be repeated in about 2 h and then again 3 h later (fifth hour after initial assessment) to ensure that the late development of envenoming, particularly coagulopathy, is not missed. In Australia a schedule of testing (clinical examination and laboratory tests) has been recommended; first test on initial presentation and, if normal, remove first aid and retest after 1 h; if normal, retest at 6-h post-bite and, if again normal, retest at 12-h post-bite; if throughout the patient has experienced no symptoms, signs, or laboratory abnormalities suggestive of envenoming, then they can be discharged, but with a caveat – in some areas where death adder bite is possible – a longer period of observation (24 h) may be justified to detect late developing paralysis (Grade II-2 recommendation). In some situations, especially some viper bites causing coagulopathy (notably the Malayan pit viper bite), envenoming may persist, develop late, or recur after antivenom therapy, so retesting over a period of several days may be required. Earlier testing is indicated if symptoms or signs develop.

A Small or Rural Hospital. Many snakebite victims will initially go to a small rural hospital with no laboratories on site. However, there are some very useful tests that can easily be performed:

- Urinalysis to look for hemoglobin/myoglobin (both test positive for blood). Simple microscopy to search for red cells or casts may help

differentiate between hemoglobinuria and myoglobinuria.

- Whole-blood clotting time and 20WBCT. This simple but effective test requires at least two standard clean *glass* test tubes or similar glass containers. A small quantity of the patient's blood (2–3 ml) is placed in one tube, a similar amount of blood from a normal control (relative or staff member) is placed in another tube, and the time taken to clot is measured. If normal, the blood should clot in 5–10 min. If just the patient's blood fails to clot or develops only a weak clot by 15 min, a coagulopathy is probably present. If neither the patient nor the control blood clots, there is a problem with the test system. It has been suggested that this test can be simplified by checking for clots only once, 20 min after taking the sample (20WBCT); a normal clot indicates no coagulopathy, whereas a weak or no clot indicates coagulopathy. The 20WBCT is now a standard test for snakebite coagulopathy in many countries and has been validated [19–21]. A recent study has questioned reliability of this test, though without providing a viable alternative if no formal coagulation testing laboratory is readily available [22].
- Only in Australia, detection of snake venom on the bite site swab (see “Venom Detection” in ► Chap. 122, “Australian and Pacific Snakes”).

A Regional or Teaching Hospital. If full laboratory facilities are available, use them! The following should be performed, labeled urgent:

- Extended coagulation studies: prothrombin time/international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen level, and cross-linked or D dimer degradation products of fibrin/fibrinogen
- Complete blood picture, especially platelet and absolute lymphocyte counts
- Electrolytes, urea, and creatinine
- Creatinine phosphokinase
- Where appropriate, arterial blood gas determination

- Examination of a peripheral blood smear for evidence of microangiopathic hemolysis, suggestive of DIC
- Only in Australia, detection of snake venom on the bite site swab (see “Venom Detection” in ► Chap. 122, “Australian and Pacific Snakes”)

Snake Venom Detection. Currently, the only commercial venom detection system is the Australian CSL Snake Venom Detection Kit (SVDK; Seqirus (previously bioCSL Ltd), Melbourne, Australia), which relies on a sensitive sandwich enzyme-linked immunosorbent assay to detect even small concentrations of snake venom. It has been in use for over 30 years and can detect even nanogram concentrations of venom, but it is applicable only for snakes native to Australia and New Guinea [23]. The best sample is a moist swab from the bite site. If systemic envenoming has occurred, urine may be tested if a bite site is not available. Blood is the least reliable test sample and should be avoided if possible. The kit gives only a qualitative result and is designed just to detect which type of venom immunotype is involved, to allow use of specific rather than polyvalent antivenom. It is not a screening test for snakebite or envenoming. A negative result does not exclude envenoming, and a positive result does not indicate either significant envenoming or a need for antivenom therapy.

A number of experimental venom detection systems have been used in various regions of the world, and it is possible that commercial snake venom detection will become more widely available in the future. Some of these detection systems may be quantitative as well as qualitative, which will give far more scope to studying the extent of systemic envenoming and may lead to far more precise guidelines on antivenom doses. However, where the only antivenom choice is polyvalent, the incentive to develop or use venom detection is likely substantially reduced.

Differential Diagnosis

The differential diagnosis issues surrounding snakebite are most commonly those including snakebite in the differential diagnosis of unexplained collapse, convulsions, coagulopathy, paralysis, myolysis, or renal failure.

Treatment of Snakebite

Treatment of snakebite is likely to be effective only if the extent and nature of the envenoming are known, hence, the importance of the diagnostic process discussed earlier.

Basic Treatment

The basics of management were listed earlier and include an IV line, initial IV fluid load, and attention to the airway, breathing, and circulation. Avoid accessing the femoral, jugular, or subclavian vessels because bleeding associated with coagulopathy may be extreme (Grade III recommendation). Keep venipunctures to a minimum (Grade III recommendation). Frequent blood tests are usually required, so consider insertion of a long line via the cubital fossa or even a radial arterial line, particularly if ICU facilities are available. Monitor the pulse, blood pressure, respiration, and cardiac rhythms regularly, preferably with appropriate monitors. Monitor urine output; if in any doubt, especially in adults, consider inserting a urinary catheter, but beware insertion trauma issues if there is a coagulopathy.

Ensure that the patient is regularly assessed for evidence of developing paralysis, coagulopathy, myolysis, or renal failure, even if initially perfectly well.

Antivenom Therapy

Antivenom is the only specific therapy for envenoming (Grade III recommendation) [10–12, 15, 20–29]. Used correctly, it is arguably effective, comparatively safe, cost-effective, and lifesaving. Used incorrectly, it is ineffective, potentially lethal, costly, and may not save lives.

Antivenom is an essentially refined antibody against venom antigens. Some newer antivenoms are Fab or F(ab')₂ fragments of IgG molecules. Such antivenoms have a reduced rate of immediate or delayed (serum sickness) reactions when compared with standard whole-antibody

preparations. Newer techniques, notably caprylic acid purification, can render whole IgG-based antivenoms comparatively safe, potentially similar to Fab or F(ab')₂ antivenoms, but at a fraction of the cost and without the rapid clearance problems associated with Fab-based antivenoms. In most countries, snake antivenom is raised in horses and is thus refined horse serum. Ovine (sheep-based) antivenom is in use (e.g., CroFab in North America) and appears to have a reduced rate of adverse reactions, at least as a highly refined Fab antivenom, with correspondingly high production costs. Less-expensive ovine-based antivenoms may be useful, but there are safety issues in using sheep in many parts of the world that have ensured horses remain the mainstay for antivenom production. Other animals, such as goats, camels, and even rabbits, have been used in either commercial or experimental antivenoms, but remain marginal as a production source. All antivenoms, particularly equine antivenoms, may cause both immediate and delayed allergic reactions. These reactions are discussed later (see section “[Complications of Antivenom Therapy](#)”). Because of these potential complications, antivenom should be used only when clearly indicated. However, the risk of antivenom reactions is usually far less than the risk of untreated envenoming; *never* withhold antivenom from a patient who needs it because of concern about reactions to antivenom!

When to Use Antivenom

Antivenom should be used only if there is clear evidence of systemic envenoming and then as soon as safely practical (Grade III recommendation). Absolute indications would be:

- Significant coagulopathy
- Any degree of paralysis
- Significant myolysis (generally, creatinine kinase > 1500 IU/L)
- Any degree of renal damage
- Rapidly advancing severe local effects (some vipers such as rattlesnakes)
- A patient with a known snakebite who had a period of collapse or convulsions before arrival

More difficult are the general symptoms, such as headache, nausea, vomiting, and abdominal pain, which may indicate either envenoming (though not necessarily severe) or anxiety. In general, these symptoms alone would not be an indication for antivenom. However, guidelines must be tailored to particular circumstances; for instance, a patient with Russell's viper bite in parts of Asia might receive antivenom if any evidence of possible envenoming developed, because of the high risks associated with delayed therapy.

Choosing the Right Antivenom

A specific antivenom for the snake involved is always preferable to a polyvalent antivenom for two major reasons:

- The specific antivenom will usually be lower volume, so the risk of reactions, particularly serum sickness, is reduced, and volume overload, important in small children, is less severe.
- Specific antivenoms are generally cheaper than polyvalent antivenom.

However, specific antivenoms can be used only if the identity of the snake is known, which may be achieved in several ways, some more reliable than others:

- A visual description of the snake. Such identification is unreliable in many circumstances and is generally a poor basis for choosing a specific antivenom. There are exceptions to this in particular regions, such as areas in Asia where Russell's viper is a major cause of snakebite and is well known by the local population and there are no other snakes with a similar appearance.
- Identification of a captured or killed snake. Quite apart from the dangers posed by trying to identify a live snake or the hazards from fangs in examining a dead snake, most doctors are ill equipped to accurately or reliably identify a snake. An attempt to capture snakes is not recommended given the potential for further envenoming, even by dead snakes (whole and decapitated). Nevertheless, in some parts of the world, it is common

practice to kill the snake and bring it with the patient, and this valuable resource should not be overlooked or hastily discarded.

- Venom detection (only available in Australia). This method is generally preferred, where available. It is mostly reliable, but not every patient with systemic envenoming will have a positive SVDK result. Occasionally, erroneous results occur. Be sure that the clinical and laboratory pattern of envenoming fits the SVDK result. If it does not, urgently seek expert advice!
- Combination of geographic location and local and systemic effects. These criteria have been developed for some regions in recent years based on studies of the effects of envenoming by each species in the region (e.g., Australia, Southeast Asia). There will always be occasional atypical cases that will render such systems less effective, but in expert hands, this type of diagnostic algorithm is the most effective [20, 21, 23].

If all the aforementioned methods fail to give a reliable result, there are two remaining choices. If the range of snake species in the area is limited, it may be possible to create a local "polyvalent" antivenom by mixing two appropriate specific antivenoms. The other alternative is to use a polyvalent antivenom. In some regions this is the only choice.

Determining the Dose of Antivenom

The quantity of antivenom required is variable and depends on the type of snake, the size of the snake, and the number of bites. Children require the same dose as adults (Grade II-2 recommendation).

Administering Antivenom

Snake antivenoms should always be given IV (Grade III recommendation). There is one school of thought that they should be diluted up to 1:10 in saline or a similar diluent and then administered over a 15- to 20-min period. Infusions should start slowly under close medical observation, and the rate gradually increased. Experience and limited evidence indicates this is not the only valid

approach, and in some parts of the developing world, where IV diluted infusions may be impractical, a slow push neat antivenom injection IV is the standard of care and does not seem to be associated with higher rates of adverse reactions.

Before giving antivenom, have everything prepared to treat anaphylaxis should it occur, particularly epinephrine (adrenaline). If available, it may be advisable to have an infusion pump set up for an epinephrine infusion and ready to piggyback into an IV line if anaphylaxis develops. Premedication before administration of antivenom is no longer a recommended practice in most regions, but this is changing. Epinephrine premedication is potentially hazardous and of uncertain value, but some recent trials have indicated that, at least for some antivenoms with high rates of adverse reactions, premedication with subcutaneous adrenaline is beneficial, while others have not found a clear benefit [30–35]. Based on this conflicting evidence, it appears reasonable to consider using epinephrine premedication SC prior to giving antivenom, at least in a setting where health/hospital resources may be suboptimal (Grade II-1 recommendation). Antihistamines and hydrocortisone are of no proven value. Pretesting for antivenom allergy, as used in North America in the past, is a useless and potentially dangerous practice because it can directly cause anaphylaxis and can fail to predict anaphylaxis, and it can sensitize the patient, causing problems on subsequent antivenom exposure; hence, pretesting for antivenom sensitivity should not be performed (Grade III recommendation).

Complications of Antivenom Therapy

The immediate adverse effects of antivenom therapy are threefold:

- Rash
- Biotoxin-based fever
- Anaphylaxis or anaphylactoid reaction

The rate of adverse reactions to antivenom is variable and appears to be dependent, at least to some extent, on the type of antivenom (how the antivenom is produced and who the producer is).

In general terms, unprocessed whole equine IgG antivenoms are historically associated with the highest rate of adverse reactions, including anaphylaxis, while highly refined Fab and F(ab')₂ antivenoms have lower rates of adverse reactions, and possibly ovine antivenoms may cause fewer adverse reactions than the same class of equine antivenoms.

Rashes are the most frequent reaction, but they are still uncommon for most antivenoms. They may herald anaphylaxis.

Febrile reactions are rare with some antivenoms, because of high manufacturing standards, but may be higher with antivenoms produced to a lower standard.

Anaphylaxis or anaphylactoid reactions, though rare (probably less than 1% of cases) with good-quality antivenoms, are potentially lethal. However, some antivenoms have high rates of adverse reaction, with rates higher than 80% noted for some products, particularly those containing unrefined IgG. Reactions to antivenom, including anaphylactic-like reactions, can occur on first exposure and are thus clearly not mediated by IgE and are not predictable. Accordingly, major life-threatening reactions to antivenom should always be anticipated and preparation for treatment made before commencing the antivenom infusion (Grade III recommendation). There are three major manifestations of these major early reactions: hypotensive shock, bronchospasm, and angioneurotic edema. They should be treated the same as for any other cause of anaphylaxis, that is, with epinephrine (very cautiously IV, via an infusion pump, or subcutaneously [SC] or intramuscularly [IM]: 6 mg/100 mL at 10 mL/h for the infusion pump or 0.5 mL SC or IM for adults, 0.01 mg/kg SC or IM for children), oxygen, IV fluids, or inhaled epinephrine for bronchospasm via a nebulizer (e.g., 2 mL of a 1:1000 solution). The antivenom infusion should be stopped while the anaphylaxis is being treated and then cautiously restarted once the reaction is controlled, with titration of epinephrine versus antivenom as required.

Delayed effects of antivenom therapy are also uncommon for many antivenoms. The only effect

of general significance is serum sickness, which may occur 4–14 or more days after exposure to antivenom and is characterized by rash, joint pains, fever, and malaise. It is treated with steroids and/or antihistamines. Though of unproven value, in some parts of the world, it is common to prescribe a 5- to 7-day course of oral steroids to every patient who has received a significant dose of antivenom (>25 mL in total) in the hope of preventing serum sickness (Grade III recommendation).

Non-antivenom Therapies

Only antivenom can neutralize venom. Few other treatments are available. For predominantly or wholly postsynaptic neurotoxins (such as bites by death adders, some coral snakes, Australian copperheads, selected cobras such as the Philippines cobra), temporary improvement can be achieved with an anticholinesterase (e.g., neostigmine), which is useful if paralysis is severe or antivenom is not immediately available.

Local infection after a snakebite varies with the species and region. In many areas, infection is the exception, so routine prophylactic antibiotics are inappropriate (Grade III recommendation). However, some snake species, notably some of the pit vipers, seem to regularly cause local infection at the bite site. The organisms involved are variable and often atypical, and culture and sensitivity studies are advisable before commencing treatment.

As discussed later, coagulation factor replacement therapy is generally inadvisable for snakebites.

Local swelling may be absent after bites by some species, notably many elapids, but it is a common feature of envenoming by some elapids (e.g., some cobras) and most (but not all) viperids and crotalids. Although the extent of local underlying tissue injury can be severe, even for most viperids and crotalids, there is rarely any underlying compartment syndrome, and fasciotomy is hardly ever required. It should be performed only if there is absolute evidence of a

compartment syndrome, such as intracompartmental pressure measurements, and any coagulopathy has been controlled (Grade III recommendation) [20, 21, 36, 37]. At least for rattlesnake bites, there is a management algorithm for possible compartment syndrome [38].

Antibiotics

In general, antibiotics are recommended only if there is secondary infection, but every attempt should be made to target a detected organism.

Other

Avoid a tetanus booster IM in the presence of coagulopathy, but most patients should have their tetanus immunization status assessed and brought up to date as soon as safe to do so (Grade III recommendation).

Treating Specific Complications of Envenoming

Many potential complications are associated with envenoming, the most important being extension of major venom effects. Only the most common and important are covered here.

Paralysis

The paralysis associated with neurotoxins can present major management problems and secondary complications. It is therefore always best to avoid severe paralysis by detecting the early signs and giving adequate appropriate antivenom (Grade III recommendation). If not possible, perhaps because the patient was initially seen late and had established major paralysis as a result of nonreversible presynaptic neurotoxins (bites by some Australian elapids, some kraits, selected other species), management must focus on maintaining adequate respiration, usually by intubation and mechanical ventilation. Intubation is preferable to tracheostomy (Grade III recommendation), at least in the short term, not least because tracheostomy is a potentially lethal procedure if coagulopathy is present. Though paralyzed by the venom, the patient may be fully awake. Such

patients require careful nursing and verbal reassurance during this period. It is helpful to talk to them, explain where they are and what is happening, and manually open their eyes and rotate their head so that they can see their surroundings and caregivers. Try to find some part of their body that they can move enough to indicate “yes” and “no” to establish a means of communication. Some patients will require sedation. There is a significant risk of secondary pulmonary infection. The period of complete paralysis is highly variable, from a few days to several months. Even after respiratory function has returned, there may be continued general weakness, and the cranial nerves are sometimes even slower to recover. Occasionally, permanent damage may occur and affect taste or smell or both.

When paralysis is due to purely postsynaptic neurotoxins, antivenom may reverse this complication, but an anticholinesterase such as neostigmine may also cause a reduction in paralysis, although repeated doses will often be required, and this should not be used as an alternative to antivenom, but rather as adjunctive treatment, or where appropriate antivenom is unavailable (Grade III recommendation).

Myolysis

The major issues with myolysis often relate to secondary renal failure and hyperkalemia, which may cause lethal cardiac complications. In the early stages, before renal damage has occurred, an IV fluid load may help spare the kidneys. Alkalinization of urine has also been suggested, but it is unproven in this situation. It is uncertain whether early physical therapy speeds or hinders the muscle healing process. Experimentally, it takes about 4 weeks to recuperate from venom-induced myolysis, but it appears that only slow-twitch fibers recover, not fast-twitch fibers. This change in muscle makeup is unconfirmed in human victims of snakebite myolysis. The extent of muscle loss can be extreme and require a prolonged period of rehabilitation to rebuild normal muscle mass.

Coagulopathy and Hemorrhage

Management of coagulopathy generally takes place in the acute stage and is achieved by

neutralizing circulating procoagulant or anticoagulant with adequate antivenom, as discussed earlier. Replacement of depleted coagulation factors and fibrinogen with fresh frozen plasma or similar products while there is still active coagulopathy and circulating venom only adds fuel to the fire and increases fibrinolysis and therefore is rarely indicated. It should be performed only after it is clear that all procoagulants are neutralized, as shown by steady improvement in coagulation parameters, the exception being catastrophic bleeding (Grade III recommendation). In most patients, return to safe coagulation function (not normal function) will be sufficiently rapid, within a few hours, that the need for replacement therapy is obviated. In a few cases, return to safe levels may be too slow or reach a plateau or there may be major active bleeding. In such situations, replacement therapy is worth consideration. A study on Australian elapid bite coagulopathy giving FFP soon after antivenom found that if antivenom and FFP were given more than 6-h post-bite, then patients receiving FFP had recovery in laboratory coagulation parameters faster than those not receiving FFP, but this did not result in overall improved patient outcomes and for patients given antivenom, then FFP less than 6-h post-bite, outcomes were actually worse. The only fatality in this study was in the FFP study arm [39]. Some species, such as the Malayan pit viper, may cause prolonged coagulopathy, in part because of depot release of venom. Repeated doses of antivenom may be required.

Occasionally, the patient may recover from the immediate coagulopathy, only to move into a phase of thrombocytopenia with continued mild DIC. This complication, discussed earlier, is sometimes associated with renal failure where it may not be due to continuing envenoming, so further antivenom therapy is unlikely to be helpful. In other cases late developing thrombocytopenia without associated hemolysis or renal failure may be indicative of ongoing envenoming and may respond to further antivenom. This latter situation is particularly noted after North American rattlesnake envenoming where Fab antivenom, with a short half life, has been used rather than longer-lasting F(ab')₂ antivenom.

Some species may cause thrombocytopenia in the early phases of envenoming as a direct venom effect; antivenom is generally the most effective treatment.

Renal Failure

As discussed earlier, renal damage is most often secondary, although it may occasionally be primary, particularly with envenoming by snakes such as Russell's viper. Management will vary depending on the extent of damage. For a simple rise in creatinine and urea without significant oliguria or anuria, expectant treatment is often sufficient, with creatinine and urea usually showing slow improvement after 5–10 days. More severe renal failure, often associated with acute tubular necrosis at biopsy, may require a period of hemodialysis, but in most cases, normal renal function will eventually return. Rarely, more severe and permanent damage occurs, such as renal cortical necrosis, and requires continued renal support.

Local Necrosis

Conservative care is generally appropriate for local tissue injury to the bitten limb. It is unclear how effective antivenom will be in minimizing injury, but it should be given in most cases in the hope of at least reducing the extent of damage, if not eliminating it (Grade III recommendation). Secondary infection can occur but is not routine. Antibiotics should be used only when indicated and should be preceded by culture and sensitivity studies (Grade III recommendation). Fasciotomy to relieve local pressure is a much overused treatment in snakebite and frequently results in long-term functional deficits. It should be reserved only for cases in which significant compartment syndrome has occurred and been proved by intracompartmental pressure measurement (direct or Doppler) (Grade III recommendation). As noted earlier, at least for rattlesnake bites, there is a management algorithm for possible compartment syndrome [38]. Tetanus is a risk after snakebite, but to avoid serious hematomas, an immunization booster (IM) should not be given until after reversal of any coagulopathy.

Psychological Issues

Snakebite, even without envenoming, is often a severe psychological shock for the victim, especially children, and particularly if major envenoming has occurred and requires prolonged and extensive treatment. This issue should not be forgotten in the process of managing the patient's care.

Follow-Up

Patients who did not sustain significant envenoming and did not require antivenom will generally not require follow-up as long as they are carefully assessed before discharge and the discharge does not occur too soon after the bite.

Patients with significant envenoming requiring antivenom therapy should not go home until it is clear that the envenoming and its complications have resolved, a follow-up plan has been determined, and the patient is made fully aware of the symptoms of serum sickness and that this complication requires immediate review (Grade III recommendation). Follow-up should be arranged at approximately 1 and 2 weeks after discharge.

Special Populations

Preexisting illness may cause problems in some forms of snakebite. For instance, patients taking anticoagulants or antiplatelet drugs (even aspirin) may have a higher risk of bleeding if bitten by a snake with a venom causing coagulopathy or with a hemorrhagin-containing venom. Conversely, such medications will influence the interpretation of coagulation tests. Patients taking β -blockers, notably propranolol, may be less responsive to the epinephrine used to treat anaphylaxis [40, 41]. This has not been demonstrated to be a major issue in antivenom therapy, and the usual recommendation that antivenom be used only when clearly indicated applies. However, for patients receiving propranolol or similar medications, the need for antivenom therapy versus the risk of nonresponsive anaphylaxis should be

carefully considered (Grade III recommendation). This decision will entail a risk assessment specific for the individual patient, the type of snake, the probable degree of envenoming, and the efficacy and safety record of the chosen antivenom. Certain disease states may predispose to more severe envenoming or outcomes; renal diseases, cardiac diseases, and respiratory diseases are most prominent, but even a history of peptic ulcer may be relevant because it may increase the chance of major bleeding associated with venom-induced coagulopathy, as may liver disease associated with varices. These are but examples; for each patient, any preexisting disease or medication should be considered in relation to its interaction with the effects of the venom.

Pediatric Patients

In part because of their smaller body weight, children, especially young children, are at greater risk of severe or lethal envenoming. They may show more rapid deterioration. Conversely, despite their smaller mass, they should receive “adult” doses of antivenom, although dilution may need to be reduced to avoid fluid overload (Grade III recommendation). There may also be special problems in diagnosis in that a history may be unobtainable. Significant envenoming may result in an irritable or distraught child who may collapse or even have convulsions.

Pregnant Patients

In pregnancy, any venom-induced coagulopathy may result in bleeding affecting the fetus, and periods of hypotension may also damage the fetus. It is unclear which venom components may cross the placenta and directly affect the fetus, although most procoagulants have a large molecular weight and thus may not pass. Certainly, the health of the fetus should be closely monitored, but should major complications ensue, it may be necessary to sacrifice the fetus to save the mother. Surgical delivery should not be

contemplated in the presence of coagulopathy, except when it is the only remaining course of action to save the mother. It is unclear whether paralysis affecting the mother will affect the fetus, although it may not. Similar uncertainty surrounds myolysis. Antivenom should not be withheld because of pregnancy (Grade III recommendation).

Elderly Patients

The elderly and infirm are at greater potential risk from envenoming and should be managed with great caution and possibly more aggressive therapy.

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In Africa, snakebites are neglected medical and surgical emergencies despite their high incidence and severity. Lacking mandatory reporting, in contrast to most Latin America and Asian countries, there is no official and consolidated epidemiological data. The main consequence is the lack of accurate assessment of therapeutic needs.

According to Chippaux [1], about 1 million snakebites occur every year in Africa involving 500,000 envenomings and about 20,000 deaths, although less than 10,000 are reported to health services. Kasturiratne et al. [2] estimated that 90,622–419,639 envenomings resulting in 3,529–32,117 deaths, excluding North Africa where around 1,500–40,000 snakebites and 20–40 deaths could occur, were reported every year. More recently, a new estimation by Chippaux [3], also based on medical literature, found that 314,078 [CI 95% = 251,513–377,462] envenomings were treated in modern health facilities, including 7,331 [CI 95% = 5,148–9,568] deaths and about 10,000 [CI 95% = 5,908–14,614] amputations. However, these figures reflect only part of the reality – probably less than half of the actual cases – because many victims do not reach the health center.

Although throughout Africa envenoming remains a public health problem, there is a strong epidemiological and clinical heterogeneity. This results from a wide variety of snake fauna, with very different behaviors and venom compositions, but also human activities mainly dependent on environmental and economic factors [4].

Finally, limited access to health centers and insufficient equipment and supplies limit the efficiency of snakebite management, leading to high mortality rates and complications.

The Snake Fauna

African snakes occupy all ecological environments, from desert to rainforest and high mountains, and all strata from the canopy to the subsoil and even the coast of Indian Ocean where a species of marine elapid (*Hydrophis platurus*) occurs.

The venom apparatus of snakes belong to four types [5]:

- The aglyphous lack fangs and are therefore unable to inoculate venom. Saliva may be toxic [6] and penetrate into the wound during a bite and generate clinical signs, usually locally; some of these snakes are now considered as “non-front-fanged colubrid (NFFC)” snakes.
- The opisthoglyphous, “non-front-fanged colubrid (NFFC)” snakes, have grooved teeth connected to a gland (Duvernoy’s gland) that produces venom in at least some species; they are located toward the rear of the mouth and may inject the venom into the flesh.
- The proteroglyphous possess few teeth that are also connected to a venom gland; grooved teeth are situated at the front of the maxilla; they are immobile and can inject the venom under pressure during the bite.
- Finally, the solenoglyphous have mobile teeth, very long and able to inoculate venom in depth and under pressure.

Of the 3,500 species of snakes in the world, nearly 500 live in Africa. The Scolecophidia, primitive burrowing snakes (over 50 species), are not dangerous to humans and are rarely encountered. The Henophidia, boas and pythons (ten species), can reach large sizes and sometimes inflict significant trauma because of their strong teeth, but they are not venomous. Only Caenophidia (recent snakes) have venomous species.

In Africa, Caenophidia are represented by four families (Table 1).

The Colubridae comprise less than a hundred species, most of them nonvenomous. However, two genera (*Thelotornis* and *Dispholidus*) are opisthoglyphous and may be responsible for severe envenoming [7]. Both are arboreal. The first genus inhabits the forest and extends from West Africa to East and Southern Africa. The second one lives in savannah from West Africa to East Africa.

The Lamprophiidae include somewhat less than 150 species, showing various types of dentition, including opisthoglyphous (e.g., *Psammophis*, a very common terrestrial genus, and *Crotaphopeltis* of which one species,

Table 1 Main African snakes (Caenophidia or recent snakes)

Family	Genus	Venom apparatus	Type of venom	Habitat	Geographical zone
Colubridae	<i>Dispholidus</i>	Opystogl.	Hemorr.	Arboreal	Sub-Saharan forests
	<i>Psammodphis</i>	Opystogl.	Inflamm.	Terrestrial	Wide distribution in Africa
	<i>Thelotornis</i>	Opystogl.	Hemorr.	Arboreal	Sub-Saharan forests
	<i>Toxicodryas</i> ^a	Opystogl.	Neurotox.	Arboreal	Sub-Saharan forests
Lamprophiidae	<i>Atractaspis</i>	Solenogl.	Necrot. Cardiotox.	Burrowing	Su-Saharan Africa and Middle East
Elapidae	<i>Aspidelaps</i>	Proterogl.	Neurotox.	Burrowing	South Africa
	<i>Boulengerina</i> ^b	Proterogl.	Neurotox.	Aquatic	Congolese forest
	<i>Dendroaspis</i>	Proterogl.	Neurotox. Hemorr.	Arboreal	Sub-Saharan forests and wet savannah
	<i>Elapsoidea</i>	Proterogl.	Neurotox.	Terrestrial burrowing	Sub-Saharan savannah
	<i>Hemachatus</i>	Proterogl.	Neurotox.	Terrestrial	South Africa
	<i>Naja</i>	Proterogl.	Neurotox. Necrot.	Terrestrial	Wide distribution in Africa
	<i>Paranaja</i> ^b	Proterogl.	Neurotox.	Terrestrial burrowing	Congolese forest
	<i>Hydrophis</i> ^c	Proterogl.	Neurotox.	Aquatic	Indian Ocean
	<i>Pseudohaje</i>	Proterogl.	Neurotox.	Arboreal	Sub-Saharan forests
	<i>Walterinesia</i>	Proterogl.	Neurotox.	Terrestrial burrowing	Northeast Africa and Middle East
Viperidae	<i>Adenorhinos</i>	Solenogl.	Unknown	Terrestrial	Tanzania
	<i>Atheris</i>	Solenogl.	Hemorr.	Arboreal	Sub-Saharan forests
	<i>Bitis</i>	Solenogl.	Hemorr. Necrot.	Terrestrial	Wide distribution in Africa, except Northeast Africa
	<i>Causus</i>	Solenogl.	Inflamm.	Terrestrial burrowing	Wide distribution in Africa, except North Africa
	<i>Cerastes</i>	Solenogl.	Hemorr. Necrot.	Burrowing	Sahara and North African Sahel
	<i>Echis</i>	Solenogl.	Hemorr. Necrot.	Terrestrial	Sahel and savannah, north of the equator
	<i>Monthatheris</i>	Solenogl.	Unknown	Terrestrial	Mt. Kenya
	<i>Proatheris</i>	Solenogl.	Hemorr. Necrot.	Terrestrial	East Africa

Hemorr. hemorrhagic; Inflamm. inflammatory; Neurotox neurotoxic; Cardiotox cardiotoxic

^aAlso known as *Boiga*

^bCurrently ranked among *Naja* genus

^cPreviously named *Pelamis*

C. hotamboeia, is ubiquitous and abundant even in towns) and a solenoglyphous snake genus, *Atractaspis*, or mole viper, consisting of burrowing species whose venom is necrotizing and cardiotoxic.

The Elapidae – 40 species – are all proteroglyphous and have a neurotoxic venom, sometimes necrotizing. These include *Naja* (cobra), which are terrestrial snakes exceptionally

arboreal or aquatic; *Dendroaspis* (mamba), all arboreal; and some rarer genera generally occupying the primary forest (*Pseudohaje*) or dry regions (*Elapsoidea* and *Aspidelaps*, both burrowing snakes found, respectively, in north of the equator and in Southern Africa).

Finally, the Viperidae (less than 50 species) are solenoglyphous. The venoms are inflammatory, hemorrhagic, and necrotizing. Most are terrestrial

(*Bitis*, *Echis*), but some genera are more or less burrowing (*Causus*, *Cerastes*) or arboreal (*Atheris*).

The snakes are territorial, and their home range is limited to a few hundred square meters for species whose biomass is low and can reach several hectares for large species like *Python sebae*, a nonvenomous python (Pythonidae), or *Bitis arietans*, a very venomous viperid (Viperidae) whose adult weight exceeds 5 kg and the litters range between 25 and 40 [5]. The home range of pregnant females is further reduced, sometimes to a few m². The ecological environment influences the extent of the home range, depending on food production: it is often larger in savannah than in forest, for snakes of equal size.

In tropical countries, particularly those where the dry season is long and rough, reproduction is generally seasonal, leading to birthing at the beginning of the rainy season [8]. This optimizes the chances of survival of juveniles. However, predation is high, and in the equatorial areas, for example, over 90% of the snakes born in the year disappear [9]. Among the predators, humans are probably the most important, either for economic reasons (bush meat or leather) or accidentally, especially by crushing on roads or because of the use of agricultural insecticides toxic for reptiles [10, 11].

Snakes live hidden and exit hiding in three main circumstances, unless they are disturbed, the latter influencing the encounter with a human, especially if the habitat of the snake occurs in a place where humans cultivate or inhabit. The main stimuli that induce the snake out of hiding are hunting, mating, and giving birth (or laying eggs, dependent on species). Snakes feed at a rate that varies from one to several weeks, depending on the size of the previous meal, opportunities, and physiological needs. They seek prey either through ambush predation (e.g., a puff adder, *Bitis arietans*, positioning itself near an animal movement pathway) or through active hunting of prey (e.g., mambas, *Dendroaspis* spp., actively searching out prey) depending on species. The mating is seasonal in most species [12]. The male looking for a female to mate with may move widely during long trips

that increase the apparent abundance of snakes by a factor of 5–7 [9]. Finally, the timing of births – birth for oviparous snakes and farrowing for ovoviviparous – increases temporarily the demography and is manifested by a greater flow of young snakes in search of their new territory.

While many species disappear because of the human impact on the environment, including urbanization, some others are likely to adapt to environmental changes. This has been observed even in a few venomous snakes – like *Echis ocellatus* or *Naja melanoleuca* – in cities [3, 12]. However, the most significant phenomenon is the abundance and composition of ophidians living in large industrial plantations. The special habitats created by this type of plantation determine a selective environment that allows certain species to find favorable conditions for their development [13–17]. The risk for the workers of these plantations depends on the species attracted to these artificial biotopes, e.g., western green mamba (*Dendroaspis viridis*) in rubber plantations or rhinoceros viper (*Bitis nasicornis*) in cocoa farms [13, 18].

Selected African Venomous Snakes

Carpet or Saw-Scaled Vipers: Genus *Echis*

Arguably the medically most important snakes in African savannahs, carpet vipers have a wide distribution from West Africa across to the Middle East (and beyond as far as Sri Lanka). Though small, with small fangs and venom which is not technically as potent as some other snakes, the effects of this venom on humans can be devastating and the high frequency of bites by these snakes, which have thrived in agricultural and even urban areas, ensures their medical importance. There is significant venom variability across species which complicates choice of anti-venom. Bites cause both moderate to severe local effects (pain, swelling, blistering, bruising, bleeding, necrosis, fluid shifts into the bitten limb resulting in hypovolemic shock) and potentially lethal systemic effects including coagulopathy (defibrination), anemia, and less commonly thrombocytopenia, with renal failure

occasionally. Fatality is usually associated with the severe hemorrhagic coagulopathy.

Classic African Vipers: Genus *Bitis*

There are numerous *Bitis* species and they do not all share similar clinical effects. The most medically important species, the puff adder, *B. arietans*, causes moderate to severe local effects (pain, swelling, blistering, bruising, bleeding, necrosis which can be extensive, fluid shifts into the bitten limb resulting in hypovolemic shock), but major systemic effects (other than secondary shock and cardiac compromise) are not prominent and despite the local bleeding, systemic coagulopathy is not usually a feature, though thrombocytopenia does occur. Death is usually due to shock or cardiac compromise. The closely related Gaboon viper, *B. gabonica*, and rhinoceros viper, *B. nasicornis*, causes clinical effects similar to puff adders, except that they are also associated with hemorrhagic coagulopathy, plus early autopharmacologic collapse. In contrast, some other *Bitis* spp. cause predominantly systemic effects, notably the berg adder, *B. atropos*, which can cause flaccid paralysis in addition to local pain and swelling, but without necrosis or systemic coagulopathy.

Horned Desert Vipers: Genus *Cerastes* (Fig. 1)

These North African desert-dwelling snakes mostly cause local effects (pain, swelling,

blistering, bruising, necrosis (uncommon), potentially fluid shifts into the bitten limb resulting in hypovolemic shock), with secondary systemic effects (shock, cardiac compromise), but there are reported cases with severe coagulopathy, hemorrhage, microangiopathic hemolytic anemia, and secondary renal failure, and they can cause fatalities. As with *Echis*, there is significant venom variability across their geographic range and species, with consequent issues in selecting antivenom.

Night Adders: Genus *Causus*

Night adders are a common cause of snakebite in sub-Saharan Africa and can cause local pain and large swelling and regional lymphadenopathy, but not necrosis or major systemic effects, and fatality is not reported. No antivenom is available although there is a good paraspecificity of African polyvalent antivenoms.

Bush Vipers: Genera *Atheris*, *Protoatheris*, and *Montatheris*

In Africa there is little clinical data on these snakes and so bites are assumed to be uncommon to rare, but they are popular outside Africa as captive snakes, and at least one species, *A. squamiger*, has caused a fatality. Bites cause both local effects (pain, swelling which may be severe, bruising, not necrosis) and severe systemic hemorrhagic coagulopathy which can persist for days and is potentially fatal. They can also cause shock and renal failure. There is no antivenom available.

Fig. 1 *Cerastes gasperettii*
(Photo courtesy of Julian White)



Eurasian Vipers: Genera *Macrovipera* and *Vipera*

These classic vipers are represented in Africa by *M. lebetina*, *M. mauritanica* and *V. monticola*, all found in North Africa. From limited clinical data, it appears *M. lebetina* can cause moderate to severe local effects (pain, swelling, blistering, necrosis, fluid shifts into the bitten limb resulting in hypovolemic shock), while systemically there can be coagulopathy, bleeding, anemia, hemolysis, thrombocytopenia, and possibly renal failure, and an older report claims a 50% fatality rate, though this is certainly too high. There is no corresponding information on bites by *M. mauritanica* or *V. monticola*, which could be assumed to be similar to *M. lebetina*.

Other African Vipers: Genera *Pseudocerastes* and *Adenorhinos*

There is minimal clinical data for the false horned viper, *Pseudocerastes persicus*, but based on this, it appears likely to cause on mild to moderate local effects, without systemic effects of consequence. Despite this apparent lack of clinical significance, there is an antivenom available (Iran) that includes *P. persicus* venom in the immunizing mix. There is no case data for *Adenorhinos barbouri* bites, though it has been compared to small *Atheris* spp. and might be expected to cause only mild to moderate local effects. There is no antivenom available for this snake.

Cobras: Genera *Naja*, *Hemachatus*, *Walterinnesia*, and *Pseudohaje*

The cobras represent the most medically important elapid snake group throughout Africa. In the dominant genus, *Naja*, typical cobras (and now including the water cobra, *Naja (Boulengerina) annulata*) are the most common and important and may be divided clinically into the spitting and non-spitting cobras. Spitting cobras within genus *Naja* have modified fangs and associated venom delivery apparatus, allowing them to defensively spit a dual tightly fanned stream of venom up to 2–3 m, generally aiming for their opponent's eyes. Upon contact with the eyes, the venom causes intense pain and can damage the cornea unless promptly washed. Systemic

envenoming from venom spit is not expected. In general spitting cobras have locally active venom that causes ulceration and/or necrosis around the bite site, with only nonspecific systemic effects. If there is major tissue damage in the bitten limb, there may be secondary fluid shifts resulting in shock, and its sequelae and secondary infection and long-term scarring are common. Though neurotoxic (postsynaptic only) flaccid paralysis may occur, it appears generally uncommon and usually not severe, for most spitting cobra species. In contrast, the non-spitting cobras include a number of species that cause relatively mild local reactions, but do cause sometimes severe, even lethal, neurotoxic paralysis, and the latter may sometimes develop rapidly as classic descending flaccid paralysis, usually first seen as ptosis, an important early warning sign. There is clinical data on bites by only some of these cobra species. In some local pain and swelling may be significant, but without necrosis. Regional lymphadenopathy is reported. Several antivenoms are available covering some species, but it is unclear if there is sufficient cross-reactivity to assuredly treat envenoming by some of the other species, especially the rarer species. African cobras are not reported to cause rhabdomyolysis and, in general, seem not to cause coagulopathy, although there are limited reports for a few species such as the black spitting cobra, *N. nigricincta*, suggesting it may cause at least laboratory-detectable coagulation anomalies, though possibly not clinical bleeding. Though cobra venom contains "cardiotoxins," cardiotoxicity is not clinically described, and a recent report of takotsubo cardiomyopathy following a Cape cobra, *Naja nivea*, bite concluded this was not a direct envenoming effect, but rather related to anxiety-mediated catecholamine release [19]. Despite being locally common, the red-necked spitting cobra, *Hemachatus haemachatus*, has limited published clinical data. From this it appears to typically cause local pain, swelling, and ecchymosis, but blistering and necrosis are rare, and while fatalities due to neurotoxic respiratory paralysis are recorded, major paralysis appears to be uncommon to rare. This species is covered within a polyvalent antivenom. The black desert cobra,

Walterinnesia aegyptia, appears to be an uncommon cause of bites and generally causes predominantly local effects (pain, swelling, but not blistering or necrosis) and nonspecific systemic effects, but does not appear to cause paralysis, coagulopathy, or rhabdomyolysis, based on current limited clinical data. It is covered by several North African/Middle East polyvalent antivenoms. There is essentially no information on bites by tree cobras, *Pseudohaje* spp., and it is presumed they are a rare and inconsequential cause of bites, without any apparent need for or availability of specific antivenom. Similar comments apply to the burrowing cobra, *Naja* (formerly *Paranaja*) *multifasciata*.

Mambas: Genus *Dendroaspis*

The mambas; the three green mamba species, *Dendroaspis angusticeps*, *D. jamesoni*, and *D. viridis*; and the black mamba, *D. polylepis*, are among the most feared African venomous snakes, especially the black mamba. As discussed elsewhere in this chapter (under venoms), these snakes possess unique neurotoxins which work synergistically at the neuromuscular junction (NMJ) to cause both muscle fasciculation and paralysis. Bites may cause significant local pain and swelling and for the green mamba species, occasionally local necrosis, plus often severe abdominal pain and rapid onset of neurotoxicity, the latter especially following black mamba bites. Neurotoxicity may develop within 15 min or be delayed many hours. There may also be autonomic effects and increased sweating and salivation. Antivenom is available and raised against the black mamba.

Other African Elapids: Genera *Aspidelaps* and *Elapsoidea*

Shield nose snakes, *Aspidelaps* spp., appear to be a rare cause of bites, but the limited clinical data indicates they can cause neurotoxic flaccid paralysis, with at least one fatal case reported. Local effects may include pain, swelling, and regional lymphadenopathy, but not blistering or necrosis. There is no current evidence they cause coagulopathy, though the venom has procoagulant activity. No antivenom is available.

There is virtually no clinical data on African garter snakes, *Elapsoidea* spp., but this very limited information indicates bites are rare and cause no more than local effects (pain, swelling, regional lymphadenopathy), with no fatalities recorded. No antivenom is available.

African Atractaspine Snakes: Genera

Atractaspis* and *Homoroselaps

The side-fanged and burrowing snakes, family Lamprophiidae and subfamily Atractaspinae, are a significant cause of bites in Africa, particularly the mole vipers, *Atractaspis* spp., at least some of which have caused fatalities. These snakes are adapted to a subterranean existence including sideswiping their prey with the fang which can be protruded from the side of the mouth. This latter positioning makes these snakes difficult to safely hold behind the head, compared to other venomous snakes. At least some (notably *A. engaddensis*) have unique endothelin-mimicking cardiotoxins and sarafotoxins that can cause myocardial ischemia, infarction, and cardiac arrhythmias. However, the majority of patients bitten by *Atractaspis* spp. develop predominantly local (pain, swelling, blistering, sometimes necrosis, painful regional lymphadenopathy) and nonspecific systemic effects (headache, nausea, vomiting, diarrhea, fever, nonspecific weakness), rather than cardiotoxicity. At least two species (*A. corpulenta*, *A. engaddensis*) have caused coagulation abnormalities, but it is unclear if this is a primary venom effect or secondary. Bites by harlequin snakes, *Homoroselaps* spp., appear to be rare and are associated with mild, occasionally severe local pain and swelling, with local bleeding reported, but not necrosis or cardiotoxicity, based on current limited clinical data. There is no antivenom available for these snakes.

Major African Non-front-fanged Colubrids (NFFCs): Genera *Dispholidus*, *Thelotornis*, *Malpolon*, *Psammophis*, and *Toxicodryas*

The boomslang, *Dispholidus typus*, is a widespread arboreal “rear-fanged” snake, family Colubridae (Colubrinae), which has caused a

number of fatalities due to severe coagulopathy. The bite may cause minimal pain and swelling, but severe defibrination coagulopathy with active bleeding (hematemesis, hematuria, melena, widespread ecchymosis, intracranial hemorrhage) can develop over subsequent hours in addition to nonspecific systemic effects (headache, nausea, vomiting, abdominal pain), and there is a risk of microangiopathic hemolytic anemia and secondary renal failure. A specific antivenom is available from South Africa. Vine or twig snakes, *Thelotornis* spp., also arboreal, can cause similar clinical effects to the boomslang, with fatalities recorded, but there is no effective antivenom available. The Montpellier snake, *Malpolon monspessulanus* (family Lamprophiidae, subfamily Psammophiinae), is a “rear-fanged colubrid” (NFFC) snake with an uncertain clinical record and significance. It has been reported to cause difficulty with swallowing and respiration, which was presumed to indicate neurotoxicity, but this has not been confirmed with either venom studies or further cases documenting paralytic features. Bites cause mild to moderate local pain and swelling, without blistering or necrosis. *M. monspessulanus* is found only in the north-western part of Africa (West of Maghreb), but a close species, *M. moilensis*, is present in all the Sahelian area of north and sub-Saharan Africa. No antivenom is available. *Psammophis* sp., belonging to the same subfamily, is the most current NFFC in whole Africa. Bites are frequent but generally with no or mild clinical effects, i.e., limited pain and swelling. *Toxicodryas*, closely related to Asian *Boiga*, are arboreal. *T. blandingii* bite may cause mild neurotoxic effects (myalgia, cramps, and sensitivity troubles; [20].

There are many other NFFC snakes in Africa for which there is either limited or no clinical data and, in many cases, not even venom data. It is conceivable that some of these species might, occasionally, have a capacity to cause at least mild to moderate non-necrotic local envenoming. Given the lack of clinical data, all bites by captive specimens where the identity is assured should be reported, even if no detectable clinical effects occur. Given that NFFC species previously

considered “harmless” have subsequently caused lethal envenoming, usually due to coagulopathy, it may be prudent to manage bites by all these species with some suspicion and test for coagulopathy.

Venom Composition

Snake venom consists of a mixture of numerous substances (toxins) including many proteins, either low molecular weight peptides or high molecular weight enzymes. Peptides and enzymes bind their target with high specificity, which does not prevent the redundancy, potentiation, or competition between multiple components present in the same venom.

The main toxins found in African snake venoms are neurotoxins from elapids, sarafotoxins in *Atractaspis* venom, and disintegrins and other toxins acting on hemostasis, found in viper venoms. However, the old view that vipers cause bleeding and local necrosis and elapids cause paralysis is an inaccurate oversimplification. Some elapids, indeed many African species, may cause significant local tissue injury, and this may be more important than neurotoxicity.

All African Elapidae have a neurotoxin- α (curare-like or three-finger toxin) whose molecular weight is 7 or 8 kDa, and the number of amino acids ranges between 60 and 74 with four disulfide bridges [21]. In addition to this neurotoxin- α (α -bungarotoxin-like), mambas (*Dendroaspis*) have three other types of neurotoxin, muscarinic toxin, fasciculin, and dendrotoxin, whose molecular weight is 6–7 kDa (57–65 amino acids and three disulfide bonds). Their structure is very similar to neurotoxin- α , but they bind to other neuroreceptors resulting in other clinical effects. Binding of the neurotoxins to their receptor may be irreversible, resulting in a direct proportionality between the amount of injected toxin and the effect it causes.

The sarafotoxins of *Atractaspis* contain 20 amino acids and two disulfide bridges totalling 2.5 kDa. They are cardiotoxic, are homologous to mammalian endothelins, and possess similar pharmacological properties [22].

The disintegrins are peptides of 5–15 kDa, i.e., 49–84 amino acids with four to eight disulfide bridges [23], depending on whether they are monomeric (*Echis ocellatus*) or polymeric (*Bitis arietans*).

Among the enzymes observed in African snake venoms, the most frequent are phospholipases, acetylcholinesterase, proteases, and some others of lesser importance (L-amino acid oxidase whose role is unknown and hyaluronidase supposed to facilitate the spread of venom).

Phospholipases A₂ (PLA₂) may be in the form of a monomer (8 kDa) or a polymer (36 kDa). They hydrolyze soluble phospholipids present in the plasma and cell membrane phospholipids, although some PLA₂-derived toxins have little or no residual antiphospholipid activity. Phospholipases active on the presynaptic membrane, also known as β -neurotoxin (β -bungarotoxin-like), have not been isolated from African snake venom.

The mamba fasciculins, acetylcholinesterases (126 kDa), degrade acetylcholine.

Proteinases (20–100 kDa) are classified into two structural groups: serine proteinases that use serine to bind to their substrate [24], which includes thrombin-like enzymes [25], and metalloproteinases, characterized by the presence of an ion in their structure, usually zinc, acting according to their size, on fibrinogen, fibrin, or the vascular endothelia [26]. Initially, these enzymes activate clotting by forming a generally incomplete or unstable clot. The consumption of coagulation factors explains afibrinogenemia and the lack of blood coagulability.

Pathophysiology of Envenoming

Toxins diffuse rapidly throughout the body and bind specifically to cellular receptors causing disruptions. Their clearance may take several days or weeks. They are considered as dose dependent. Enzymes diffuse more slowly and transform their substrate molecule in 1/1000th per second until the exhaustion of the substrate. Although the inoculated dose plays a major role, a low concentration can produce significant effects before the release of the enzyme that takes several days: they are chrono-dependent.

Inflammatory Action

The enzymes of snake venoms, especially those from Viperidae, are responsible for the intense inflammatory process that is observed in most of ophidian envenoming.

Phospholipases A₂ release arachidonic acid, a precursor of inflammatory substances, such as leukotrienes, which increase capillary permeability, and prostaglandins that activate bradykinin and thromboxanes, which increase the vasodilatation and extravasation, resulting in hypotension and edema [27]. In addition, the release of inflammatory cytokines will also stimulate the nonspecific defense mechanisms [28].

Proteases, particularly metalloproteinases, destroy the vascular endothelium causing bleeding and accentuating the inflammatory response [29].

Action on the Nervous System

The specificity of the different α -neurotoxins explains the pharmacological and clinical features [30]. Neurotoxins from elapid venoms block the transmission of nerve impulses specifically at the neuromuscular junction (NMJ), either presynaptically (β -neurotoxins; β -bungarotoxin-like) or postsynaptically (α -neurotoxins; α -bungarotoxin-like). Not all elapids have both types of toxin, and African elapids (cobras specifically) appear to possess just α -neurotoxins that bind to (or adjacent to) the nicotinic acetylcholine receptor on the muscle end plate at the NMJ, thereby preventing binding of acetylcholine and thus blocking neurotransmission, resulting in curare-like descending flaccid paralysis. Clinically this is first manifest in cranial nerves (ptosis, then partial, becoming complete ophthalmoplegia, loss of facial expression, open mouth, drooling, fixed dilated pupils, loss of upper airway protection) and extends to all the skeletal motor muscles, including the intercostal muscles and the diaphragm. Dendrotoxins found in mamba snake venom, while also targeting the NMJ, block the voltage-gated potassium channels of the presynaptic membrane, increasing acetylcholine release.

The fasciculins inhibit acetylcholinesterase, the role of which is to regulate the transmission of nerve impulses by degrading acetylcholine after its action on the postsynaptic receptor. The synergistic actions of dendrotoxins plus fasciculins result in massive oversupply of neurotransmitter at the NMJ, with muscle fasciculation and paralysis. The muscarinic toxins bind to the M₁ acetylcholine receptors of the postsynaptic membrane possessing a highly excitatory activity on the parasympathetic system [31].

Actions on Blood Coagulation

Bleeding is related to the action of several factors [32].

Locally – and sometimes far from the bite – the hemorrhagins, which are metalloproteinases, perforate the vascular endothelium and cause local bleeding and extravasation of the blood from the vascular compartment. This phase is very fast and essentially mechanical [29].

Other metalloproteinases, such as ecarin present in the venom of saw-scaled vipers (*Echis* sp.), are activators of prothrombin. They hydrolyze the latter to form meizothrombin [33] resulting in fibrin formation, the skeleton of the blood clot, with simultaneous activation of fibrinolysis, resulting in rapid and devastating consumption of circulating fibrinogen.

Thrombin-like enzymes are very common in Viperidae. They hydrolyze the fibrinogen, releasing fibrinopeptides A and/or B, allowing the formation of fibrin [32]. However, the role of these components in African viperid snakebite is less clear.

Finally, there are several enzymes acting on platelets, activating or inhibiting platelet aggregation [34]. The cerastobin, cerastocytin, and cerastatin, for example, are serine proteinases isolated from the venom of *Cerastes cerastes*, a North African viperid. They show both thrombin-like and platelet-aggregating properties but act at different levels of the blood coagulation pathway and platelet function.

Mambin and dendroaspin, found in the venom of *Dendroaspis*, are proteins showing the same

general structure as the three-finger toxins. However, they do not act on neuromuscular transmission but inhibit platelet aggregation [35, 36].

The activation of coagulation pathways, resulting from the action of most components of vipers and some colubrid venoms, causes the consumption of plasma coagulation factors making the blood unclottable (afibrinemia, afibrinogenemia, thrombocytopenia, etc.).

In Africa, vascular thrombosis and visceral infarctions are uncommon during the procoagulant phase, i.e., at the beginning of envenoming. However, it has been described, especially after *Echis ocellatus* and more often after *Cerastes cerastes* envenoming as either cardiac infarctions [37] or ischemic strokes [38–40].

Various Actions

The sarafotoxins from some *Atractaspis* sp. are cardiotoxic. They cause coronary vasoconstriction and cardiac ischemia [41].

Various proteolytic enzymes are responsible for tissue destruction, causing a more or less extensive necrosis [42], which can be amplified by a secondary anoxia, resulting from the edema or iatrogenic complications after placing a tourniquet, for example, or superinfections following traditional treatment [43, 44].

Epidemiology of Envenoming

In tropical Africa, snakebites are highly underestimated [1, 3]. Several reasons explain the underreporting. Snakebites are attributed to supernatural and not casual or medical reasons, punishment, revenge, spell, witchcraft, etc., which require the intervention of a traditional healer to lift the curse. Over 90% of victims consult a traditional healer at first instance, and between 40% and 60% do not attend hospital, either because it's too late or because they do not trust modern medicine [3, 45–48]. The accessibility of health facilities is poor, equipment and drug supplies are low, and availability and training of health personnel are insufficient. Data collection

and reporting systems are inefficient or nonexistent, which limits epidemiological assessments. In addition, antivenom is expensive, often difficult to preserve in remote health centers, and its administration remains poorly codified [49, 50]. However, a better assessment of the incidence and morbidity is essential for improving care. It would help to provide appropriate amounts of antivenom and determine their positioning for rational use [51].

The economic evaluation of the cost of snakebites is not yet a common practice. It is necessary to take into account the patient's disability time during the treatment, the cost of the latter, and the complications of the envenoming, either the patient's death or disability resulting from necrosis or surgical treatment. Long-term or permanent disability can be measured by the disability-adjusted life years (DALYs).

Available data are incomplete and come from two sources [3, 52]:

- The records of health centers (more or less well kept) lead to an estimation of 300,000 envenomings and nearly 10,000 deaths a year in sub-Saharan Africa.
- The community surveys suggest that there are two to three times more cases (1 million per year) and three to four times more deaths (about 30,000 per year).

Three quarters of the bites occur during agricultural work, hunting, or movement related to work [3]. The agriculture practiced using traditional methods leads to high exposure, which is strengthened by the attraction of snakes to agribusiness plantations where human activity is intense (see section “[The Snake Fauna](#)”).

Young men undergo between 50% and 75% of bites. Children, although they represent almost half of the general population, are bitten less often than might be expected, similarly women, the latter contributing to agricultural work as much as men.

The seasonal incidence of accidents is related to the behavior of snakes and the agricultural agenda, both related to the climate. Geographical variations are largely dependent on agricultural

practices: in forest regions, bites are more spread out throughout the year, while in the savannah, snakebites are more frequent during the rainy season. The relationship with rainfall reflects its close involvement in both behavior of ophidians and human activities.

A majority of snakebites occur in late afternoon or early evening. Some occur at night and occur while the human is sleeping, bitten by snakes searching for food inside houses.

Over 80% of the bites are located on the lower limb, especially below the knee, but significant geographical variations are observed. Bites to the hand are uncommon to rare, but not exceptional, especially among farmers who work with tools with a short handle or in children who dig with bare hands in burrows in search of small vertebrates to supplement their diet [53].

Finally the main factors that influence the incidence are [3]:

- Annual rainfall exceeding 500 mm
- A population density below 100 inhabitants per km²
- A dominant agricultural activity, some types of cultivation associated with an increased incidence, and/or severity of bites, like cotton or sugar cane plantations where *Echis ocellatus* and *Bitis arietans* are particularly abundant

Clinical Presentation of Envenoming

The severity of bites is influenced by several factors [3, 50, 54]. The toxicity of the venom and the amount injected by the snake are obviously important factors. They depend on the snake species, its size, capacity of its venom glands and current content, and circumstances of the bite. Multiple bites are more likely to result in major envenoming. The age, size, health status of the victim, and the location of the bite are also important. The time to use first aid or nonmedical treatment and the type of first aid or other nonmedical treatment are important as many nonmedical treatments are either ineffective or actually cause harm and may even speed envenoming. Finally, the time between the bite and effective treatment

will also have major consequences. Delayed treatment may induce complications and reduce the effectiveness of treatment. As a result, this is one of the main factors predicting mortality after envenoming [54].

The frequency of asymptomatic bites, i.e., inflicted by nonvenomous snakes or venomous ones not injecting their venom (“dry bites”), is on average 40% in savannah and 60% in forest where they can reach 80% in some countries [1, 3, 50, 55].

At least four envenoming syndromes can be described. Presentation may involve more than one syndrome and this can complicate diagnosis and treatment.

Inflammatory Syndrome

It consists of severe pain, a more or less extensive edema, sometimes fever and leukocytosis higher than 10,000 leukocytes per mm^3 . Development is generally rapid and lasts for 2–5 days. Edema decreases slowly (1–3 weeks), even with treatment by antivenom.

If significant edema appears, it is necessary to look for distal signs of cyanosis and perform, if possible, an ultrasound and measure the intracompartmental pressure [53, 56]. Surgical intervention for compartment syndrome (fasciotomy) should never be performed unless true pathological raised intracompartment pressure has been confirmed by appropriate measurement (see later).

Hemorrhagic Syndrome

It manifests with local and or systemic bleeding (Fig. 2).

Bleeding from the fang marks appears immediately after the bite. It can persist for several days or even a week or two, resulting in anemia that can be severe (hemoglobin below $5 \text{ g} \cdot \text{dL}^{-1}$). Remote bleeding (gums, nose, old scars) or cutaneous manifestations (purpura, blisters) usually begin 30 min to 3 h after the bite, but can be delayed for 2 or 3 days when the amount of venom injected is minimal. Internal bleeding should be



Fig. 2 Hemorrhagic syndrome after *Echis ocellatus* bite. Note the blood tears whereas the child was bitten on the left foot (Photo courtesy of Jordan Benjamin)

considered clinically and, if possible, determined using imaging such as an ultrasound. Meningeal or peritoneal hemorrhage and extensive bruising are the most frequent manifestations.

Hematology and coagulation tests are very useful but often not feasible due to the lack of an effective functional laboratory in the African setting. However, it is always possible to perform a whole blood clotting test (20WBCT) in a clean dry glass tube or vessel, even in the peripheral health centers (Fig. 3). The global standard test is the 20WBCT, described subsequently in this chapter.

Neurological Syndrome

This commences with sensory disturbances, initially locally (anesthesia, tingling) and then central (tinnitus, blurred vision, diplopia, dysgeusia) accompanied by a descending flaccid motor paralysis, ptosis, dysphonia, dysphagia, and dyspnea, and then limb weakness progressing to respiratory paralysis causing asphyxia and death if not treated

Fig. 3 Whole blood coagulation test

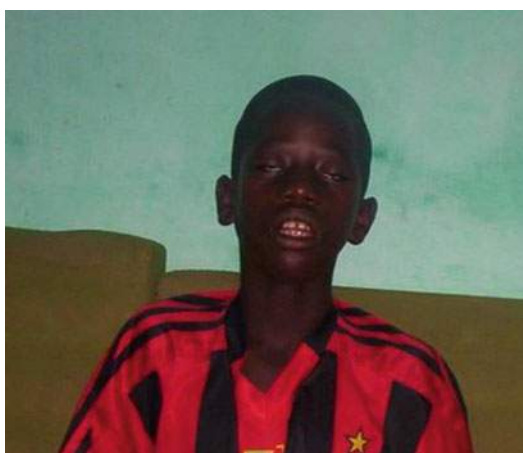
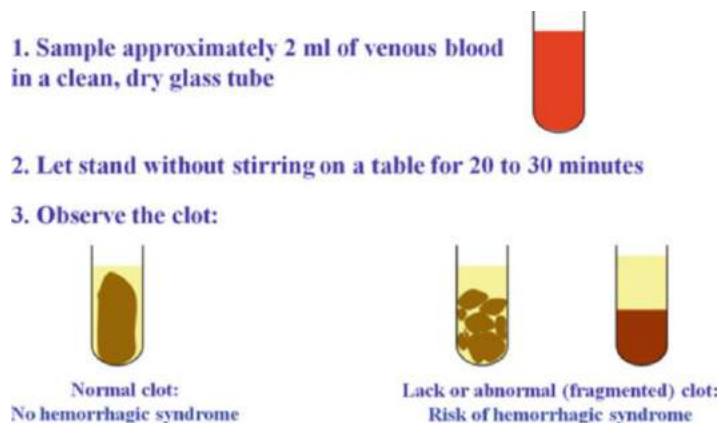


Fig. 4 Neurotoxic syndrome after *Naja melanoleuca* bite. Note the typical ptosis and rictus (Photo courtesy of Cellou M. Baldé, IRBAG, Kindia, Guinea)

(Fig. 4). In Africa this is associated with bites by some elapid snakes.

Dendroaspis venoms, besides the neurotoxic syndrome described above, are responsible for a hypersecretory syndrome (= muscarinic syndrome). Soon after the bite, the patient shows sialorrhea, excessive perspiration, vomiting, diarrhea, abdominal pain, and miosis (Fig. 5). Further, the synergistic actions of dendrotoxins (cause excess presynaptic release of acetylcholine) and fasciculins (anticholinesterases blocking normal removal of excess acetylcholine from the synaptic cleft) result in atypical neurotoxicity, with muscle fasciculation in addition to paralysis.

Necrosis

Necrosis can appear quickly after the bite. It is usually dry but can become secondarily infected and purulent (Fig. 6). It extends slowly stabilizing in about a week, unless a secondary gangrene develops and complicates the evolution (Fig. 7). It may also develop in the areas of initial blistering and bleb formation, though not all cases with such an initial local reaction will progress to skin necrosis.

Diagnosis of Envenoming

The diagnosis is mainly clinical. The lack of laboratory facilities in most African health facilities severely limits the biological confirmation of the envenoming, etiologic diagnosis of hemorrhagic syndrome, and prevention of complications, including kidney failure.

History should include specific circumstances and time of the bite, the description of the snake, and treatments taken before arrival in hospital, plus past medical history including any previous snakebites or exposure to antivenom.

The examination evaluates for fang marks, checks for multiple bites, and determines the size and grade of the edema (Table 2). Presence and depth of necrosis should be determined and specified. Check draining lymph nodes for enlargement and/or tenderness, potentially indicating venom absorption and movement.

The location and size of bleeding are estimated and graded (Table 3). The 20WBCT is performed in all cases of bite showing an inflammatory syndrome and, a fortiori, hemorrhagic syndrome.

Neurological disorders are evaluated in detail and are also subject to severity grading (Table 4).

These evaluations and gradations are important in assessing the severity of envenoming, decision on (the dose of) antivenom, and monitoring the clinical course of envenoming.

Note that the use of a grading system to evaluate any aspect of envenoming is controversial and not universally accepted. Grading is also limited by the timing of assessment, and because

snakebite envenoming is generally a progressive disease, it is important to frequently reassess the grading level, to detect change that might require a different level of therapeutic intervention. Irrespective of grading, some clinical common sense is required to assess the overall patient and the impact of envenoming, including the contribution of preexisting disease and therapy. Because of their smaller body mass, children are potentially more likely to suffer severe envenoming and may progress from minimal effects to major envenoming more rapidly.

In rural Africa, ultrasound examinations are rarely possible although they could facilitate diagnoses of internal bleeding. Measuring intracompartmental pressures is essential for accurate diagnosis of compartment syndrome which can complicate a significant edema and indicate a need for surgical treatment such as fasciotomy [56].

Whenever possible, a complete blood count should be performed to evaluate for anemia and leukocytosis, which are useful in assessing the severity and evolution of hemorrhagic and inflammatory syndromes, respectively. Platelet counts, prothrombin time, fibrinogen, and D-dimer levels that allow monitoring therapy for hemorrhagic syndrome should be performed, if available, and repeated to monitor for change. The presence of thrombocytopenia highlights the effect of disintegrins. Creatine phosphokinase (CPK; CK) levels higher than 5,000 U/L may be a good



Fig. 5 Muscarinic syndrome after *Dendroaspis polylepis* bite. In addition to the neurotoxic syndrome, note the hypersecretion syndrome (Photo courtesy of Cellou M. Baldé, IRBAG, Kindia, Guinea)

Fig. 6 Necrosis after *Bitis gabonica* bite (Photo courtesy of Cellou M. Baldé, IRBAG, Kindia, Guinea)



Fig. 7 Gangrene after *Bitis arietans* bite (Photo Courtesy of Pierre XX)



Table 2 Clinical gradation of edema

Grade	Symptoms
1	Localized edema reaching the nearest joint
2	Progressive edema not exceeding two joints
3	Extensive edema not exceeding the limb
4	Edema beyond the root of the limb (anasarca)

Table 3 Gradation of bleedings and hemorrhages

Grade	Symptoms
1	Persistent local bleeding over an hour
2	Bleeding from the mouth, nose, or scars
3	Hematoma, ecchymosis, purpura, blisters
4	Internal hemorrhages (peritoneal, meningeal, etc.)

Table 4 Clinical gradation of neurological disorders

Grade	Symptoms
1	Anesthesia, tingling, local pins, and needles
2	Sweat and abundant saliva, vomiting, miosis
3	Ptosis, troubles of vision, hearing, and swallowing
4	Respiratory distress, impairment of communication

indicator of the extent of necrosis, allowing monitoring of the subsequent action of the proteolytic enzymes on the myolysis. Note that direct venom-induced rhabdomyolysis, a risk with snakebites in

some other parts of the world, has not been reported as a risk with African snakebite, at least so far. Very high CK levels should raise suspicion of systemic rhabdomyolysis which might require muscle biopsy for confirmation (only consider once any coagulopathy has fully reversed). Renal involvement is detected by maintaining good fluid balance charts (looking for polyuria, oliguria, or anuria) and the measurement of creatinine and urea levels.

However in the absence of laboratory, it is always possible to perform a whole blood clotting test (20WBCT) (Fig. 3).

Treatment of Envenoming

The management of snakebites raises two types of issues: firstly, antivenom supply and, secondly, training of health personnel. In fact, when both factors are resolved, victims quickly attend health centers, and the mortality is reduced by a factor of five to tenfold [57].

Ineffective management due to the lack of health structures, or appropriate equipment and medication, as is common in many African countries, increases the risk of poor outcomes whatever the time between the bite and treatment. First aid, when aggressive – tourniquet, incisions, scars, traditional poultice – may worsen the

envenoming. Superinfection, for example, aggravates the local lesions and causes disabling sequelae.

Any snakebite requires thorough washing of the wound and ensuring that tetanus immunity is up to date [58]. However, it is important to avoid injections while there is active coagulopathy.

In case of severe wound damage or infections, local treatment using Dakin's solution (boiled water with sodium hypochlorite solution 0.5% + sodium permanganate 100 mg · L⁻¹) is repeated twice a day, at the same time that evacuation of lesions is performed to assess the clinical evolution. Where possible, standard culture and sensitivity testing should be performed to allow targeted antimicrobial therapy, if clinically indicated.

Specific Treatment: Antivenom Immunotherapy

The antivenom must meet precise specifications of efficiency, i.e., manufacture using immunizing venoms from the relevant species and geographic area, and production methodology including removal of contaminants [59, 60]. Its price must be affordable and distribution correspond to epidemiological needs to supply the peripheral health centers, among others. This requires a functional and efficient notification system to identify the locations where antivenoms should be positioned. Competition among producers may be a theoretical price control factor, but the reality in Africa is that the range and supply quantity of antivenoms are inadequate, so such competition is unlikely. Complementary financing schemes (insurance, equalization, partial support by the national or local governments, private companies, and orphan drug policy) should be adapted in each country. Furthermore, the problem of product preservation must be resolved either by an appropriate cold chain or the lyophilization of the antivenom to reduce the risk of protein degradation and facilitate inventory management [49, 50]. However, lyophilization is a delicate process and requires that the solubilization of the antivenom can be obtained in less than 5 min, which is uncommon [61, 62].

The cost-effectiveness of antivenom was evaluated by comparing the evolution of snakebites between patients treated with or without antivenom [63]. A decision-analytic model was developed and tested using the following variables: species of snakes causing the bite, effectiveness of antivenom, case fatality rate in the absence of treatment, risk of adverse reactions involving life-threatening effects, mean age at the time of the bite, remaining life expectancy, and risk of disability. The price of treatment included all costs related to patient care including logistics and the risk of serious side effects and the cost of the antivenom. This demonstrated that treatment using antivenom was highly cost-effective: a benefit higher than \$2,330 per death averted and nearly \$100 per year of life adjusted for permanent disability. Subject to proper management of envenoming, systematic use of antivenom is likely to reduce mortality and permanent disability by 90%, not to mention the reduction in the duration and costs of hospitalization. Antivenom treatment might well spare each year more than 38 million US dollars annually, 15.7 for deaths and 22.5 for preventable disabilities, representing more than double the cost of antivenoms and their administration.

Training of health personnel is based on a simple and appropriate treatment algorithm. Moreover, besides the initial training during medical or nursing school, it is necessary to ensure regular updating of knowledge.

The antivenom is administered intravenously, allowing rapid neutralization and elimination of constituents of the venom [64, 65]. The dose is determined by the amount of venom injected by the snake, estimated by the clinical effects, and is identical for all victims including children. There is no pediatric or patient weight-based dosing.

In mild envenoming (i.e., without bleeding or neurological disorders), the administration of a minimal dose is usually sufficient. Depending on the type of antivenom and type of snake, this may be as little as a single vial. The presence of a hemorrhagic or neurologic syndrome requires the administration of more substantial doses (e.g., for some antivenoms this may equate to, respectively, two and four vials; see Fig. 8).

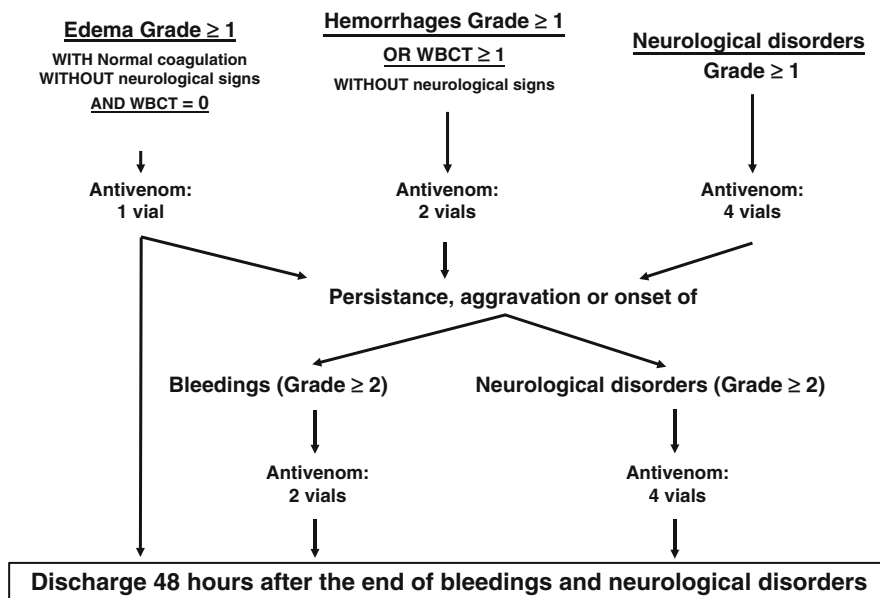


Fig. 8 Algorithm of snakebite treatment

However, dosage depends also on the neutralizing potency of the antivenom.

A first assessment of the efficacy of treatment should be carried out after 2–3 h and then at 6, 12, 24, and 48 h. A repeat dose of the antivenom can be given if bleeding or neurological disorders persist, worsen, or appear (Fig. 8).

Finally, the major remaining challenges concern the availability of appropriate antivenom and administration within a reasonable time, which ideally is less than 10 h after the bite, although late antivenom administration remains effective in some circumstances [66]. Antivenom when manufactured according to the recommendations of the World Health Organization [60] is generally expensive, one of the main reasons for the lack of antivenoms in peripheral health centers [15, 49, 50]. Conversely, many antivenoms are sold, often at low cost, but do not correspond to WHO recommendations and are dangerous or fake [67]. Table 5 lists the antivenoms currently used in Africa (it is important to note that the range of antivenoms available is changing, not static). Finally, the important delay in patients seeking medical care which is frequently observed is related to many factors such as treatment-seeking behavior [45, 47, 55], remoteness and poor supply

of health centers, poverty, and cost of treatment, all inducing a vicious circle leading to the abandonment of antivenoms [50].

Symptomatic treatment includes analgesics, anti-inflammatory drugs (avoiding salicylates if there is a hemorrhagic syndrome), and correction of hypovolemic shock and electrolytes, especially in hypotensive patients or those with significant complications (edema, necrosis, cardiopulmonary or renal failure).

Blood infusion or administration of blood substitutes (platelets, fibrinogen, fresh frozen plasma, etc.) should only be performed after the venom present in the victim has been neutralized by the antivenom. Otherwise, hemorrhagic syndrome may be reactivated [68].

Airway protection and artificial respiration should be initiated in cases of severe dyspnea or respiratory arrest. Kidney failure is treated by peritoneal dialysis or hemodialysis when it is feasible.

Compartment syndrome, provided that the diagnosis is confirmed by measuring intracompartmental pressures, should be treated by a fasciotomy. However, the high risks of complications (bleeding and secondary infections in particular) and significant sequelae (unsightly scars and

Table 5 Availability and characteristics of African antivenoms

Manufacturer	Country	Type	Specificity	Animal	Price (US\$)
Bharat ^a	India	F(ab') ₂	Polyvalent	Horse	50
Butantan ^b	Brazil	F(ab') ₂	Polyvalent	Horse	?
Clodomiro Picado ^{b,c}	Costa Rica	IgG	Partial polyvalent	Horse	?
Inosan ^c	Mexico	F(ab') ₂	Polyvalent	Horse	50
Protherics ^{b,c}	Great Britain	F(ab') ₂	Monovalent (<i>Echis</i>)	Sheep	?
South African Vaccine Producers ^b	South Africa	F(ab') ₂	Polyvalent and monovalents	Horse	?
Sanofi ^{c,d}	France	F(ab') ₂	Polyvalent	Horse	150
Serum Institute of India ^{a,d}	India	F(ab') ₂	Polyvalent	Horse	50
Vacsera ^a	Egypt	F(ab') ₂	Polyvalent	Horse	?
Vins Bio ^a	India	F(ab') ₂	Polyvalent	Horse	50

Preclinical performance of some antivenoms was poor, either because venoms used for the horse immunization were not relevant (Asian snakes instead of Africa ones) or the manufacture process was insufficient

^aUncontrolled valences and purification

^bRestricted diffusion

^cAppropriate valences and purification and clinical trials

^dNo longer manufactured

functional impairments) must be considered, and surgical treatment should be used only after careful consideration [69] and only once any coagulopathy is reversed.

Necrosis will be treated surgically after final stabilization of the lesion (the spread of necrosis halted for 2 consecutive days and CPK decreased below 5,000 U/L).

Corticosteroids do not appear to have significant therapeutic value, whether to treat neurological symptoms [70] and edema [71] or to prevent early adverse reactions following antivenom administration [72].

Routine administration of antibiotics has not been fully evaluated [73]. However, it should be reserved for cases with confirmed bacterial infection and adapted to the circumstances and context.

First Aid

1. Reassure victims.
2. Immobilize bitten limb with splint or sling. Firm crepe bandage may be used as long as it does not compromise circulation (tourniquet effect); beware of progressive limb edema causing tightening of bandages resulting in circulatory compromise.

3. Remove any rings or other jewelry from the bitten limb (to prevent them becoming constrictive if swelling develops).
4. Observe airway and ensure airway patency. Support respiration if impaired.
5. Hasten transfer to hospital and take dead snake along if feasible.
6. Avoid harmful and time-wasting procedures such as incisions, applications of native herbs, black stones or extracting devices, electroshock, and application of icepacks.
7. Avoid use of tourniquets, constricting bands, etc., as it has been shown to have minimal or no beneficial effects unless the snake was identified as a dangerously neurotoxic elapid and medical care can be reached in under 40 min from time of application.
8. Relieve pain with oral paracetamol.
9. Irrigate eyes with plenty of clean flowing water following cobra venom spits in eyes.

Hospital Care

1. All victims should be admitted to the hospital for at least 24 h (better if less than 10 h) except in clear nonvenomous bites where snake has been reliably identified by an expert.

2. Pain may be managed with either oral paracetamol or narcotics. Tramadol may be substituted for narcotics. **Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) may aggravate bleeding and should therefore be avoided. Beware of respiratory depressant medications, particularly in bites by neurotoxic species (elapids).**
3. Persistent vomiting may be treated with antiemetics such as intravenous chlorpromazine, metoclopramide, or ondansetron. Antivenom may sometimes also reduce GIT symptoms of envenoming.
4. Intramuscular injections should be avoided in bites where coagulopathy might occur because of the likelihood of significant local hematoma formation. Bites by any viper or boomslang or vine or twig snake may carry such a risk, but bites by African elapids are not currently noted as causing coagulopathy.
5. Clinical evaluation of victims:
 - (a) History – elicit site of bite, circumstances of bite, time of bite, type of snake, severity of bite, number of bites, local features, and systemic features, plus past medical history, any medications, and past exposure to snakebite or antivenom
 - (b) Examination:
 - (i) Elicit vital signs, blood pressure (BP), heart rate (and regularity), respiration, and urine output.
 - (ii) Note severity and nature of local injury (extent and girth of swollen limb compared to healthy limb) and local bleeding. These initial and subsequent daily measurements would be used to monitor progress and effectiveness of interventions. If possible mark the upper/outer extent of swelling, noting the date and time; this allows assessment of progression of swelling. Check for enlargement or tenderness of draining lymph nodes in groin or axilla.
 - (iii) Elicit presence of systemic bleeding [bleeding from oro-gingiva, nose, vomitus, urine, stools, skin], neurologic abnormalities [drooping eye lids (ptosis), other cranial nerve paresis, drooling, respiratory muscle weakness, impaired consciousness, meningism], cardiac arrhythmias, pulmonary edema, renal angle tenderness, and other abdominal tenderness (possibility of retro-abdominal bleeding in patients with severe coagulopathy, notably saw-scaled viper bites).
 - (c) Investigate:
 - (i) Do the 20 min whole blood clotting test (20WBCT). In this test 2 ml of venous blood is placed in a new, clean, dry, glass test tube and left undisturbed for 20 min at room temperature. The tube is then tipped to see if blood runs out or has clotted.
 - (ii) Packed cell volume and full blood counts, blood film morphology, urea, electrolytes and creatinine, liver function tests, PT-PTT, and fibrin degradation products. Group and crossmatch for whole blood transfusion. (Note: All of these tests will likely be unavailable in a rural African health center setting, but should be utilized in a developed nation setting, when dealing with an exotic snakebite.)
6. Intravenous fluids should be given to patients especially those with hypotension or shock who require an IV fluid load. Infusion of dopamine may be considered in refractory shock.
7. Antivenom should be administered if indicated, as “poisonous (venomous) snakebite is not necessarily the same thing as snakebite poisoning (envenoming),” and bites may also be by nonvenomous snakes (see Fig. 8).

Administration of antivenom is by slow intravenous infusion or injection in at least 10 mins (or at 1 ml per min). If available, dilution of antivenom in sterile IV fluid (normal saline or similar) may be useful, but is not mandatory.

Hypersensitivity reactions are not uncommon (5–30% depending on type of antivenom) and should be anticipated, ensuring adrenaline and resuscitation equipment are immediately available plus staff to use them, prior to commencing antivenom. Patients should be monitored closely for early adverse reactions like pruritus, urticarial rashes, hypotension, bronchospasm, and anaphylaxis.

Effectiveness of antivenom is judged by the clinical response, i.e., reduction in limb swelling through daily measurement of extent and girth, bleeding from bite site, 20WBCT, and changes in clinical or biological features.

Anticoagulants have no place in management.

8. Fresh whole blood may be required with low hematocrit and/or active bleeding, once sufficient antivenom has been administered.
9. Patients with neurotoxic envenoming should:
 - (a) Be given a Tensilon (edrophonium) test: atropine sulfate is given intravenously (50 µg per kilogram without exceeding 0.6 mg) followed by an injection of edrophonium chloride (0.25 mg per kilogram without exceeding 10 mg); if the test is positive, continue as per below; otherwise (if negative) observe and monitor.
 - (b) Be considered for anticholinesterase agents (neostigmine: three intravenous injections of 2.5 mg each at 30 min intervals) as it may improve neuromuscular transmission abnormality if the Tensilon test is positive. Note this is not an alternative to antivenom, but rather a short-term ancillary treatment. If there is no discernible response to neostigmine, it should be ceased.
 - (c) Be continuously assessed for airway or respiratory compromise, and if this develops, immediately receive at least airway protection and respiratory support, preferably intubation and mechanical ventilation in an ICU setting. Manual Ambu bagging may be needed

temporarily until intubation and ventilation can be implemented.

10. After discharge victims should be followed up 7–14 days post antivenom for features of late adverse reactions (e.g., serum sickness). Patients who have received antivenom should be given clear instructions, prior to discharge, about the symptoms of serum sickness and advised to seek medical care if these develop.
11. Manage and rehabilitate disabilities like amputations, blindness (from venom ophthalmia), limb contractures, etc.
12. Provide psychological support for all snakebite patients, especially those who have had major envenoming, to reduce the extent of post-snakebite depression and other psychological effects of such a stressful event.

Special Risk Groups

Children

Snakebites in children are less frequent than expected considering the youth of the African population [3]. However, they are especially serious, firstly because the volume of distribution is reduced, resulting in a higher concentration of venom in the vascular compartment and deep organs, and secondly children are often bitten on the hand, which causes severe damage and disability [53].

Pregnant Women

Snakebites in pregnant women are rare but severe because of the risk of placental bleeding, abortions, and death in utero [74, 75].

Elderly

They are subject to more frequent complications (renal failure, cardiac, respiratory, hemorrhagic or ischemic stroke, etc.).

Indications for ICU Admission

In Africa, ICUs are rare and often very distant from places where bites occur. In addition, patient evacuation to an ICU is complex because transportation means are deficient (no ambulance, no cars or helicopters), the roads are often in poor condition, and patients are unwilling to go far from home and may not be able to afford the cost of either the transport or the higher-level hospital care:

1. Three major circumstances must, however, lead to consideration of hospitalization in an ICU.
2. Severe edema considering diameter or extension, with the disappearance of distal pulses, can cause compartment syndrome, requiring fasciotomy. Additional tests should be performed in an ICU: intracompartmental pressures, necessary to assess the need for fasciotomy, ultrasound, etc.
3. Patient with systemic bleeding that does not stop in 1 hour after antivenom administration, especially if treatment has been renewed, should be evacuated to an ICU where additional blood coagulation tests could be done.
4. A patient showing neurological syndrome with dyspnea or respiratory paralysis that fails to improve after administration of four vials of antivenom must also be evacuated for ICU admission where resuscitation, intubation, and prolonged ventilation can occur.

Common Errors and Misconceptions

- Ineffective treatment may be due to the use of inappropriate antivenom.
- Ineffective treatment can also be due to an inadequate dose: dose depends on the amount of venom inoculated which is assessed by the symptomatology; the dose should be identical regardless of age or weight.
- Unnecessary repetition of antivenom: neither edema nor the 20WBCT are good

criteria for the repeating antivenom administration because of delayed normalization. The best criteria for the renewal of antivenom are the persistence or relapse of bleeding or neurological disorders.

- Blood infusion or administration of blood substitutes too early, i.e., before the antivenom has neutralized the venom, may induce the relapse of hemorrhagic syndrome due to consumption of the injected blood factors.
- Post-therapeutic follow-up should continue for 2 or 3 weeks: serum sickness appears in about 15% of treatments, in 7–15 days after the treatment [76].

Key Points

- Population at risk is young (15–45 years) and predominantly male.
- Over 95% of deaths occur in rural areas.
- Over 90% of victims consult a traditional healer at first instance, and 30–50% of them do not attend a modern health center.
- More than half of the victims arrive at the health center more than 10 h after the bite.
- Using a polyvalent antivenom may avoid having to identify the snake. Note: Available polyvalent antivenoms do not cover all major snake species (notably boomslangs are not covered and require a specific antivenom).
- The effectiveness of the new generation of polyvalent antivenoms reduces mortality by nearly 90%.
- The cost-benefit ratio of antivenom use is particularly excellent despite initial investments.
- Although there is evidence of antivenom efficacy and benefits, availability remains low particularly in remote health facilities.
- The training of health personnel is currently insufficient.

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This is an update and expansion of chapters written by Michael V. Callahan, Charles Lee, and Richard Y Wang for the first edition of this book

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Overview

Asia, the largest landscape on Earth, provides habitat to the majority of Earth's human beings as well as to a colossal diversity of snakes. More than 150 venomous species, representing several snake families: the Viperidae (e.g., vipers, pit vipers, and Fea's viper), the Elapidae (e.g., kraits, cobras, king cobras, and Asian coral snakes), and the broad assemblage previously contained within Family Colubridae (e.g., non-front-fanged-colubrids (NFFC snakes), including "rear-fanged" snakes) are known to exist.

Asia has the highest incidence of snakebite in the world [1]. Due to sociocultural structures and views, snakes are regarded very differently in Asia than in other parts of world, and for many Asian people, snake encounters are a daily occurrence. In many areas, snake envenomation is regarded as an occupational hazard. Certain occupations, such as rice farming, rubber harvesting, forestry, and fishing, are known to be associated with an increased frequency of snakebite. They are also known to have a seasonal variation mostly related to monsoon and harvesting. Natural calamities like flooding also increase the chance of encounter by forcing snakes and humans into closer contact. In Bangladesh, during the flood of 2007, snakebite was the cause of the second highest mortality after drowning [2]. In many parts of India, Sri Lanka, and Southeast Asia, snakebite has increased along with more recent agricultural development projects. The need for arable land, in particular rice fields, has destroyed habitat and displaced snakes into populated areas. In many regions, people share their living place with cattle and stored grains. This practice has increased the chance of snake-human encounters by attracting rodents and the snakes that prey on them. Throughout much of Asia, the rural poor are the main victims of snake envenomation. In those resource limited settings, inadequate and inaccessible medical care and the high cost of treatment compound the damaging effects of snakebite. The cost of treatment and loss of daily wage may be as high as the average per capita income. When the primary wage earner of the household is disabled

as a result of snakebite, the ensuing economic hardship may impoverish entire families [3].

The emerging economies of Asia, in particular in India, Thailand, and Vietnam, have driven improvements in medical care and in many regions have increased the number of medical intensive care units (ICUs). The availability of ICUs allows for improved care of severely envenomed patients. A correlate scenario is found in Western countries, where patients bitten by imported species benefit from ICU-level monitoring and treatment.

This chapter mainly focuses on the assessment and management of Asian snake envenomation with a focus on both treatment in resource-constrained settings typical of small hospitals in rural Asia and treatment in modern ICUs. Detailed herpetological, morphological, or taxonomic discussion of snakes and ultrastructural in-depth discussion of pathophysiology are beyond the scope of this chapter. The physician caring for patients envenomed by Asian species can benefit from an understanding of the snakes themselves. For this reason, a brief natural history of important Asian species and unique features of their venom are presented. An overview of snake venoms is presented in another chapter.

There is no reliable bedside diagnostic test kit available in most parts of Asia to determine the identity of the offending snake. Only a limited number of patients present with the caught culprit snake and description by the victim are not always available or reliable. Thus physicians must rely on the constellation of symptoms and signs resulting from envenomation. These "syndromes" play a key role in the effective treatment of snakebite patients. Examples of this information at work include the rapid diagnosis of nonenvenoming or "dry" bites and rapid bedside determination that the bite was caused by a viper, a rear-fanged "colubrid," or an elapid (e.g., coral snake, krait, or cobra). Envenoming by Asian coral snakes (*Calliophis*) and kraits (*Bungarus*) produces minimal local reactions but results in severe systemic neurotoxicity; missing these diagnoses can have tragic consequences. In contrast, cryptic envenoming by Asian cobras is unlikely to occur

because the venom of most species causes significant local reactions. In the case of Asian vipers, envenoming is *reliably confirmed* by the presence of pain, swelling, ecchymosis, or bleeding from fang marks. This finding is *not always true* for viper bites in other parts of the world. Conversely, bites by the rear-fanged yamakagashi (*Rhabdophis*) may cause minimal local symptoms but result in systemic coagulopathy. An understanding of the spectrum of these envenoming syndromes allows the physician to make decisions regarding optimal therapy for each case and to avoid mishaps in antivenom selection. Familiarity with the characteristics, range, and habits of snakes, a detailed clinical history covering the circumstances of the bite, and an appreciation for the clinical effects of envenoming are beneficial in suggesting the responsible species when the snake itself is not available [4].

Kinematics of Asian Snakebite

In humans, the evolution of snake envenomation and outcome depends on the amount and composition of venoms injected. Venom antigenemia has been found to correlate with clinical severity in several species of snakes including Burmese Russell's viper [5]. Bites by venomous snakes, including the most dangerous Asian species, include cases of nonenvenoming. The observations that snakes invariably strike humans in defense and that 15–45% of these bites are nonenvenoming have suggested to some that the snakes regulate the amount of venom injected based on circumstance. In the field, when snakes are trod on and respond reflexively with a strike, the event seems to take the snake and the human by surprise. It is likely that the serpent's sudden and desperately delivered strike often results in incomplete fang penetration. Factors that interfere with envenoming include inefficient strike trajectories, such as when the snake delivers a backward strike to the foot that stepped on it; the large size, shape, and unfamiliarity of humans as targets; and the interference caused by clothing and footwear. The idea that a snake's venom has been exhausted after a recent strike, and therefore the snake will

be less venomous after eating, or after striking another victim, has been refuted [5]. The opposite scenario is also a cause for concern, such as when the patient is bitten by a captive and habituated venomous species. A high percentage of these cases occur when captive snakes smell food animals in advance and anticipate imminent feeding. Hungry, enthusiastic specimens may confuse the caretaker's hand for a food animal and respond with a venom-laden strike. Snakebites that occur during the feeding of captive specimens often produce effects more severe than those seen after defensive bites by wild specimens. Details surrounding snakebite involving captive specimens require close investigation because these cases may prove to be particularly severe [6]. The severity of envenoming tends to increase with the size of the offending snake, although the largest of specimens do not always inflict the most venomous bite and juveniles of some species can deliver lethal bites.

Representative and significant Asian terrestrial species are listed in Table 1 and many genera, with approximate distribution maps and some representative species are shown in Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, and 36. The determination of the range is derived from reports in the herpetology literature or case series of snake envenoming. The species presented are representative of the genus, are responsible for significant mortality, or possess venom with unique clinical properties.

Regional Distribution and Pathophysiology

Asia is the only region on earth where all three Viperidae subfamilies are found: the Viperinae, or Old World vipers; the more advanced Crotalinae, or pit vipers; and the Azemiopinae, containing the attractive monotypic species, Fea's viper (*Azemiops feae*), found along the China-Laos-Vietnam border.

Physicians with experience treating snakebite in Asia generally agree that although elapids (cobras and kraits) account for the most deaths, vipers cause the most bites (Figs. 37, 38, 39, and 40).

Table 1 Terrestrial Asian venomous snake families and representative species

Family	Genus	Species	Common Name	Range
Viperidae (Azemiopinae)	<i>Azemiops</i>	<i>A. feae</i>	Fea's viper	Vietnam, Laos
Viperidae (Viperinae)	<i>Cerastes</i>	<i>C. gasperettii</i>	Horned sand viper	
	<i>Daboia</i>	<i>D. russelii</i> complex	Russell's viper	Asia
	<i>Echis</i>	<i>E. multisquamatus</i>	Tibetan saw-scaled viper	Western Asia
	<i>Vipera</i>	<i>V. xanthina</i>	Steppe/ottoman viper	Western Asia
Viperidae (Crotalidae – pit vipers)	<i>Gloydius</i>	<i>G. brevicaudus</i>	Chinese mamushi	Southern China
	<i>Calloselasma</i>	<i>C. rhodostoma</i>	Malayan pit viper	Southern Myanmar–Malaysia–Java
	<i>Deinagkistrodon</i>	<i>D. acutus</i>	Sharp-nosed viper	North Vietnam–central China
	<i>Hypnale</i>	<i>H. nepa</i>	Sri Lanka hump-nosed viper	Sri Lanka
		<i>H. hypnale</i>	Merrem's hump-nosed viper	Western India–Belgaum
	<i>Ovophis</i>	<i>O. convictus</i>	Penang pit viper	Central China
		<i>O. monticola</i>	Mountain pit viper	Nepal–China–Southeast Asia
	<i>Trimeresurus</i>	<i>T. stejnegeri</i>	Chinese bamboo pit viper	Southern China
	<i>Tropidolaemus</i>	<i>T. wagleri</i>	Wagler's temple viper	Indonesia
Elapidae	<i>Bungarus</i>	<i>B. fasciatus</i>	Banded krait	India–Laos
		<i>B. caeruleus</i>	Indian krait	Western India–Nepal–Sri Lanka
	<i>Calliophis</i>	<i>C. bibroni</i>	Bibron's coral snake	India–Thailand
		<i>C. bivirgata</i>	Blue long-glanded coral snake	Malaysia–Indonesia
	<i>Naja</i>	<i>N. atra</i>	Taiwan–Chinese cobra	China–northern Laos, Vietnam
		<i>N. naja</i>	Indian cobra	Pakistan, Nepal, Sri Lanka
		<i>N. kaouthia</i>	Monocellate cobra	India, Thailand
		<i>N. oxiana</i>	Central Asian cobra	Northern India–Nepal
		<i>N. sumatrana</i>	Malay spitting cobra	Sumatra–Malaysia
		<i>N. philippinensis</i>	Philippine cobra	Philippines
	<i>Ophiophagus</i>	<i>O. hannah</i> (only)	King cobra	India–Philippines
	<i>Walterinnesia</i>	<i>W. aegyptia</i> (only)	Desert cobra	Western Asia
Snakes previously grouped within Family Colubridae, encompassing non-front-fanged-colubrids (NFFCsnakes)				
Colubridae	<i>Ahaetulla</i>	<i>A. nasuta</i>	Long-nosed vine snake	India, Southeast Asia
Natricidae	<i>Balanophis</i>	<i>B. ceylonicus</i>		Sri Lanka

(continued)

Table 1 (continued)

Family	Genus	Species	Common Name	Range
			Sri Lankan keelback	
Colubridae	<i>Boiga</i>	<i>B. dendrophilia</i>	Mangrove snake	Thailand, Singapore-Sulawesi
		<i>B. ceylonensis</i>	Cat snake	Sri Lanka, southern India
Homalopsidae	<i>Cerberus</i>	<i>C. rhynchops</i>	Dog-faced watersnake	India, Southeast Asia, Philippines
Colubridae	<i>Coluber</i>	<i>C. ravergeri</i>	Steppe racer	Northwest India, Xinjiang province
Homalopsidae	<i>Enhydryis</i>	<i>E. enhydryis</i>	Rainbow watersnake	Southern India–southern China
Natricidae	<i>Rhabdophis</i>	<i>R. subminiatus</i>	Red-necked keelback	Southeast Asia–eastern China/Sulawesi
		<i>R. tigrinus</i>	Yamakagashi	Japan, China, Taiwan, Vietnam



Fig. 1 Russell's viper, *Daboia russelii* (specimen from West Bengal). This widely distributed snake, with two closely related species (*D. russelii* and *D. siamensis*) is among the most medically important venomous snakes of the Asian region, accounting for large numbers of cases and fatalities. The venom shows great regional variation, such that the clinical picture varies depending on which geographic population of Russell's viper is considered, with effects that can include one or more of local pain, local necrosis, local ecchymosis, shock, coagulopathy, AKI, systemic bleeding, anterior pituitary infarction/Sheehan's syndrome, rhabdomyolysis, neurotoxic paralysis (Photo copyright © Dr. Julian White)

The venom of Asian vipers is rich in enzymes, which induce local pain, swelling, tissue damage (Figs. 41 and 42), coagulopathy (Figs. 38, 39, 40, and 43), and, for some species, damage to the



Fig. 2 Russell's viper, *Daboia russelii* showing erect fangs (Photo copyright © Dr. Julian White)

kidneys, the adrenals, or the pituitary gland. Postenvenoming sequelae after viper bites account for significant disability among certain occupational groups, such as rubber plantation workers and rice farmers.

An understanding of the habits, range, and preferred niche of certain viper species provides meaningful epidemiologic clues to the treating physician. Bite injuries to the hands of fruit and coffee plantation workers in Central Malaysia or



Fig. 3 Russell's viper, *Daboia siamensis* (Thailand)
(Photo copyright © Dr. Julian White)

home gardeners living in Bangkok or wood cutters in Bangladesh commonly are caused by the arboreal green tree vipers (*Trimeresurus*; Figs. 11, 12, 13, and 14) [7], rubber-tappers in Southeast Asia often fall victim to Malayan pit viper (*Calloselasma rhodostoma*; Figs. 9 and 10). In contrast, nocturnal bites to the feet caused by ground-dwelling vipers in Pakistan, India's arid plains, and the Shavakacheri region in Sri Lanka usually are caused by saw-scale vipers (*Echis*; Figs. 5, 6, 7, and 8). Bites in less arid areas, especially in rice paddies, from Sri Lanka, through India, Myanmar (Burma), into SE Asia and as far east as Taiwan are commonly caused by varieties of Russell's viper (*Daboia* spp.; Figs. 1, 2, 3, and 4).



Fig. 4 Approximate distribution for Russell's viper (*Daboia russelii* and *D. siamensis*) (Map copyright © Dr. Julian White)



Fig. 5 Saw-scaled viper, *Echis carinatus*. Saw-scaled vipers cause local pain, ecchymosis, blistering, swelling, necrosis, shock, and severe, potentially lethal coagulopathy with systemic bleeding (Photo copyright © Dr. Julian White)



Fig. 6 Saw-scaled viper, *Echis carinatus* showing erect fangs (Photo copyright © Dr. Julian White)

Natural History of Important Species and Unique Features of Their Venom

Viperidae

The venoms of Asia's vipers, similar to the vipers themselves, are not without their peculiarities. The venom of most species contains a mixture of peptides with direct toxic or indirect enzymatic activity. From a clinical standpoint, the most important of the proteolytic enzymes are the phospholipases A₂ myoneurotoxins [8], which destroy tissue and serve as presynaptic neurotoxins, and



Fig. 7 Saw-scaled viper, *Echis sochureki* (Photo copyright © Dr. Julian White)

shock-inducing hemorrhagins [9], which destroy blood vessel walls, leading to extravasation and third spacing of fluid. Additional enzymes possess procoagulant, anticoagulant, and fibrinolytic activity. More recently, unique disintegrins have been identified in the venom of several species; these disintegrins inhibit platelet aggregation by preventing von Willebrand's factor and fibrinogen from binding to platelet (glycoprotein IIb/IIIa) integrin receptors [10].

In the first 48 h after viper bite, death may result from the effects of defibrination-related hemorrhage, shock secondary to vascular leak, or, in several species, respiratory paralysis. Death after 72 h is more likely to result from internal (especially intracranial) hemorrhage, renal failure, adrenal insufficiency, or secondary infection arising from necrotic tissues. Several clinical aspects of Asian viper venom require additional discussion.

Local Effects

Local envenoming is usually more severe than that caused by other non-Viperid snake species. Local swelling and erythema result from the combined effects of vasoactive compounds and enzymatic toxins. Swelling may develop immediately or may take several hours. Spread may be slow or rapid involving the whole limb and adjacent trunk. There may be associated pain, tenderness, and local/regional lymphadenopathy. Blisters



Fig. 8 Approximate distribution for saw-scaled vipers, genus *Echis*, within Asia (note other *Echis* spp. found in the Middle East and parts of Africa) (Map copyright © Dr. Julian White)

containing clear or blood stained fluid may appear near the bite site within a few hours. Necrosis of skin, subcutaneous tissue, and muscles occur in about 10% of hospitalized cases for some vipers, especially in pit vipers (e.g., *Calloselasma*, *Deinagkistrodon*, some *Trimeresurus*) and saw-scaled vipers (*Echis*). Bites on digits or in areas draining into tight fascial compartment (anterior tibial compartment) are particularly likely to develop raised intracompartmental pressure resulting in ischemia. Together with direct effects of venom this is more likely to result in necrosis [11]. Raised intracompartmental pressure should be suspected when there is severe pain associated with tense swelling, segmental anesthesia, and pain on stretching the intracompartmental muscles (e.g., dorsiflexion of the

foot). In viper bite, local toxicity is usually universal and absence of local swelling 2 h after bite usually means absence of venom, but systemic envenoming by the Burmese Russell's viper (*Daboia siamensis*) may occur in the absence of local signs. Local tissue necrosis results from the direct action of myotoxins (phospholipases A_2) and cytotoxins. The factors responsible for increased vascular permeability leading to local swelling and bruising, include endopeptidases, metalloproteinase hemorrhagins, membrane-damaging polypeptide toxins, phospholipases, and endogenous autacoids such as histamine, 5-hydroxytryptamine, and kinins. The presence of coagulopathy is first noted at the bite site, where incoagulable blood drains from teeth and fang marks. Local necrosis may be significant



Fig. 9 Malayan pit viper, *Calloselasma rhodostoma*. This snake can cause marked local pain, swelling, ecchymosis, blistering, shock, severe coagulopathy, and systemic bleeding (Photo copyright © Dr. Julian White)

after envenoming by the Malayan pit viper (*Calloselasma*), Russell's vipers (*Daboia*; Figs. 41 and 42), green tree vipers (*Trimeresurus*), and saw-scaled vipers (*Echis*), all of which are discussed subsequently. Minor necrosis may follow envenoming by hump-nosed vipers (*Hypnale*), hundred pace viper (*Deinagkistrodon*; Figs. 23 and 24), habus (*Ovophis*; Figs. 17 and 18), and Mamushis (*Gloydius*; Figs. 19 and 20).

Systemic Effects

Coagulopathy

The most common systemic symptom after envenoming by Asian *Daboia*, *Trimeresurus*, *Calloselasma*, and *Echis* spp. is coagulopathy (Figs. 38, 39, 40, 43, 44, and 45). Viper venom



Fig. 10 Approximate distribution for the Malayan pit viper, *Calloselasma rhodostoma* (Map copyright © Dr. Julian White)



Fig. 11 Common green pit viper, *Trimeresurus albolabris*. This snake, common in urban/semiurban environments within its range, can cause moderate to severe envenoming, with local pain, swelling, ecchymosis, and systemic coagulopathy. In more severe cases there can be shock, with rare cases of local necrosis and AKI reported (Photo copyright © Dr. Julian White)



Fig. 13 Brown-spotted green pit viper, *Trimeresurus venustus*. This species, in the past included within *T. kanburiensis*, may cause at least moderate envenoming with local pain, swelling, ecchymosis, possibly shock, systemic coagulopathy, and bleeding (Photo copyright © Dr. Julian White)

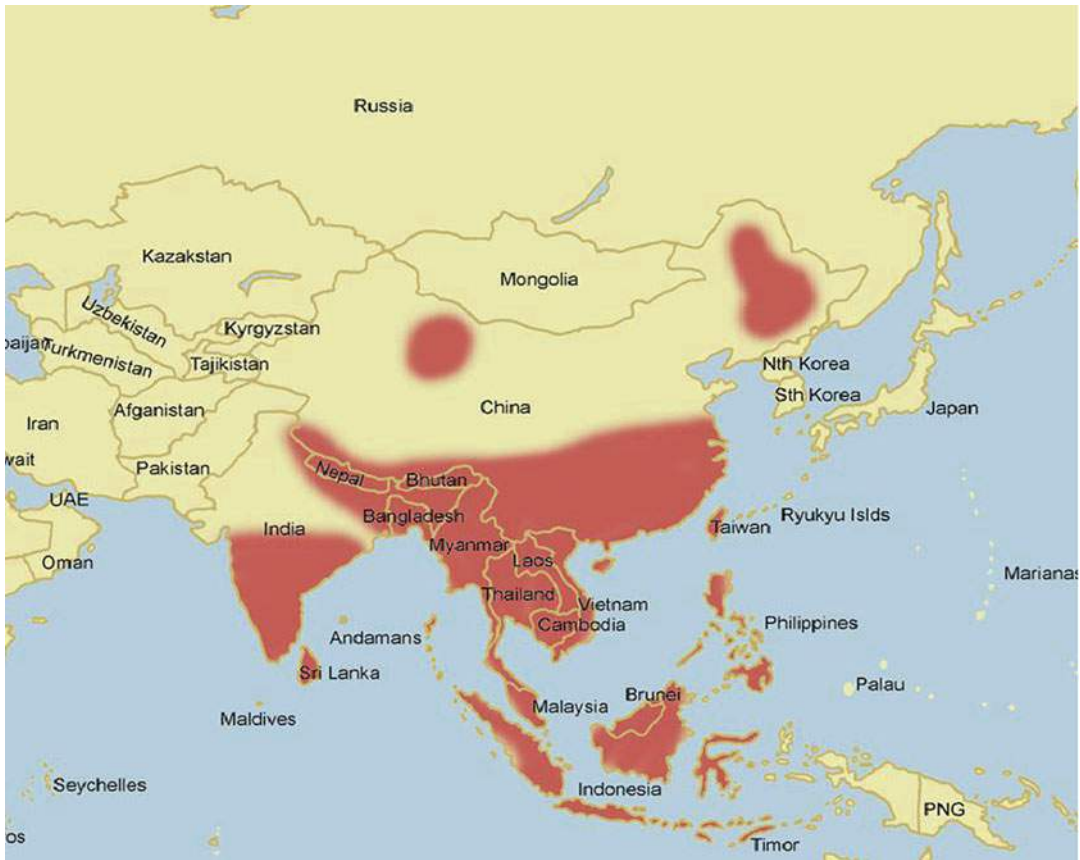


Fig. 12 Approximate distribution for snakes of genus *Trimeresurus* (Map copyright © Dr. Julian White)



Fig. 14 Indian green pit viper, *Trimeresurus gramineus*. Though common, little information on the clinical effects of bites by this snake are documented, but like many other green pit vipers across Asia, it may possibly cause both local pain and swelling and ecchymosis and shock with systemic coagulopathy, as the venom contains a variety of coagulopathic and hemorrhagic toxins (Photo copyright © Dr. Julian White)



Fig. 15 Japanese habu, *Protobothrops flavoviridis*. This species and other habus, such as the Chinese habu, *P. mucrosquamatus*, can cause moderate to severe envenoming, with local pain, swelling, ecchymosis, blistering, necrosis, shock, and systemic coagulopathy and bleeding, AKI are possible, at least for some species (Photo copyright © Dr. Julian White)

contains procoagulants and procoagulant activating factors that can activate intravascular coagulation resulting in consumption coagulopathy. Some of them have a direct thrombin-like action on fibrinogen, while others activate the

endogenous fibrinolytic system. Anticoagulant activity is due to phospholipases. Thrombocytopenia is a frequent finding, most likely caused by platelet agglutination. Spontaneous systemic bleeding results from damage to vascular endothelium due to the action of distinct venom components, hemorrhagins. The combination of incoagulable blood, thrombocytopenia, and vessel wall damage may produce massive local and systemic bleeding which may be fatal. In the hospital setting, a leading cause of death is spontaneous hemorrhage or iatrogenic hemorrhage resulting from attempts at vascular access or ill-advised attempts at fasciotomy. Bleeding into anatomic compartments, such as the muscles of the thigh and the retroperitoneum, should be suspected and actively searched; otherwise they may be missed until hypotension/shock results.

Neurotoxicity

The venom of several Asian vipers – the *Daboia*/Russell's viper group and several species of mamushis (*Gloydius*) – contains neurotoxins. In southern India and Sri Lanka, envenoming by local *Daboia* subspecies (*Daboia russelii russelii*; previously, *Daboia russelii pulchella* in Sri Lanka) can cause neurotoxic symptoms, in addition to intravascular hemolysis and myolysis seen throughout the species' range [12]. In severe cases, *Daboia*-induced paralysis may progress to the respiratory muscles [13]. The neurotoxin is a phospholipase A₂. In Japan, China, and South Korea, envenoming by several subspecies of mamushi (*Gloydius blomhoffii brevicaudus* group) also can result in neurotoxic symptoms ranging from mild ptosis to complete respiratory paralysis [14–17]. Envenoming from two other *Gloydius* spp., the Ussuri mamushi (*Gloydius ussuriensis*) [18, 19] and the central Asian pit viper (*Gloydius intermedius*) [20], also is reported to cause neurotoxic symptoms, although these seem to be less severe.

The venom of many Asian viper species differs among regions. Asian vipers known to have geographically heterogeneous venom are *Daboia*, *Calloselasma*, *Echis* (particularly between Asia and Africa), and *Trimeresurus* spp. The variability



Fig. 16 Approximate distribution for snakes of genus *Protobothrops* (Map copyright © Dr. Julian White)



Fig. 17 Mountain viper, *Ovophis monticola*. These snakes can cause at least moderate envenoming with local pain, swelling, ecchymosis, and systemic coagulopathy and bleeding (Photo copyright © Dr. Julian White)

in venom is reflected by heterogenous results with antivenom treatment. Economic constraints in antivenom manufacture often result in the use of venom from snakes whose collection was convenient, usually from the region where the antivenom was produced. Antivenoms are rarely prepared using pooled venom obtained from specimens from different regions. Many antivenoms may not effectively neutralize the venom of the same species from another region. This observation has implications for health centers that are purchasing antivenom from foreign manufacturers and for pharmacists who need to protect zoo and research personnel from bites by imported species.



Fig. 20 Approximate distribution for snakes of genus *Gloydius* (Map copyright © Dr. Julian White)

the range of clinical effects seen in patients envenomed by species from different regions.

In addition to phospholipase A₂ myoneurotoxins, Russell's viper venom contains hemorrhagins, platelet-aggregating factors, and venom enzymes that activate factor V, IX, and X and induce fibrinolysis [22]. In certain regions, Russell's viper venom also possesses plasminogen and antiplasmin activity. Together, these factors induce chaotic activation of extrinsic and intrinsic coagulation pathways with simultaneous formation and destruction of blood clots. *De novo* thrombus formation, presenting as cortical disturbances, syncope, and sudden cardiac death, is rare but may occur soon after intravenous envenoming. The result of these clotting

abnormalities is eventual defibrination with marked elevation of fibrin degradation products [22]. Intravascular hemolysis is variable after Russell's viper envenoming.

Differences in venom composition have resulted in variations in the clinical manifestations of envenoming throughout the range of distribution [23–28]. The clinical presentation of envenomed patients may vary dramatically among regions. Throughout the range, the procoagulant effects of Russell's viper venom may cause consumption of fibrinogen and incoagulable blood. In eastern Pakistan and central India, envenoming by *D. r. russelii* also causes intravascular hemolysis and excessive damage to local skeletal muscle. In Sri Lanka and southern



Fig. 21 Temple pit viper, *Tropidolaemus wagleri*. Most bites by this common snake cause only mild-to-moderate local envenoming with pain, swelling, possibly ecchymosis, rarely necrosis, but it is unclear if they can also cause shock and coagulopathy (Photo copyright © Dr. Julian White)

India, however, envenoming by local *D. r. russelii* (previously *D. r. pulchella* in Sri Lanka) may result in neuromyotoxic symptoms (attributable to PLA₂) that can progress to respiratory paralysis and rhabdomyolysis. In Sri Lanka, reported features are ptosis (77%), external ophthalmoplegia (82%), inability to open the mouth (23%), to swallow and protrude the tongue, generalized muscle tenderness (32%), and myoglobinuria (27%). Most patients showed evidence of intravascular hemolysis. Panhypopituitarism, presenting between 1 month and 1 year after the bite, was reported from Kerala, south India (7 out of 1000 cases). The clinical presentation of envenoming also varies in the eastern species, *D. siamensis*. In Myanmar, envenoming by *D. siamensis* is more likely to be severe, characterized by a systemic capillary leak syndrome,



Fig. 22 Approximate distribution for snakes of genus *Tropidolaemus* (Map copyright © Dr. Julian White)



Fig. 23 Hundred pace snake, *Deinagkistrodon acutus*. This snake causes moderate to severe envenoming with local pain, severe swelling, ecchymosis, blistering, necrosis, shock, systemic coagulopathy, and bleeding (Photo copyright © Dr. Julian White)

conjunctival hyperemia (chemosis), pulmonary edema, and infarction of the anterior pituitary gland [29, 30]. Systemic capillary leak syndrome, first described for Russell's viper bite in Burma, characterized by orbital and conjunctival edema with conjunctival hemorrhages (Fig. 46 and 47), develops in severe cases and is evidence of generalized increase in capillary permeability. Other manifestations of this permeability syndrome are facial edema, pleural effusions, ascites, pulmonary edema, and transient proteinuria with hypoalbuminemia [31]. In Thailand, though the snake is the same species as in Myanmar, clinical features are generally less severe; the most severe complications resulting from incoagulable blood and renal failure. In Indonesia, an isolated population of *D. siamensis*, separated by more than 2000 km from the nearest consanguineous species, is implicated in bites with an excessively high case-fatality rate of 38.5% and a mean interval between bite and death of only 14.5 h, far faster than that observed in other parts of the species' range [32] (Table 2).

Despite the variability in presentation, all Russell's viper venoms produce some pain and swelling within minutes of envenoming. Pain and swelling may be less significant in Madras, India, and Sri Lanka than observed elsewhere.

Clinical events reflecting the activity of the venom include pain, swelling, ecchymosis, and bulla formation [35, 36]. Within 1 h of envenoming, evidence of regional coagulopathy is manifest by persistent bleeding from fang and maxillary teeth wounds. The combined loss of blood from fang marks, intravenous (IV) access sites, and the gastrointestinal and urinary tract [37] is often considerable, contributing to hypovolemia and hemorrhagic shock. Local necrosis is common in many parts of the Russell's viper range (Figs. 41 and 42), although it is less severe than necrosis after envenoming by *Calloselasma rhodostoma* (Malayan pit viper) and many species of cobra (*Naja naja*; Fig. 48), which share much of the range.

In southern India, Sri Lanka, Myanmar, and Thailand, Russell's viper envenoming is a common cause of renal failure [37–41]. In Kerala, India, Russell's viper envenoming is the leading cause of acute renal failure in adults and children [38]. Clinical evidence that Russell's viper venom contains a unique nephrotoxin is supported by the high incidence of renal failure in patients with negligible coagulopathy, rhabdomyolysis, or history of hypotensive episodes and with recent identification of a nephrotoxic effect [42]. Renal biopsy data has shown a variety of histopathological changes including proliferative glomerulonephritis, toxic mesangiolysis with platelet agglutination, fibrin deposition, ischemic changes, acute tubular necrosis, distal tubular damage ("lower nephron nephrosis") suggesting direct venom nephrotoxicity, and bilateral renal cortical necrosis with subsequent calcification [43].

In Taiwan, bites by local *D. siamensis* (formerly *D. r. formosensis*) are a leading cause of acute renal failure and are implicated in neurotoxicity [40]. The neurotoxin of this species was found to constitute 40% of the venom and to consist of two distinct phospholipases, which combine to produce a postsynaptic neurotoxin [44, 45].

Little is known about the clinical effects of Russell's viper envenoming in mainland China. One epidemiologic study indicated that Chinese Russell's vipers account for fewer bites than other



Fig. 24 Approximate distribution for the hundred pace snake, *Deinagkistrodon acutus* (Map copyright © Dr. Julian White)

species (e.g., *Trimeresurus*, *Gloydius*). Although specimens from southern China are morphologically similar to specimens in neighboring north-western Laos, northern Thailand, and Myanmar (variant *D. siamensis*), few comments can be made with regard to characteristics of the venom. One case series studying bites by *Trimeresurus albolabris* mentioned a single case of envenoming by an imported Chinese Russell's viper, resulting in defibrination, intracranial hemorrhage (Fig. 45), acute renal failure, and death. Along the Thailand-Laos border, 18 cases of confirmed envenoming by *D. siamensis* treated by the author developed prolonged clotting times, hemolysis, microalbuminuria, hemoglobinuria, and

hemorrhagic bulla formation. Mild necrosis was present in three bites to the hand or fingers. None of these patients developed acute renal failure. One patient developed severe pulmonary hemorrhage requiring blood transfusion, prolonged respiratory support, and antivenom therapy.

Neurotoxicity after Russell's viper envenoming is seen most frequently in Sri Lanka, southern India (*D. russelii*), and Taiwan (*D. siamensis*). In one Sri Lankan series, envenoming ("*D. r. pulchella*") resulted in diplopia and ptosis between 30 min and 7 h after the bite [8]. Compared with envenoming by *Naja* and *Bungarus*, neurotoxicity resulting from Russell's viper bites tends to be less severe; however,



Fig. 25 Malayan krait, *Bungarus candidus*. Kraits cause minimal local effects, no necrosis, but progressive onset of moderate to severe flaccid neurotoxic paralysis, but not coagulopathy. In some species there may be systemic rhabdomyolysis and hyponatremia, and severe abdominal pain is a common feature (Photo copyright © Dr. Julian White)



Fig. 26 Indian krait, *Bungarus caeruleus* (Photo copyright © Dr. Julian White)

progression to respiratory paralysis is known. In western India and Bangladesh, envenoming by local Russell's viper species induces coagulopathy, hypotension, renal failure, and anemia. In Myanmar, Russell's viper bites may cause incoagulable blood, hemolysis, acute renal failure (the commonest cause of acute renal failure in Myanmar), and endocrinopathies secondary to infarction of the anterior pituitary gland [30, 36, 46], but no evidence of neurotoxicity. Pituitary insufficiency may manifest months after envenoming when patients return with complaints



Fig. 27 Banded krait, *Bungarus fasciatus* (Photo copyright © Dr. Julian White)

of low libido, amenorrhea, loss of pubic hair, and diabetes insipidus [29, 47]. Postmortem examination of Russell's viper victims, for which there is no shortage of opportunities, shows hyperemia and congestion of vascular beds in the anterior pituitary gland, adrenal gland, gastrointestinal tract, and alveolar beds and within the coronary vessels. The well-studied venom phospholipase A₂, VRV-PL-VIIIa, has been implicated in alveolar hemorrhage and myotoxicity, neurotoxicity, and regional edema reported previously [48]. The variability between Russell's viper venoms from different regions has limited the usefulness of antivenoms produced in other countries [13, 49]. At present, there is considerable interest in the development of polyvalent/panregional Russell's viper antivenoms that would be effective throughout the species range.

Saw-Scaled Vipers (*Echis*)

The medically important genus *Echis* (saw-scaled viper; Figs. 5, 6, 7, and 8) is widely distributed, in the northern third of Africa from Senegal in the west, south to the Tana River in Kenya, through the Middle East and western Asia, as far north as the Aral Sea, and throughout the Indian subcontinent, including Sri Lanka and as far as the border of West Bengal. Each of the 12 *Echis* spp. is characterized as small, ground-dwelling vipers with disproportionally large eyes, a blunt snout, heavily keeled scales, and a pugnacious disposition. The saw-scaled viper's name arises from the

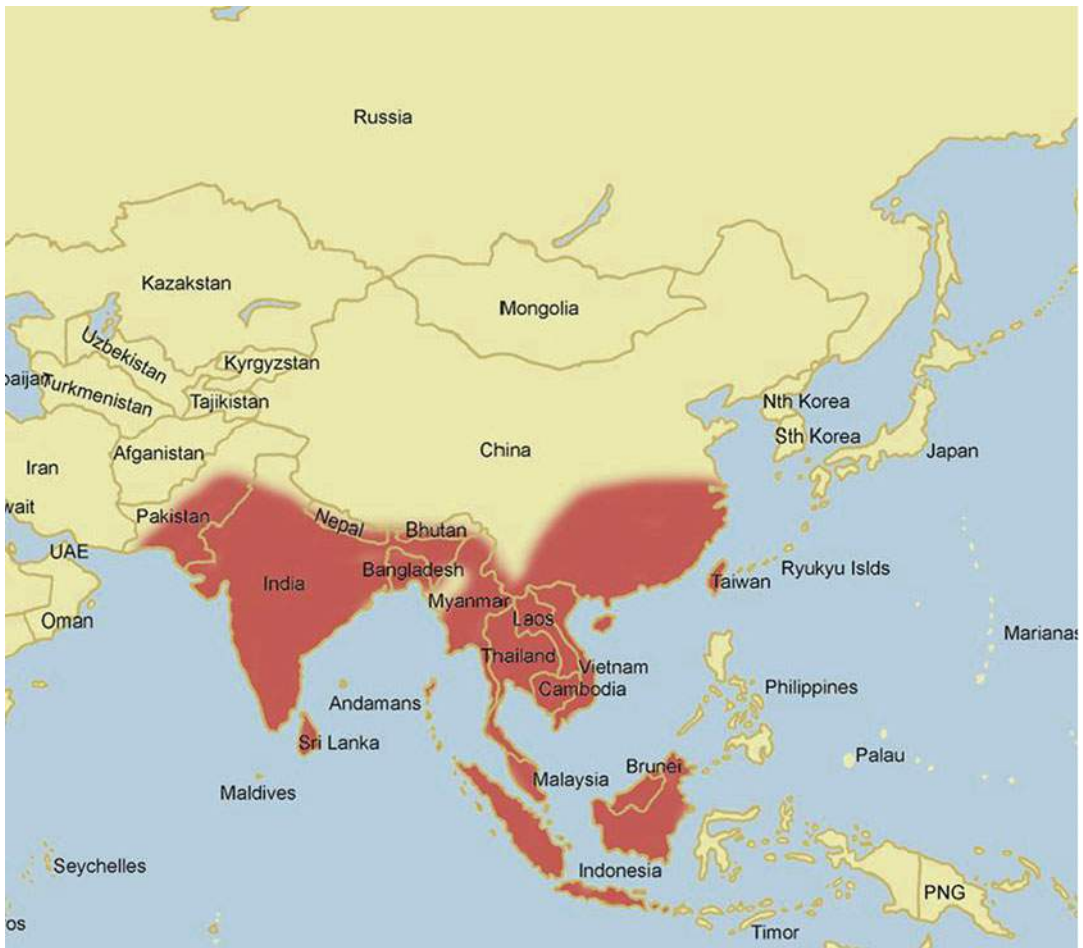


Fig. 28 Approximate distribution for snakes of genus *Bungarus* (Map copyright © Dr. Julian White)

noise created when the snake becomes irritated and rubs its keeled scales together to warn other animals. In captivity, *Echis* remain highly strung and prone to bite. In Asia, *Echis* bites are caused by three species: the far-ranging, prototypic *Echis carinatus*, which is found in peninsular India as far east as Maharashtra and Tamil Nadu; the largest and most dangerous species, *Echis sochureki* (Sochurek's saw-scaled viper), found in northern India to Pakistan; and *Echis multisquamatus* (central Asian saw-scaled viper), found in eastern Pakistan and northern India. In some areas of India and Pakistan (e.g., in Sind and Jammu), it is the major cause of snakebite morbidity and mortality [50, 51]. In southern India and Sri

Lanka, *Echis* (probably *E. c. sinhaleyus*) is infrequently implicated in envenoming.

The venom of *E. carinatus* activates factor X and prothrombin (both Group A and B prothrombin activators) and inhibits thromboxane-induced platelet activation. *Echis* venom also contains hemorrhagins, which contribute to vascular leak, third spacing of fluids, hypovolemia, and shock. As with the Russell's viper, local effects of *Echis* bites include pain, swelling, blistering, and discoloration, which often transition to ecchymosis and become necrotic. Lymphangitis and tender draining lymph nodes are common. The most important clinical feature of *Echis* envenoming is severe hemorrhage resulting from coagulopathy.

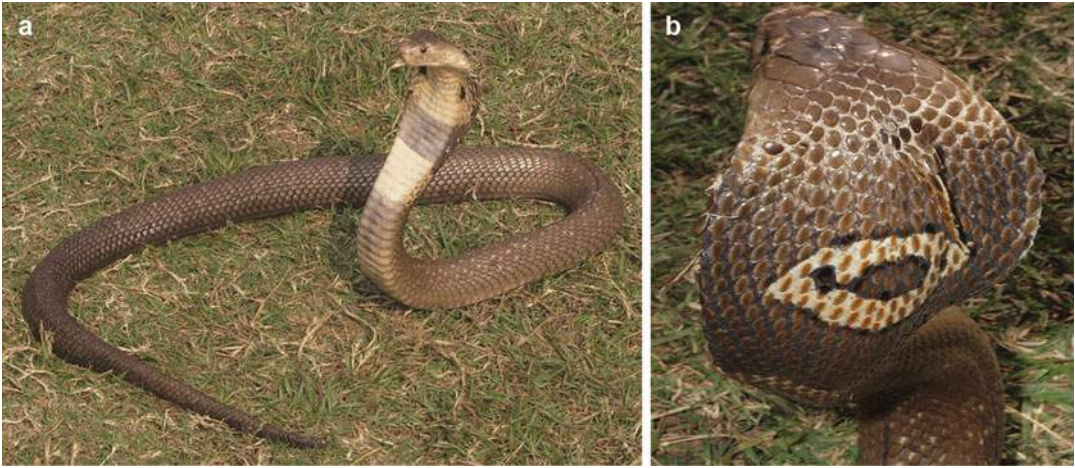


Fig. 29 (a) Indian spectacled cobra, *Naja naja*. A very common snake causing moderate to severe envenoming with local pain, swelling, sometimes ecchymosis, blistering, necrosis, and flaccid neurotoxic paralysis, but not

coagulopathy (Photo copyright © Dr. Julian White). (b) Indian spectacled cobra, *Naja naja* showing classic markings on the back of the hood (Photo copyright © Dr. Julian White)

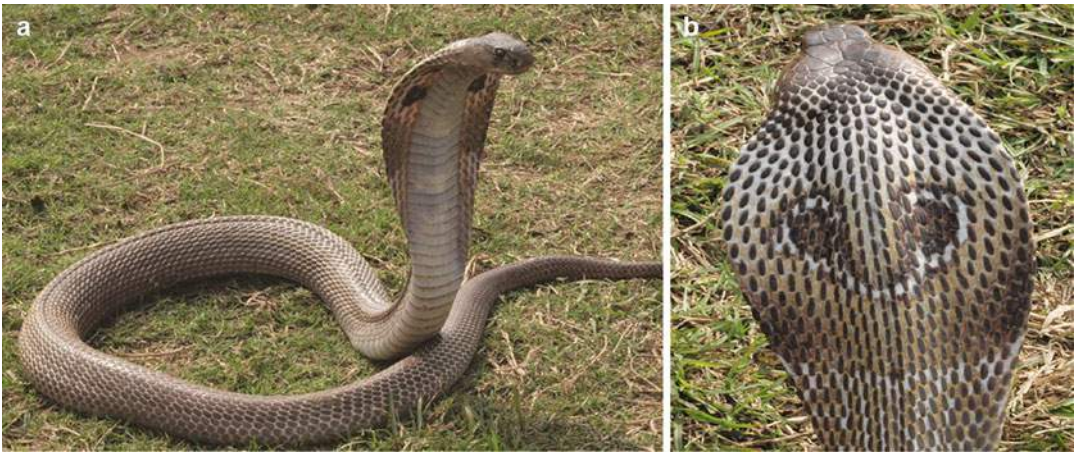


Fig. 30 (a) Monocellate cobra, *Naja kaouthia*. These cobras cause similar effects to *Naja naja*, though possibly the local effects may be less severe and the neurotoxicity more prominent (Photo copyright © Dr. Julian White).

(b) Monocellate cobra, *Naja kaouthia* showing classic single eye marking on the back of the hood (Photo copyright © Dr. Julian White)

When the identity of the snake cannot be confirmed, the patient's description of the viper's unique defense behavior, time of day (night) of the bite, familiarity with the viper's range, environmental preference, and clinical presentation of pain, blistering, and coagulopathy provide sufficient evidence to support treatment with *Echis*-

specific antivenom [4]. As with Russell's viper, *Echis* venom is known to vary throughout the species' range. Cases of treatment failure using *Echis*-specific antivenom imported to treat bites in northern Nigeria [51] and Pakistan [52] serve as a warning for the clinician treating *Echis* bites with antivenom produced in other regions.

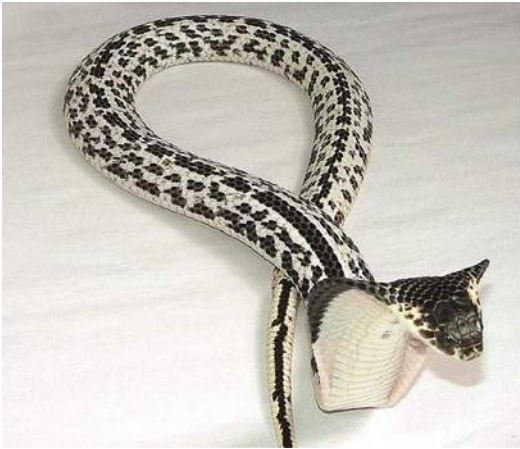


Fig. 31 Siamese spitting cobra, *Naja siamensis*. Spitting cobras, in addition to causing corneal pain and damage from spat venom, on biting cause local pain, swelling, and necrosis, but paralytic effects may be less prominent (Photo copyright © Dr. Julian White)

Malayan Pit Viper (*Calloselasma Rhodostoma*)

Adult vipers are thick-bodied, ground-dwelling, dark-colored snakes, usually covered with dark, triangular markings along the dorsum (Fig. 9). In many countries of Southeast Asia, the Malayan pit viper *Calloselasma* is either the most common cause of snakebite [53] or the most common cause of snakebite deaths [54]. It is likely that rural environs and failure to access medical care heavily influence the number of fatalities. *C. rhodostoma* is found throughout Thailand, Cambodia, Laos, West Malaysia, Sumatra, and Java (Fig. 10). A smaller subspecies is found in southwestern Vietnam and adjacent Cambodia. Throughout the species range, rubber and tea plantation workers, rather than rice farmers, are most commonly bitten; a major occupational hazard. This predilection reflects the species' preference for drier, alkaline soils; partial canopy; and preference for rodents, which concentrate around farms. A crepuscular hunter, the viper is most active when workers are traveling to and from the fields. Most cases occur when the snake is stepped on and the foot and lower leg are bitten.

Calloselasma venom contains ancrod, a potent serine protease that cleaves fibrinopeptide A from fibrinogen, which is used clinically as an

anticoagulant (Arvin) [55]. The protease works in concert with other venom antigens to defibrinate the patient's coagulation system. The process involves thrombin formation, often with sequestration of platelets; thrombocytopenia is a common laboratory finding after bites by this species. In most cases, the thrombocytopenia, but not the coagulopathy, resolves within hours of treatment with antivenom. A second feature of *Calloselasma* venom is the presence of proteases that specifically hydrolyze vitamin K-dependent clotting factors VII, IX, and X and protein C [56]. Early after envenoming by *C. rhodostoma*, a transient increase in the prothrombin time-to-partial thromboplastin time ratio is observed. The observation is of limited utility after the first few hours because generalized activation of extrinsic and intrinsic factors results in uniform elevation of prothrombin time and partial thromboplastin time.

There is minimal or no envenoming in about half of the patients, with local swelling starting within minutes and reaching its maximum after 24–72 h found in the rest. Patients bitten by *C. rhodostoma* may experience significant tissue destruction, which invariably extends beyond the border of bullae that form on the bitten extremity. The bullae contain bloody, rather than serous, fluid and closely resemble hemorrhagic bullae seen in New World rattlesnake (*Crotalus*) bites. The extent of blistering, bullae, and local tissue destruction is distinctive to *C. rhodostoma* envenoming, and in areas without Russell's viper and when cobra bites are unlikely, blistering, bullae, and local tissue destruction serve as an indication for preemptive treatment with *Calloselasma*-specific antivenom. Necrosis and gangrene complicating secondary infection by the bacteria from the oral cavity of the snake is common [57]. In one series, the leading cause of death after *Calloselasma* envenoming was cerebral hemorrhage followed by hemorrhagic shock [54].

Green Tree Vipers (*Trimeresurus* Species and Related Genera)

The genus *Trimeresurus* (Figs. 11, 12, 13, and 14) and related genera (*Protobothrops*, *Ovophis*;

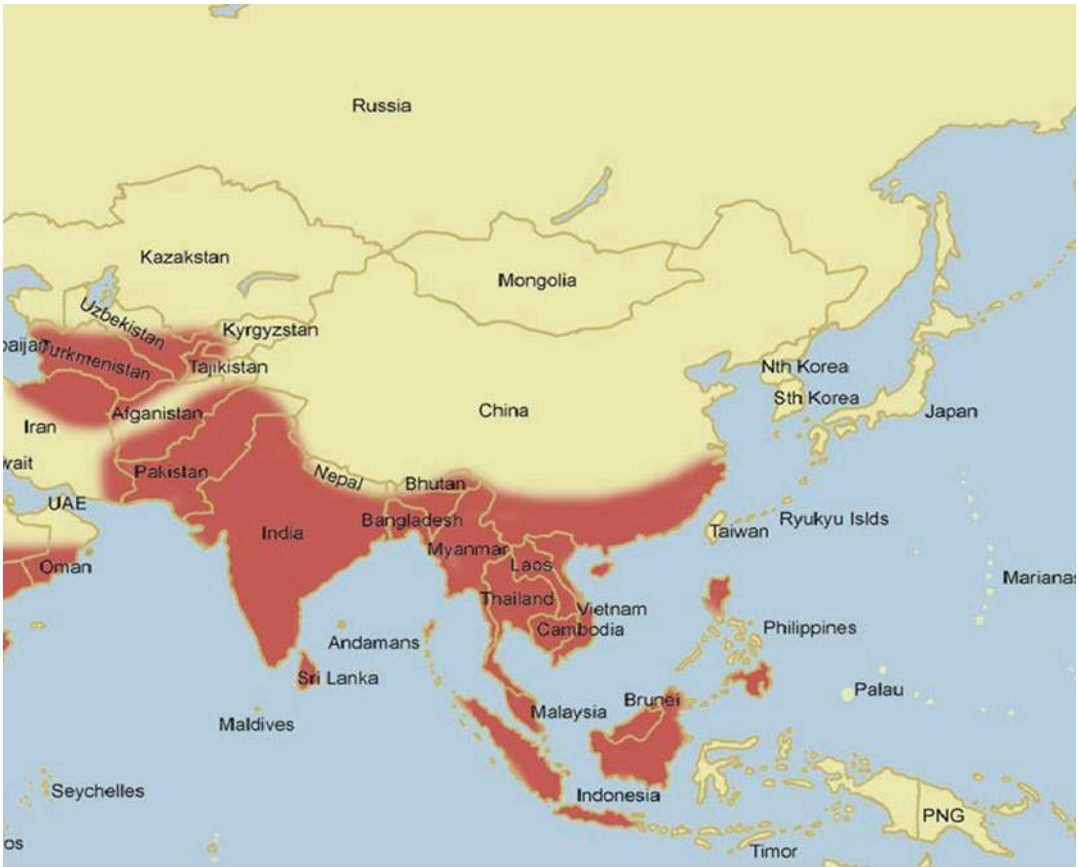


Fig. 32 Approximate distribution for snakes of genus *Naja* (note other *Naja* spp.) found in the Middle East and parts of Africa (Map copyright # Dr. Julian White)



Fig. 33 King cobra, *Ophiophagus hannah*. The largest known venomous snake species, king cobras can cause moderate to severe envenoming with local pain, swelling, occasionally blistering and necrosis, shock, and rapid onset flaccid neurotoxic paralysis (Photo copyright © Dr. Julian White)

Figs. 15, 16, 17, and 18) covers an extensive range from Pakistan to Japan and south to the Philippines and the Indonesian islands. More than 36 species are recognized, including several ground-dwelling, brown-colored species (e.g., *Protobothrops mucrosquamatus* and *Protobothrops flavoviridis*); however, most of the species are arboreal, and most arboreal species are green. Genus *Trimeresurus* has been the subject of recent taxonomic contention, with the genus split into seven genera (*Trimeresurus*, *Cryptelytrops*, *Himalayophis*, *Parias*, *Peltopelor*, *Popeia*, *Viridovipera*), but most recently recombined into the single genus *Trimeresurus* for most species, except a few reassigned to



Fig. 34 Approximate distribution for the king cobra, *Ophiophagus hannah* (Map copyright © Dr. Julian White)



Fig. 35 Red-necked keelback, *Rhabdophis subminiatus*. This NFFC snake can cause severe systemic coagulopathy and bleeding, which may persist for several weeks and the related *R. tigrinus* has caused AKI; both can cause fatal envenoming. Local effects are usually minor (Photo copyright © Dr. Julian White)

Protobothrops. The term *green pit viper* is used with reservation because the designation has led to confusion in herpetology and medical literature and mishaps in the preparation of antivenoms. Similarities in coloration and intergrade species have confused the taxonomy, prompting efforts to define species using molecular approaches, rather than descriptions of range, eye color, and scale counts.

In Thailand, China, Japan, and several Asian islands, green tree vipers are the leading cause of venomous snakebite [53, 58]. Many *Trimeresurus* spp. are tolerant of human activity, and many bites occur in household gardens and urban parks. In parts of eastern Cambodia, the related Wagler's viper (*Tropidolaemus*) is found in Buddhist temples, where snake and monks coexist

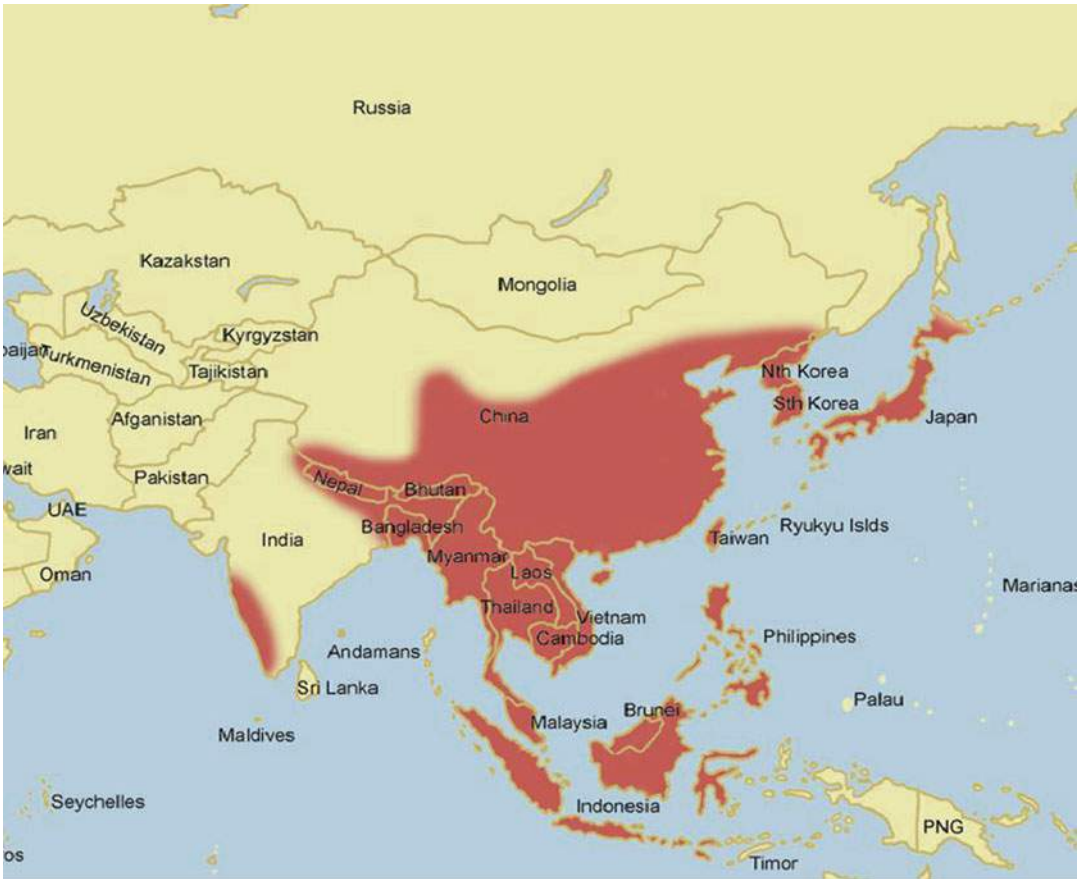


Fig. 36 Approximate distribution for snakes of genus *Rhabdophis* (Map copyright © Dr. Julian White)



Fig. 37 Severe envenoming. The patient was a 13-year-old boy with respiratory paralysis 9 h after being bitten by an unknown krait (*Bungarus*). He received antivenom after symptoms appeared without effect, but he made a full recovery after 6 days of ventilation support. Note bulbar palsy

without apparent problems. Most *Trimeresurus* vipers are arboreal, which explains the high incidence of bites to the hands and the high occupational risk to fruit pickers, forestry workers, and gardeners. Many bites by the ground-dwelling pit vipers, *Protobothrops* spp. and *Trimeresurus* spp., such as the Chinese habu (*P. mucrosquamatus*) [59] and the Japanese/Okinawan habu (*P. flavoviridis*), occur in homes. In all regions, household envenoming is of great concern because it is more likely to involve children.

Similar to all vipers, the fangs of *Trimeresurus*, *Protobothrops*, and *Tropidolaemus* spp. are continuously replaced, although in these species, new fangs may move into position before older fangs are shed. Many *Trimeresurus* bites result in three or more fang marks at the bite site.

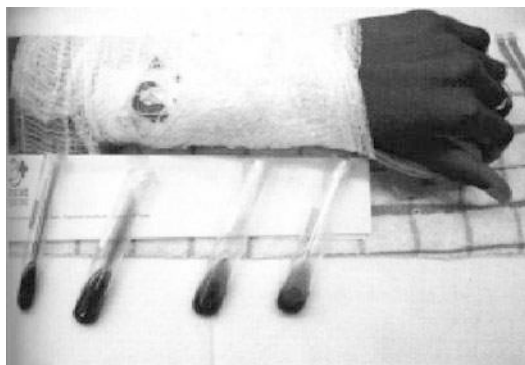


Fig. 38 A 23-year-old woman with severe envenoming by *Daboia russelii*. The splint and gauze bandage help to stabilize the bitten extremity. Coagulopathy is checked using the whole-blood clotting test. The two tubes on the left, collected at 0 and 2 h, lack clot formation. The two tubes on the right, collected at 5 and 10 h after antivenom treatment, show return of clot formation. Note continued bleeding from the fang wounds to the forearm



Fig. 40 The whole-blood clotting test is a simple bedside test to measure anticoagulation. Clean glass tubes are filled with 2–3 mL of blood and left undisturbed for 20 min, then gently inverted. Coagulopathy is present if there is absence of a clot, as shown by liquid unclotted blood flowing down the tube (*left* two tubes). Antivenom may produce a return of clotting function, with formation of a clear clot in the tube (*right* two tubes)



Fig. 39 Caregivers should be vigilant for evidence of systemic anticoagulation, as occurred in this critically envenomed *Echis* bite. Note gingival bleeding after field intubation

The venom of *Trimeresurus* and *Protobothrops* vipers also varies among species and within species from different regions. Several species, *P. flavoviridis*, *Trimeresurus gramineus*, and *P. mucrosquamatus*, contain high concentrations of metalloproteinases with hemorrhagin activity [57, 60–62]. The physiologic activity of the hemorrhagins, notably their attack on the walls of blood vessels [63], is shown clinically with extensive swelling and ecchymosis at the bite



Fig. 41 Russell's viper bite with local necrosis, partially healing (Myanmar)

site. Systemic bleeding is more common in children than in adults. *P. flavoviridis* venom also contains a phospholipase A₂ myotoxin [64], which is a likely cause of myoglobinuria observed in patients envenomed by this species. Investigation has shown that the venom of the far eastern habu species possesses venom antigen with unusual activity. *Protobothrops elegans* (Sakishima-habu) possesses a thrombin-like



Fig. 42 Russell's viper bite with extensive severe local necrosis. This will progress to a long term functional deficit, if the patient survives (Myanmar)



Fig. 43 Bilateral bruising of arms, distant to bite site, as a result of systemic coagulopathy following a Russell's viper bite (Myanmar)

enzyme, elegaxobin, which has potent activity against mammalian systems [65]. Investigation has shown that the venom of *Ovophis okinavensis* (Himehabu) possesses potent hemagglutinating activity [66]. In a hospital-based series of 29 patients envenomed by *Trimeresurus* (likely *T. albolabris*) in and around Bangkok, 46% of patients developed immediate pain, swelling that involved more than half of the limb, and regional tender lymphadenopathy [67]. Although bruising was observed in 58% of these patients, necrosis was seen in only two cases involving bites to the digits.

Elapidae

Asian elapids include the Asian cobras (*Naja*; Figs. 29, 30, 31, and 32), Asian coral snakes (*Calliophis*), king cobra (*Ophiophagus hannah*; Figs. 33 and 34), and kraits (*Bungarus*; Figs. 25, 26, 27, and 28). Sea snakes (previously Hydrophiidae) are specialized elapids found along Asia's tropical coasts.

The venoms of Asian elapids are well known for their neurotoxic and/or cytotoxic effects. These effects are mediated by presynaptic phospholipase A₂ neurotoxins, small postsynaptic peptide neurotoxins, and peptides that contribute to local tissue injury. Until recently there was no report of myotoxic effect from any Asian elapid venom. Generalized rhabdomyolysis has not been previously recognized as a feature of envenoming by any terrestrial Asian elapid snake, but recent cases suggest that venoms of some populations of *Bungarus candidus* and *Bungarus multicinctus* in Thailand and Vietnam and *Bungarus niger* in Bangladesh have this effect in human victims. A study reported edema and necrosis of extrafusal muscle fibers in envenomed rat soleus muscles confirming the myotoxic effect of *Bungarus niger* venom collected from snakes from Bangladesh, attributable to phospholipases A₂ [68].

Neurotoxins

Neurotoxicity manifested as acute neuromuscular paralysis is an important cause of morbidity and mortality related to Elapidae snakebite. The traditional view of snake venom neurotoxins causing only two types of neuromuscular blockade, presynaptic and postsynaptic, may be an oversimplified one and needs to be reviewed in view of the recent insights into neuromuscular transmission and descriptions of different patterns of neurotoxicity.

The presynaptically active neurotoxins (beta-neurotoxins (also known as β -bungarotoxin-type neurotoxins) – mostly neurotoxic phospholipase A₂ toxins, PLA₂s) target the motor nerve terminals (neuromuscular junction), specifically binding to the terminal axon, then entering the axon via endocytosis, then cause intracellular

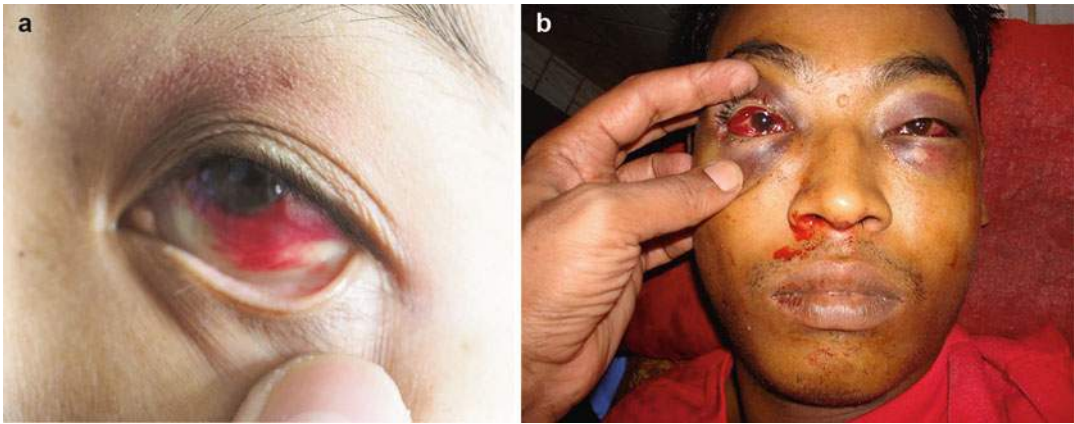


Fig. 44 (a and b) Chemosis and hemorrhage of conjunctiva, a sign of developing capillary leak syndrome; Russell's viper bites (Myanmar)



Fig. 45 Swollen, bruised leg secondary to systemic coagulopathy; green pit viper bite (Thailand)



Fig. 46 Extensive necrosis around the bite to a hand from a spitting cobra bite (Vietnam)

disruption of synaptosomes and synaptosome production. This causes synaptic ACh vesicles depletion, leading to impaired release of acetylcholine (ACh). The degeneration of the terminal axon intracellular structure can result in prolonged paralysis [69–72]. The resulting neuromuscular blockade occurs in three phases: an immediate depression of ACh release, followed by a period of enhanced ACh release, and then complete cessation of neuromuscular junction transmission due to lack of synaptic vesicles, following a latency period of 20–60 min [69, 73–78]. This binding of toxins to the nerve terminal is irreversible, resulting in a slow clinical recovery as it is dependent on regeneration of the nerve terminal and formation of a new neuromuscular junction. This seems to be the basis of patients requiring prolonged respiratory support after Krait bite. This also explains why treatment with antivenom or acetylcholinesterase inhibitors (AChEIs) is often unsatisfactory in presynaptic neurotoxicity, and incomplete recovery and delayed effects are more likely. Presynaptic toxins are best illustrated by beta-bungarotoxin (b-BuTX) of kraits (*Bungarus* spp.) which predominantly has potent PLA₂ enzymatic activity [79].

The postsynaptically active neurotoxins (alpha-neurotoxins; also known as α -bungaotoxin-type neurotoxins) are found in Asian cobra venom (*Naja atra*, *N. kaouthia*), king cobra, and several kraits. They belong to

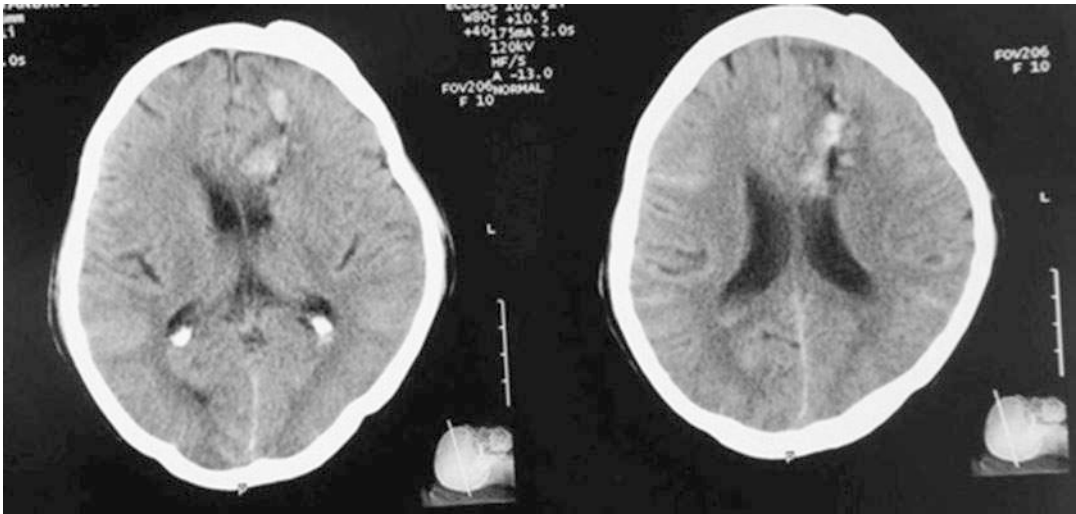


Fig. 47 CT head scan demonstrating hemorrhagic lesions secondary to coagulopathy; pit viper bite

Table 2 Different clinical profile for Russell’s viper bite from four important geographic populations

	<i>Daboia russelii</i>		<i>D. siamensis</i>	
	India	Sri Lanka	Myanmar	Thailand
Coagulopathy	++	++	++	++
Renal failure	++	++	++	+
Sheehan’s syndrome	+	+ ^a	++	–
Hemolysis	+	++	–	+
Neuro-myo-toxicity	+	++	–	–
Systemic capillary permeability (capillary leak syndrome)	+ [33, 34]	–	++	–
1° shock	+	–	++	–

^a + Hypokalemia

the group of “three-finger toxins” (3FTXs), resembling three outstretched fingers of a hand and characterized by a shared toxin structure. They bind to the postsynaptic muscle nicotinic acetylcholine receptors (nAChRs). The postsynaptic neurotoxins are small, which likely explains their fast onset of activity. Postsynaptic toxins are classified into three groups: long-chain, short-chain, and nonconventional alpha-neurotoxins. “Short” peptides (<62 amino acids) are found in the cobras, and “long” toxins (70 amino acids) are found in the venom of king cobras and several kraits. Postsynaptic neurotoxins are the major constituents of the venom of many Asian cobras (*Naja*) and the king cobra (*Ophiophagus*) [80]. They are called “curare-mimetic”

neurotoxins due to their resemblance to the action of d-tubocurarine, a reversible, nondepolarizing postsynaptic block by competitive inhibition of ACh binding to the muscle nAChR [81]. The importance of this finding is that even profoundly paralyzed patients, such as patients requiring ventilator support, may recover quickly after treatment with appropriate antivenom. However, it has also been shown to inhibit the presynaptic neuronal nAChRs, producing the characteristic TOF or tetanic fade. Most of the long-chain 3FTXs such as alpha-bungarotoxin, however, bind almost irreversibly to the postsynaptic nAChRs, therefore, are not so readily reversible by antivenom or AChEIs. The clinician’s familiarity with the venom of the offending snake plays



Fig. 48 Developing local necrosis following a cobra bite



Fig. 49 Partial ptosis due to developing flaccid neurotoxic paralysis

a central role in differentiating paralytic cases that would respond to antivenom from cases in which antivenom stockpiles would be squandered.

Local Toxins

The venoms of Asian cobras also contain destructive polypeptides implicated in tissue necrosis. With the exception of kraits and one cobra species

discussed subsequently, envenoming bites from all Asian cobras (*Naja*) and the king cobra (*Ophiophagus*) are distinguished from nonenvenoming bites by the onset of local pain and minimal-to-moderate swelling. In contrast, the venom of the Philippine cobra (*Naja philippinensis*), all kraits (*Bungarus*), and Asian coral snakes (*Calliophis*) produces minimal local symptoms but often causes severe neurotoxic morbidity. Bites by these species may go unnoticed or be dismissed as nonenvenoming because of the paucity of local symptoms. Victims, usually farmers, frequently give the history of being bitten while sleeping in the rice field at night and waking up in the morning with weakness, not remembering any bite event. It may be that the victim had rolled onto questing kraits, resulting in a defensive bite. The krait bite may be painless and may not wake the farmer. The first evidence of envenoming may be ptosis or ophthalmoplegia when the farmer awakes the next morning. Occasionally, field biologists incorrectly identify a juvenile krait or Asian coral snake as a harmless species or dismiss any bites received as nonenvenoming, with tragic consequences.

Clinical Presentation

Several points may be made regarding the clinical presentation of patients envenomed by Asian elapids:

1. All elapid venoms possess some degree of neurotoxin; however, envenoming by cobras is often associated with local symptoms and local tissue damage, and this may dominate the clinical picture (Figs. 47, 48, 49a–c).
2. Envenoming by the Philippine cobra, all kraits, and coral snakes may result in minimal local symptoms but may cause life-threatening paralysis.
3. Envenoming by most cobras (*Naja*) (except for *N. philippinensis*) and the king cobra (*Ophiophagus hannah*) results in pain, swelling, discoloration, and necrosis.
4. Neurotoxic symptoms may appear quickly or be delayed more than 18 h.
5. Asian elapid venoms are not associated with coagulopathy, though a single study of

common cobra (*Naja naja*) bites in Sri Lanka noted three patients had a positive bedside test for coagulopathy (20WBCT) without any clinical evidence of bleeding [82].

An understanding of neurotoxic effects allows the physician to recognize severe cases and anticipate the need for advanced medical resources. The earliest symptoms suggesting envenoming by neurotoxic species, which may be delayed for hours, include tingling or aching sensation and occasional fasciculations in the bitten extremity.

The earliest symptom of systemic envenoming is repeated vomiting, but frequent use of emetics/herbals by the patient or “traditional healers” makes the interpretation difficult. Other early

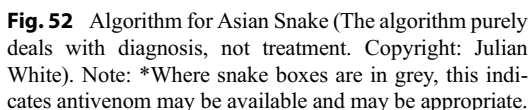
preparalytic symptoms include contraction of the frontalis muscle (deliberate attempt by patient to overcome the ensuing ptosis), blurred vision and loss of visual accommodation (due to mydriasis), perioral paraesthesiae, hyperacusis, loss of the senses of smell and taste, headache, dizziness, vertigo and hypersalivation, congested conjunctivae, and piloerection (“goose-flesh”) due to autonomic stimulation. Patients with systemic envenoming may complain of headache, malaise, generalized myalgia, and may be restless. Paralysis usually starts as ptosis and progresses to external ophthalmoplegia, as ocular muscles are most sensitive to neuromuscular blockade (Figs. 37, 50, 51). Ptosis can be carefully diagnosed by formally assessing the lid retraction during upward gaze as tiredness may cause drooping eyelids. Signs of neurotoxicity may appear as early as 15 min after the bite (cobras) but may be delayed for 10 h or more following krait bites. Then a descending paralysis ensues involving the facial muscles, palate, jaws, tongue, vocal cords, neck muscles (“Broken neck” sign Fig. 51), and muscles of deglutition. Speech becomes muffled and indistinct. Many patients are unable to open their mouths, but in some cases, unable to close. Paralysis of pharyngeal muscles and muscles of deglutition put the patients in danger of aspiration or airway blockade. Respiratory arrest may be precipitated by obstruction of the upper airway by the paralyzed tongue or inhaled vomitus. Interco-



Fig. 50 “Broken neck” sign in a patient with flaccid neurotoxic paralysis



Fig. 51 (a–c) Evolution of a cobra bite from local bruising and early blistering, through more extensive blistering, to full thickness necrosis in the healing stage



muscles may be affected before the limbs, diaphragm, and superficial muscles, and the pattern of breathing becomes abdominal or paradoxical (protrusion of the abdomen during inspiration). Patients with hypoxemia due to respiratory paralysis may present with impaired consciousness and generalized convulsions. However, drowsiness, before the development of significant paralysis, has often been described (attributed to endorphin) but remains unexplained. Intractable hypotension can occur in patients envenomed by Asian cobras.

despite adequate respiratory support. Neurotoxic effects are completely reversible, either acutely in response to antivenom or (for example in Asian cobras) to anticholinesterases [83–86], or they may slowly wear off spontaneously [87, 88]. There are examples of patients, supported by mechanical ventilators, recovering sufficient diaphragmatic movement to breathe adequately in 1–4 days; ocular muscles recover in 2–4 days, and there is usually full recovery of motor function in 3–7 days in the absence of specific

antivenom. However, especially in the absence of antivenom treatment, paralysis may persist. Patients have recovered after 30 days of manual ventilation (in a case of envenoming by the Chinese krait, *B. multicinctus*).

Patients requiring prolonged mechanical ventilation may tie up valuable ventilators, resulting in interruption of surgical and obstetric services. In austere medical settings, patients often develop iatrogenic complications as a result of a lack of skilled nursing care; clinical laboratory monitoring, in particular, blood gas analysis of ventilated patients; or adequate enteral feeding.

Asian Cobras (*Naja* Species)

Cobras are ubiquitous throughout tropical Asia (Figs. 29, 30, 31, and 32). The combined factors of high fecundity, toxic venom, tolerance of human activity, and close association with rice fields make cobras one of the leading causes of snakebite fatalities worldwide. The spectrum of local and neurotoxic symptoms seen in cobra envenoming is highly variable. Many cobra bites, 45% in one study [89], are nonenvenoming. Cobra venom contains fewer enzymes, compared with the venom of vipers; however, several venoms contain cofactors that enhance migration in tissue. *N. naja* venom contains nerve growth factor, which, as implied, stimulates the growth of mammalian nerve tissue [90] but also induces degranulation of mast cells. The resulting release of histamine and proinflammatory chemokines induces vasodilation. *N. naja* venom also contains cobra-venom factor, a glycoprotein that cleaves complement into the cytokine-inducing anaphylatoxins C3a and C5a [91, 92]. The venom of several species contains varying concentrations of unique polypeptide cytotoxins, which are implicated in local tissue injury. The bites of several Asian cobras (*N. sumatrana*, *N. kaouthia*, *N. atra*) can cause significant tissue destruction (Figs. 47, 48 and 49a–c), which may equal that seen after envenoming by Malayan pit vipers. In one series of 47 patients envenomed by *Naja* spp., 44% developed local necrosis, and 12% showed signs of neurotoxicity [89]. Laboratory studies indicate that the venom of several *N. naja* species possesses a nonenzymatic

cardiotoxin that exacerbates platelet aggregation by adenosine diphosphate and thrombin activation [93]. Despite seemingly well-designed laboratory studies, procoagulant and anticoagulant activity is not observed in envenomed patients.

In India, most cobra bites are caused by *N. naja naja* (Indian spectacled cobra; Fig. 30) [94]. In Bangladesh, Malaysia, and Thailand, most cobra bites are caused by *N. kaouthia* (Monocellate cobra; Fig. 29) [53, 89] with rice farmers and aquaculturists being the most common victims [95].

Patients envenomed by *N. kaouthia*, *N. atra*, and *N. naja* and by bites by the smaller Asian spitting cobras (see later) experience immediate pain and aching at the bite site. In the first few hours, there is soft tissue swelling and discoloration of the skin. Four to 60 h after the bite, the tissue surrounding the fang marks becomes mottled and gray, and dependent migration of blistering is often observed (Fig. 49a–c). The first systemic symptoms are drowsiness, nausea, vomiting, and ptosis. In one case, neurotoxicity developed within 30 min of the bite [96]; however, symptoms usually are delayed more than 3 h and may appear 20 h after envenoming. The delay in neurotoxicity likely reflects the time required for the neurotoxin to reach the neuromuscular junction. In children, the earliest and most common evidence of neurotoxicity after cobra bites is ptosis, drowsiness, and inability to keep the head upright [96].

Asian Spitting Cobras

Many Asian cobras defend themselves by spitting fine droplets of venom into the eyes and mucous membranes of animals, resulting in severe contact ophthalmia. The species most frequently implicated in “spitting” venom injury are the Thai spitting cobra (*Naja siamensis*; figure 31), the Javan cobra (*Naja sputatrix*), the Malay-Sumatran spitting cobra (*N. sumatrana*) [89], and the Sumar cobra (*Naja sumarensis*). There is limited evidence that some *Naja kaouthia* from the West Bengal region can spit venom, but it is unclear if this has occurred in human patients (Julian White, Personal Communication.). It is suggested that spitting cobras have the ability to target the eyes

of the offending animal. Spitting cobras can spit venom 2 m or more; however, as the twin venom streams travel toward the target, the streams degrade into an aerosol of fine droplets. Venom ophthalmia develops when this venom comes in contact with the eyes resulting in immediate pain and swelling. Within minutes, the victim experiences conjunctival and palpebral edema, blepharospasm, and leucorrhea. In African species, the venom of similar species may traverse the conjunctiva and enter the lymphatics, resulting in paralysis of the facial nerve [97]. There is no evidence that local spat venom can be absorbed and cause systemic envenoming. Corneal erosions and secondary infection are reported after spit venom injury from several African species (ringhals). Venom sprayed onto oral and nasal mucous membranes results in tingling sensation followed by irritation, which quickly escalates in severity. The bites of Asian spitting cobras may cause local pain, swelling, blistering, and necrosis, which may be severe. While the venom may contain neurotoxins, paralytic envenoming is unlikely following spitting cobra bite, though should always be tested for, both on initial presentation and over subsequent hours of observation.

King Cobra (*Ophiophagus Hannah*)

The king cobra (*O. hannah*; Fig. 33) is the world's longest venomous snake, with documented lengths greater than 5 m. The species has an extensive range, from western India to southern China, Malaysia, Indonesia, and the Philippines (Fig. 34) [98]. The species is brown green in India, olive green throughout most of Southeast Asia, and dull yellow on Mindoro and Negros islands. King cobras are obligate reptile predators that prey almost exclusively on other snakes, including venomous species. The species are highly evolved and are among the minority of snakes known to construct nests and to defend the eggs. This behavior may explain the reputation for aggressiveness and accounts of "unprovoked" attacks on humans. During field collection, king cobras seem more intent on escape and defend themselves only when restrained by the snake hook or when cornered. Specimens quickly acclimate to captivity, becoming tolerant of humans, and quickly learn that

human activity near the cage indicates the likelihood of a meal. Many bites involving captive animals occur when snakes and snake handlers lose their fear of each other.

King cobras can deliver large amounts of venom through fixed fangs, which may exceed 9 mm in length. During venom extraction procedures, 1200 μ L of venom may be obtained from a single 4-m long specimen. The venom is composed primarily of heterogeneous postsynaptic neurotoxins, and deaths usually result from respiratory paralysis. Locally active toxins include hyaluronidase; cobra-venom factor; hannahtoxin, an enzyme with hemorrhagin-like activity; and a unique protein toxin with multiple activities [99]. These factors likely explain the ecchymosis and swelling observed in the envenomed extremity. The presence of local symptoms should alert the physician to the probability of systemic envenoming. The case-fatality rate in king cobra envenoming is high. In a Myanmar series [100], 22 of 35 (63%) bitten patients died, and in a Chinese series [59], 7 of 13 (54%) bitten patients died. Antivenom treatment of severe bites may require many vials. Little quality research has been performed on the variability of venom from king cobras from different regions.

Kraits (*Bungarus*)

Kraits are highly venomous snakes of the genus *Bungarus*, Family Elapidae (Figs. 25, 26, and 27). Kraits are a widely distributed group of snake-eating species that are found throughout the South and East Asian region (Fig. 28). Inhabiting Southeast Asia, southern China, Indonesia, and the Indian subcontinent, they feed primarily on lizards and other snakes. Many species are reportedly docile during the day but become fast moving and more prone to bite at night. In general, they tend to be slender snakes, and similar to other elapids, they have relatively short fangs mounted on the anterior maxilla. Kraits can be found at altitudes ranging from sea level to 1600 m above, and they often inhabit lowland forest terrain. In many parts of India, Bangladesh, Sri Lanka, and Myanmar, humans often are bitten while sleeping in the fields or on the floors of huts. Interestingly, in Myanmar, kraits are

welcomed by rural villagers who know they kill and eat other venomous snakes, such as Russell's viper, which overall are perceived as presenting a higher risk (Julian White, Personal communication).

Seven of 15 krait species have been implicated in human envenoming, and each of these species possesses venom with presynaptic neurotoxins. In several regions, kraits rival the cobras as the leading cause of snakebite-related fatalities [101, 102]. Although they are not considered aggressive snakes, and the reported incidence of bites is relatively low, all species should be considered capable of delivering a potentially lethal envenomation. Kraits deserve special mention due to the burden that krait-bite paralysis places on ICU resources, particularly in rural hospitals.

Bungarus caeruleus, also called the *common Indian krait*, is a relatively uncommon cause of envenomation in India, Pakistan, Bangladesh, Nepal, and Sri Lanka (Fig. 26). With mortality rates for envenoming untreated with antivenom of 77–100% [101, 102], *B. caeruleus* is considered one of the most dangerous snakes in the Indian subcontinent.

Bungarus multicinctus, the *Chinese* or *many-banded krait*, is similar to *B. candidus* (its sister species), but distributed from northern Laos/northern Vietnam north across southern China and into Taiwan. Together with *Naja atra*, the clinico-epidemiologically most important elapid snake in this region, *B. multicinctus* accounts for roughly 8% of all snakebites in China and Taiwan. The venom of this species is included in AV production in Taiwan and China, also attempted in Vietnam. Clinically they produce “typical” *Bungarus* envenoming with recent reports suggesting natriuretic effects and permanent damage to the eye (persisting mydriasis) in northern Vietnam. Mortality rates were 10% and 23% in two case series [59, 103].

Bungarus candidus, also called the *Malayan krait* (Fig. 25), can be found from Thailand, Laos, Cambodia, southern Vietnam south through West Malaysia into Indonesia (on Sumatra, Java, Bali) and has been identified as a major cause of snakebite mortality in Thailand and southern Vietnam. It was recently included in AV production by

QSMI/Thai Red Cross Society. Clinically it causes “typical” krait envenoming with recent reports suggesting myotoxicity/myoglobinuria in some cases (Thailand/Vietnam). In a case series of five patients bitten by this snake, only one patient died, and two patients never developed any signs or symptoms of envenomation [84].

Bungarus fasciatus, also known as the *Asian banded krait* (Fig. 27), is found from eastern Indian states to southern China and south through West and East Malaysia into Indonesia (on Sumatra, Java, Borneo). It is very common regionally and often seen by humans but rarely implicated in envenoming bites. It is an uncommon but significant cause of snake envenomation in China. In mice the venom is about 10 times less toxic than that of other kraits, but venom yield is also much higher than that of other kraits (probably also by a factor of 10). Severe and fatal envenoming has been reported. It is included in AV production in Thailand (also China, Indonesia). It eats other snakes including kraits, cobras and viperids. In parts of India and Myanmar, its presence around the village and in the field is regarded as a sign of luck because people know about its feeding habits and claim that its presence will reduce the number of “dangerous” snakes (by eating them and by other snakes fearing the smell of *B. fasciatus*). It is very sluggish and reluctant to bite during the day. One study reported a 7.7% mortality rate [59], whereas another study reported two of four bitten patients dying from systemic envenomation [104].

Bungarus flaviceps occurs commonly in southernmost Vietnam, southern Myanmar and Thailand, West and East Malaysia, and parts of Indonesia (Sumatra and Borneo only). This is a very docile and shy snake, living only in undisturbed primary rainforest. There are no bites on record where the snakes naturally occur. The venom contains toxins of the same toxin families as other Kraits (e.g., beta-bugarotoxins, kappa-bungarotoxins characterized, others like alpha-neurotoxins are likely also present based on mass spectrometry).

It is important to identify patients who are bitten by kraits because they may present before the onset of significant symptoms, when antivenom would be more effective. Early recognition

of krait bites provides a crucial opportunity to make maximal use of antivenom resources and intervene in the progression of paralysis. Such efforts are advantageous for health clinics located in remote settings because they allow critical ICU resources, such as ventilators, to be conserved for other patients. Local symptoms warning of krait envenoming include numbness, paresthesias, mild discomfort, and aching of extremity muscles. Ecchymosis is not likely with most krait bites. Kraits are not expected to cause coagulopathy. Envenoming by several species (e.g., *Bungarus caeruleus*, *Bungarus candidus*) may be associated with abdominal discomfort [88]. Many patients report generalized muscle pain within hours of the bite. Laboratory evidence of envenoming is restricted to modest elevations of plasma myoglobin and marked neutrophil leukocytosis [41, 102], although hyponatremia has also been reported.

Sea Snakes

Sea snakes are highly venomous and inhabit tropical waters of the Indian and Pacific Oceans, from the Persian Gulf eastwards through Sri Lanka to Southeast Asia, and the southwest Pacific, along the northern coast of Australia and north to the southern islands of Japan [105, 106]. *Enhydrina schistosa* (*Hydrophis schistosus*) is one of the most clinically important species; it lives in the coastal waters, lagoons, river mouths, and estuaries. It is considered as one of the most aggressive sea snakes. Other important species include some other *Hydrophis* spp., *Lapemis curtus*, *Pelamis platurus*, and *Laticauda colubrina*.

There is a lack of epidemiological data concerning sea snakebite in most regions, apart from occasional case reports. Victims of sea snakebites are often treated by traditional healers and fatalities are not reported to the health authority. Majority of sea snakebites (68%) could be dry bites [107]. Another analysis documented that a significant envenoming occurs in about 20% of cases, and deaths occur in about 3% of all bites [108].

Venomous sea snakes have flattened paddle-like tails, and their ventral (belly) scales are greatly reduced in size or lost.

Generalized rhabdomyolysis with consequent gross myoglobinuria, high creatine kinase (CK) levels, and hyperkalemia and neurotoxicity resulting in respiratory muscle paralysis are the main features, although patients without this feature have been described. Electromyographic recordings showed myopathic features.

Envenoming by sea snakes (“Hydrophiinae”) and sea kraits (“Laticaudinae”): the bite is often painless with minimal or no local swelling and the wader or swimmer may not even notice it. Involvement of local lymph nodes is unusual. Features usually appear between 30 min and 3½ h after the bite. In the early stage, patients may complain of headache, a thick feeling of the tongue, thirst, along with sweating and vomiting. Later features of myotoxicity such as generalized aching, stiffness and tenderness of the muscles, and painful passive muscle stretching become noticeable. Trismus may be present. These are followed by progressive flaccid paralysis starting with ptosis. The patient remains conscious until respiratory failure develops due to involvement of respiratory muscles. Myoglobinemia and myoglobinuria are suspected when the serum/plasma becomes brownish and urine becomes dark reddish brown (“Coca Cola colored”). Bedside “stix” tests give a positive result for hemoglobin/blood in urine containing myoglobin. Acute kidney injury may ensue due to myoglobin and potassium released from damaged skeletal muscles. Hyperkalemia (may develop 6–12 h of the bite) may also precipitate cardiac arrest and should be managed promptly.

Not all sea snakebites present with myotoxic envenoming; in some cases, there appears to be pure neurotoxic paralysis, following the classic features and progress of flaccid descending paralysis, as noted earlier for other primary neurotoxic species such as kraits.

Colubridae

As noted earlier, the previous taxonomy of snakes that placed most species in a single Family, Colubridae, has been more recently superseded and a new term, non-front-fanged-colubrids developed, to cover the wide variability in toxin

production and venom delivery mechanisms. Thus, those NFFC snakes currently known to cause potentially significant envenoming effects in humans, and previously all placed in Family Colubridae, now are found across several snake families (see Table 1, earlier in this chapter). The secretions of Duvernoy's gland of several NFFC snakes are capable of producing envenoming injuries. Currently recognized physiologic effects include defibrination and disseminated intravascular coagulation-like reactions, generalized protease activity, phosphodiesterase activity, and phospholipase A₂ activity [109]. Although bites of many species produce local reactions, this discussion focuses on the two Asian NFFC snakes implicated in severe envenoming or fatalities.

Rhabdophis tigrinus (Japanese yamakagashi) and *Rhabdophis subminiatus* (Asian red-necked keelback; Figs. 35 and 36), both in Family Natricidae, are slender, fast-moving snakes that are common in many regions. Bites by *R. subminiatus* are rare throughout the species' range of Thailand, Laos, Myanmar, and Malaysia; however, imported specimens have caused fatal envenoming in several Western countries [110–112]. Lacking canaliculated fangs, the *Rhabdophis* spp. must introduce venom into puncture wounds made by a fixed pair of posterior-positioned maxillary teeth. Envenoming injuries usually involve the snake's hanging on and chewing on the patient. Local findings are distinctive for the absence of anterior fang marks. The local effects of venom may be minimal. Initial symptoms start 1–9 h postbite and include nausea, vomiting, gastrointestinal discomfort, and headache. Onset of coagulopathy is indicated by return of bleeding from the teeth marks. The patient's blood may become incoagulable within hours and may cause gingival bleeding, epistaxis, hematemesis, melena, subarachnoid and intracerebral bleeding, hematuria, and extensive echymosis. Laboratory studies show defibrination, with elevated degradation products, thrombocytopenia, and schistocytes appearing on a peripheral blood smear, suggesting a microangiopathic hemolytic process [113].

Envenoming by the Japanese yamakagashi, *R. tigrinus*, is more common and more severe than envenoming by *R. subminiatus*. Local reactions include swelling, which may involve the entire extremity. Coagulopathy may be severe, leading to intracranial hemorrhage [111]. In addition to severe coagulopathy, envenoming by *R. tigrinus* can cause renal failure, with postmortem studies showing acute tubular necrosis [110]. Antivenom is available for *R. tigrinus* (see Table 9).

There are reports of other species causing systemic envenoming such as *Balanophis ceylonicus* (Sri Lankan keelback) [114], or local envenoming such as *Boiga dendrophila* (mangrove snake) [115] and some other *Boiga* species (cat snakes); *Ahaetulla nasuta* (long-nosed whip snake); *Cerberus rhynchops* (dog-faced water snake); *Enhydryn enhydryn* (rainbow water snake).

Management of Snakebite

In many parts of rural Asia, patient transport to a medical facility often is delayed hours to days. Initial treatment by community health clinics encountered along the way may be rudimentary, may be inaccurate, or may result in injurious treatment. In recent years cellular phone networks have expanded into many of Asia's rural regions, allowing physicians to be notified of inbound emergencies. Prehospital communication also allows physicians to guide bystanders in obtaining basic vital signs, to counsel against injurious attempts at first aid, to measure for changes in swelling, and to observe for evidence of coagulopathy or neurotoxicity. By extending assessment into the prehospital period, the physician may determine the severity of symptoms and prepare in advance for the care for the patient (e.g., IV fluid, antivenom, ventilators, dialysis). In Western countries, a case of exotic snakebite invariably generates considerable interest among hospital staff – which does not translate into better medical care. In these different treatment environments, the gravity of the situation is the same: *Snake envenoming is a medical emergency until proved otherwise*. The time before the patient's

arrival should be used to identify the treatment team, notify the laboratory, identify local snake experts, acquaint medical staff with management priorities and pitfalls, and transport antivenom to the treatment center.

Steps in Management of snakebite [116]

- First aid treatment
- Transport to hospital
- Rapid clinical assessment and resuscitation
- Detailed clinical assessment and species diagnosis
- Investigations/laboratory tests
- Antivenom treatment
- Observing the response to antivenom
- Deciding whether further dose(s) of antivenom are needed
- Supportive/ancillary treatment
- Treatment of the bitten part
- Rehabilitation
- Treatment of chronic complications

First Aid Treatment

Principles of First Aid

The physician should be familiar with first aid measures for snakebite because he or she may need to make optimal use of these techniques while waiting for the arrival of antivenom or may need to address complications resulting from well-intentioned but damaging first aid. In resource-rich countries, first aid rarely is applied in the hospital setting. In Asia, rural medical clinics often can offer little to the patient except first aid. In this circumstance, simple procedures and precautions may benefit the patient by delaying the spread of venom until the patient reaches a hospital. First aid for snakebite in Asia is summarized in Table 3.

1. Reassurance: Snakebite is an unexpected dreadful event. The victim becomes apprehensive of the unknown outcome and is often terrified. Many of the initial features after a bite are caused by sympathetic drive due to overwhelming fear. This may obscure or mimic signs of envenomation, so it is very important to provide reassurance and to try to make the patient calm.

Table 3 First aid for Asian snakebite

ABCs: Place patient in the lateral recumbent position. If nonbreathing, insert an oral airway or pull tongue forward. Perform rescue breathing if necessary. If hypotensive, raise extremities, or use pneumatic antishock garments
Do no harm
Transport promptly to a hospital
If patient is alert, place patient at rest and provide reassurance
Wash bite wound to remove unabsorbed venom
Delay the spread of venom by keeping the patient as still as possible and immobilize the bitten extremity in a functional position at or below heart level
Remove rings, watches, and other potentially constrictive items
Painkillers, especially narcotic analgesia and NSAIDs, should not be used except at the recommendation of a physician familiar with snake envenoming
NSAIDs nonsteroidal anti-inflammatory drugs

- 2. As with any other situation, the golden rule for first aid after snakebite is “Do No Harm.” Do not tamper with the bite wound in any way, but immobilize the bitten limb using a splint or sling. If the patient is thought to have been bitten by a dangerously neurotoxic elapid snake (including sea snakes), consider pressure immobilization (see below).
- 3. Arguably the best thing that can be done for a snakebite victim is to transport them to a health care facility as quickly as possible. The ideal should be whole patient immobilization, but especially immobilization of the bitten limb, as any muscular contractions will promote spread of venom. Ideally, the patient should be transported by motor vehicle, bicycle (as a passenger), boat or on a stretcher. The system of carrying the patient on the back of a motorcycle, sitting in between two other persons has proved effective and also been shown to improve outcome [117] in a developing nation resource poor setting.
- 4. Avoid harmful and time-wasting treatments. Examples of some harmful “treatments” commonly practiced are provided below.
- 5. The offending snake should be taken along to hospital with the patient, if it has already been killed, for species diagnosis. However, catching or killing the offending snake should never

be advocated. Searching for the snake will waste valuable time and it also includes risk of further bites. Caught alive or even once dead, the snake should be handled with extreme caution and preferably by someone with experience. Snakes which appear to be dead should not be touched with the bare hands but carried in a bag or dangling across a stick. Some species (e.g., *Hemachatus haemachatus*) sham death, and even a severed head can inject venom.

Rejected or Controversial First Aid Methods

Traditional treatments are popular and widely used by people not only in rural regions in developing countries but also in some parts of the developed/western world.

These may include tight tourniquets, constriction bands, wound cauterization, incision or excision, amputation of the bitten digit, suction by mouth, vacuum pumps or “venom-ex” apparatus, instillation of chemical compounds such as potassium permanganate, application of ice packs (cryotherapy), “snake stones,” electric shocks, and many others [118]. These have no proven benefit and are discouraged [119].

In a patient with coagulopathy, incisions can cause uncontrolled bleeding. This may also inflict damage to nerves, blood vessels, or tendons and can cause secondary infection. Tissue necrosis may result from suction, application of chemicals, and cryotherapy.

Dangers of Tight Tourniquets

Tight arterial tourniquets applied for prolonged periods are known to cause necrosis resulting in loss of function and even part of an extremity. These may cause congestion, swelling leading to ischemia and gangrene, if they are applied for more than about 2 h. They can also directly damage peripheral nerves (e.g., the lateral popliteal nerve when pressed against the neck of the fibula). Increased bleeding may result from increased fibrinolytic activity. Local effects of venom may be pronounced. On the other hand, rapid development of life-threatening systemic envenoming or even pulmonary embolism may ensue after their release [120].

Pressure Immobilization

The splinting and crepe bandaging method (“pressure bandage and immobilization”; PBI) developed in Australia proved effective in limiting the absorption of Australian elapid toxins in animal experiments. The applicability of this method in a real-time setting has been questioned, with only 18–50% of the bandages in place and effective at arrival at hospital. Crepe bandaging is thought to exert a pressure of about 55 mmHg. Obstruction of lymphatic and venous drainage delays systemic absorption of large molecular-weight neurotoxins without the use of tight tourniquets, which are dangerous. However, it is difficult to apply PBI unaided and to judge the pressure applied. Any sort of external compression may increase the intracompartmental pressure and may worsen the effects of necrotic snake venoms, specifically vipers (Table 4; contraindications for use of PBI). This may not be appropriate for all cases of snakebite [120, 121]. An alternative and simpler method of application of a foam rubber pad directly over the bite wound delayed systemic envenoming, as assessed by measurements of venom antigenemia and the method appeared safe and effective in a field trial in Myanmar [122]. This has been the recommended first aid for snakebite in Myanmar for many years.

Considering the ability to delay the spread of venom and development of early respiratory paralysis, the PBI technique should be applied if

Table 4 Contraindications to pressure bandage immobilization

Bite by unknown species with local evidence of tissue damage
Any bite with pain, swelling, and bleeding from fang marks
Bites associated with severe coagulopathy
Bites >24 h, without symptoms
Bites by NFFC snakes (e.g., <i>Boiga</i> , <i>Rhabdophis</i>)
Bite by any Asian viper or pit viper (possible exception: <i>Daboia r. russelii</i> in southern India and Sri Lanka)
Any cobra bite with local pain, swelling, or significant discoloration

Comment: Pressure-immobilization bandages seem beneficial for envenoming by kraits, Asian coral snakes (*Calliopus*), king cobra (*Ophiophagus hannah*), and Philippine cobra (*Naja philippinensis*)

a bite by a neurotoxic elapid cannot be excluded. The bitten limb should be bandaged at a pressure of about 50–70 mmHg and immobilized with a splint (pressure immobilization), or a pressure pad should be applied at the site of the bite. It is very important to restrain the patient from walking or moving or using other limbs as movement of the other limbs may increase spread of venom. Patient should lie down and be carried on stretcher or kept as immobile as possible [119].

Management of Early Effects Before the Patient Reaches the Hospital

Diverse manifestations of envenoming may appear before the patient reaches hospital. These should be assessed and managed promptly and correctly, as these may dictate the outcome for the patient later on.

Local pain: one of the commonest symptoms and may be severe. Nonsteroidal anti-inflammatory agents, which carry the risk of gastric bleeding in patients with incoagulable blood, should be avoided. Oral paracetamol (acetaminophen) is preferable. Severe pain should be treated with opiates, but caution if there is a possibility of envenoming causing respiratory depression or compromise.

Vomiting: is a common early symptom of systemic envenoming. Persistent vomiting can be treated with intravenous chlorpromazine (25–50 mg in adults, 1 mg/kg in children). In patients with altered consciousness there is the additional problem of aspiration. Patients should be maintained in the recovery position (on their left side).

Syncopal attacks and anaphylactic shock: this may occur immediately within minutes of bite. This is usually due to either a vasovagal attack with profound bradycardia or due to anaphylaxis with angioedema, urticaria, asthma, abdominal colic, and diarrhea. Anaphylaxis is a medical emergency and should be treated promptly with adrenaline 0.1% (1 in 1000) (0.5 ml in adults, 0.01 ml/kg in children) by intramuscular injection followed by a histamine H1-blocker such as chlorpheniramine maleate (10 mg in adults, 0.2 mg/kg in children) which can be given by intravenous or intramuscular injection. In patients with coagulopathy, pressure dressings should be

applied to all injection sites to prevent oozing and decrease the chance of hematoma.

Respiratory distress: usually caused by weakness or paralysis of respiratory muscles but may also be the result of inability to maintain patent upper airway due to jaw, tongue, and bulbar muscle paralysis. The airway should be quickly cleared, if possible using a suction pump, an oral airway should be inserted and the jaw should be elevated, and patients should be placed in the recovery position. Oxygen should be given to patients with cyanosis, or if respiratory movements are weak. There should be a low threshold for initiation of assisted ventilation. If clearing the airway does not produce immediate relief, artificial ventilation must be initiated. Mouth-to-mouth or mouth-to-nose ventilation can be lifesaving if a mechanical ventilation facility is not available. The patient can be ventilated by manual ventilation with an Ambu bag and a cuffed endotracheal tube or a cuffed tracheostomy tube inserted. Ambu bag and anesthetic mask without an endotracheal tube are not very reliable. If no femoral or carotid pulse can be felt, external cardiac massage should be instituted.

Medical Treatment in the Hospital

Snakebite is a medical emergency. Depending on the time lapse between bite and reaching hospital, patients may show early or late signs of envenoming or its complications. Direct cardiovascular effects of the venom (e.g. *Daboia russelii*, *D. siamensis*); blood loss, persistent vomiting, or other causes of dehydration; activation/inhibition of physiological vasomotor systems (such as the angiotensin-renin-bradykinin systems) by venom toxins; and anaphylaxis due to antivenom given outside hospital and rarely, provoked by venom in sensitized habitual snake handlers by previous exposure. All of these may produce sudden profound hypotension and shock in a severely envenomed patient. In hospitalized patients, cardiac arrest may also result from hyperkalaemia in those with massive rhabdomyolysis after sea snakebites. If patients are not kept in a recovery position,

aspirated vomitus, a foreign body, or the fallen back tongue can cause blockage of the upper airway, especially in patients with evolving bulbar paralysis.

The history, symptoms, and signs of the patient with a history of snakebite should be assessed quickly. Airway, breathing, and circulation must be checked immediately. Vital signs (blood pressure, pulse rate, and respiratory rate) must be recorded. Cardiopulmonary resuscitation including clearance of the airway, oxygen administration by facemask or nasal catheters, and establishment of intravenous access are among the first things to do. Choice of venous access should be considered; avoid vessels where the risk of major bleeding is increased or difficult to control (subclavian, femoral, jugular) if at all possible. A timely resuscitation may salvage a moribund patient.

Physicians and other health care professionals should be very careful during removal of tourniquets, bands, or ligatures. There may be sudden deterioration of clinical condition after release, resulting in shock, bleeding, or respiratory paralysis [123]. Antivenom treatment should be initiated and appropriate staff and resuscitation equipment should be on hand.

History and Examination in Hospital

When in hospital each patient should be asked about the site of bite, time of bite, how many times bitten, or if the snake is brought along? If the snake is not brought, then efforts should be made to collect it, if it has already been killed. Patients/attendants should be asked in detail about the events following the snakebite: vomiting, abdominal pain, dizziness, bleeding, or any uneasiness after the bite. Any drugs or alcohol taken should be noted. Ask the patient about presence, rate of development, and progression of any symptoms and whether they have passed urine since being bitten. Table 5 summarizes important data to obtain from the patient history.

Initial symptoms may be nonspecific or attributed to other causes, such as traditional remedies (e.g., use of kava, opiates, or emetics) or fatigue or dehydration after prolonged transport. In many parts of rural Asia, the snakebite victim first

Table 5 Patient history

All cases
Name, age, weight of victim
Size, color, shape, and distinctive features of the snake (see Figs. 1–3, 5–7, 9, 11, 13–15, 17, 19, 21, 23, 25–27, 29–31, 33, 35)
Time bite occurred
Geographic location where bite occurred (swamp, forest, zoo)
Anatomic location of bites and number of bites received
Initial symptoms, timing of onset postbite
Type of first aid or traditional therapy received
Past medical history (e.g., asthma)
Medication (prescription drugs such as β -blockers, anticoagulants, NSAIDs, nonprescription drugs, recreational drugs, alcohol)
Prior history of antivenom administration
Change in symptoms during transport
Presence of priority symptoms: nausea, vomiting, blurred vision, dizziness, dyspnea, syncope, weakness, chest pain, urinary retention, bleeding nares or gums, dark-colored urine, melena, hematochezia
Tetanus immunization status
For viper and Rhabdophis bites
Blood type
Recent surgery
History of cardiac disease, anemia, or hemoglobinopathy
For cobra, krait, and coral snakebites
Time of last meal
History of prior intubation
History of bronchospasm or bradyarrhythmias
Edrophonium hypersensitivity
Location of responsible family members (to assist in care of paralyzed patients)

seeks treatment from traditional healers, which may obscure local signs of envenoming. Patients often do not disclose use of traditional therapies, such as herbal remedies, elixirs, and ointments, which could complicate assessment and management. In Laos and West Vietnam, traditional healers may administer opiate-based powders, which can cause effects that suggest neurotoxic envenoming. Many traditional healers massage herbal compounds into the fang marks, potentially increasing the spread of venom and the risk of secondary infection. These activities also may increase the flow of bloody fluid from fang marks, suggesting coagulopathy.

The earliest symptoms suggesting neurotoxicity are tingling, numbness or dull ache in the extremity, vague abdominal discomfort, restlessness, anorexia to food and fluids, drowsiness, and blurred vision (due to ophthalmoplegia). Other symptoms suggesting systemic neurotoxicity are perioral fasciculations or paresthesias (in nonhyperventilating patients), metallic taste, and dizziness. In Asia, the use of molecular detection or immunoassays for diagnosing envenoming so far has been confined to research trials.

All patients with suspected snakebite should be admitted for observation for at least 24 h even if there is no evidence of envenoming initially. Envenoming by the Philippine cobra, kraits, and coral snakes, all of which may cause insidious neurotoxicity, cannot be ruled out before 24 h of observation. This prolonged period of observation reflects experience with rare cases that present with symptoms 21 h after snakebite.

Clues That Suggest that a Patient May be Severely Envenomed

- 1. A definitely identified offending snake of a dangerously venomous species.
- 2. Early local lymphadenopathy.
- 3. Early symptoms of systemic envenoming: nausea, vomiting, abdominal pain, diarrhea, severe headache, restlessness, heaviness of the eyelids, pathological drowsiness or early ptosis/ophthalmoplegia, collapse (hypotension, shock).
- 4. Early spontaneous systemic bleeding (gums, nose, hematemesis, feces or urine), or persistent bite site/venipuncture site bleeding, dark brown/black urine.

Only if the snake can be identified confidently as non venomous can the patient be discharged after a booster dose of tetanus toxoid.

Physical Examination

Important points of the physical examination are summarized in Table 6. Patients should be evaluated very carefully before removal of any compression bandage or tourniquet. Although the presence of two or three discrete puncture marks

Table 6 Physical examination

Local and systemic examination
Vital signs: respiratory rate, blood pressure, heart rate
Presence of fang marks, bleeding, erythema, discoloration, ecchymosis, swelling, local pain; check for evidence of multiple bites
Distal pulses (capillary refill); monitor for compartment syndrome
Lymphangitis or tender draining lymph nodes
Presence of damaging first aid methods (e.g., incisions, burns, amputations, cryotherapy, electrical burns, tourniquets)
Presence of necrosis, putrefaction, myolysis, secondary infection
Systemic examination
Neurologic examination: Eye examination using finger count and cranial nerve examination, looking especially for even mild ptosis as an early marker for developing neurotoxicity. Assess motor strength and symmetry, and rule out respiratory abnormalities. Respiratory symptoms include dysphonia, dyspnea, use of accessory muscles of respiration, or decreasing peak expiratory flow (measured using a handheld device)
Coagulopathy: Evaluate for retinal and gingival hemorrhage; bleeding from nares or gastrointestinal tract; presence of petechiae or ecchymosis, particularly under elastic bands. Intracranial bleed should be ruled out with neurologic examination
Musculoskeletal examination: Evaluate for compartment syndrome. Palpate muscles for tenderness, which may suggest myolysis. Examine urine for color and presence of casts suggesting proximal tubular cells, hematuria, hemoglobinuria, or myoglobinuria

suggests a bite by a venomous snake, bite mark is not always dependable. Bite site swelling with tenderness and local lymphadenopathy are early signs of envenoming. Patients may be noticed attempting to overcome developing ptosis (raised eyebrows and puckered forehead due to contraction of the frontalis muscle; Fig. 50). Ophthalmoplegia may initially be intermittent, improving when the patient continues to focus on an object. In the case of envenoming by *Bungarus* spp., patients first lose fast saccade eye movements, followed by the development of diplopia. Complete ophthalmoplegia may be delayed many hours. Appearance of dyspnea, “paradoxical” abdominal respiration and cyanosis should alert the physician about impending respiratory failure.

Evidence of systemic coagulopathy may not be apparent at presentation. Early on, envenoming by Asian vipers may cause thrombotic events manifesting as transient cerebral ischemia, syncope, myocardial infarction, arrhythmias, and, rarely, pulseless extremities due to arterial thrombosis. At the time of presentation, most coagulopathies present as prolonged prothrombin time and activated partial thromboplastin time or as incoagulable blood. Coagulopathy usually is first apparent at the bite site, where fang and teeth marks may continue to bleed. Spontaneous hemorrhage from the gingival sulci, retinal hemorrhage, and hematuria or hemoglobinuria suggests incoagulable blood. The presence of incoagulable blood may be confirmed using several low-technology assays, such as the whole-blood clotting test (Figs. 38 and 40 with results in 20 min (20WBCT); Table 7).

The patient should be carefully examined to detect any bleeding from venipuncture sites, recent wounds or skin lesions, and the gums. The oral cavity should be examined as gingival sulci are usually the earliest site of spontaneous bleeding. If the patient is found in shock (collapsed, sweating, cold, cyanosed extremities, low blood pressure, tachycardia), the foot end of the bed should be raised, and an intravenous infusion of a plasma expander or fresh blood started immediately. The jugular or central venous pressure should be observed. Generalized

rhabdomyolysis may cause trismus and stiff and tender muscles. Urine output may decrease very early after Russell's viper bite. Dark (Coca Cola) urine suggests myoglobinuria or hemoglobinuria.

Patients should be followed up hourly for any new effects, level of consciousness, ptosis, pulse rate and rhythm, blood pressure, respiratory rate, extent of local swelling, and appearance of any other new sign. If there is any evidence of neurotoxicity or respiratory involvement, the ventilatory capacity or expiratory pressure (peak flow rate for a resource poor setting) should also be recorded every hour. Distal pulses and capillary refill should be checked periodically to ensure adequate peripheral perfusion and to provide an early warning of compartment syndromes.

A tourniquet or tight compression bandage may cause distal edema through venous congestion even in a nonenvenoming bite. A tightly applied ligature will prevent arterial supply and will cause a cold, pulseless, cyanosed extremity.

Pulseless extremities should undergo intracompartment manometry using a pressure transducer. Compartment syndromes in patients with coagulopathy pose a dilemma because fasciotomy performed under these conditions may result in severe hemorrhage. The use of "prophylactic" fasciotomy is absolutely contraindicated because true compartment syndromes from snakebite are rare.

Table 7 Bedside tests for coagulopathy

20 min Whole-blood clotting test (20WBCT)

Place 2 mL of freshly collected venous blood in a small, new or heat cleaned, dry, glass vessel

Leave undisturbed for 20 min at room temperature (>21 °C)

After 20 min, tip the vessel once

If the blood remains liquid (unclotted) and runs out, the patient has hypofibrinogenemia ("incoagulable blood") as a result of venom-induced consumption coagulopathy

In Asian snakebite cases incoagulable blood suggests envenoming by vipers or *Rhabdophis*

Note: If the vessel used for the test is not made of ordinary glass, or if it has been cleaned with detergent, its wall may not stimulate clotting of the blood sample (surface activation of factor XI – Hageman factor) and the test will be invalid. If there is any doubt, repeat the test in duplicate, including a "control" (blood from a healthy person such as a relative)

Laboratory Studies for Asian Snake

Envenoming

Bedside Studies

Whole-blood clotting test (20WBCT)

Urine dip-stick for proteinuria, hematuria, hemoglobinuria, and myoglobinuria (may require microscopy for confirmation)

Forced expiratory peak flow

Arterial oxygen saturation assessed non-invasively using a pulse (finger) oximeter in patients with respiratory failure or shock.

Priority Laboratory Studies

Type and cross match blood for cases with severe hypotension, major ecchymosis, or swelling, or active major bleeding

(continued)

Hematocrit and hemoglobin

Prothrombin time and activated partial thromboplastin time

Platelet count

Additional Studies

Complete blood count with differential

Peripheral blood smear

Fibrinogen and fibrin degradation products

Liver function test

Serum electrolytes, blood urea nitrogen, and creatinine

Creatine phosphokinase and other enzymes

Urine examination

Electrocardiogram

Caution: Arterial puncture is contraindicated in patients with haemostatic abnormalities (Viperidae).

Plasma/serum: May be pinkish or brownish if there is gross hemoglobinemia or myoglobinemia.

Hemoglobin concentration/hematocrit: More often, there is a decrease reflecting blood loss or, in the case of Indian, Thai and Sri Lankan Russell's viper bite, intravascular hemolysis. There may be a transient increase due to hemoconcentration resulting from a generalized increase in capillary permeability (e.g., in Russell's viper bite).

Platelet count: May be decreased in envenoming, particularly by vipers.

White blood cell count: An early neutrophil leucocytosis is suggestive of systemic envenoming from any species.

Blood film: Microangiopathic hemolysis may cause fragmented red cells ("helmet cell," schistocytes).

Biochemical abnormalities: Severe local or generalized muscle damage (due to sea snake, some krait, and Sri Lankan and South Indian Russell's viper bites) will cause elevation of muscle enzymes (creatine kinase, aldolase, etc.).

Bilirubin will be elevated if there is massive extravasation of blood. Renal failure following Russell's viper, hump-nosed viper and sea snake-bites will cause a rise in potassium, creatinine, urea or blood urea nitrogen levels. Early

hyperkalemia may be a problem following extensive rhabdomyolysis in sea snake bites, particularly if there is secondary renal failure. Bicarbonate will be low in metabolic acidosis (e.g., renal failure). Hyponatremia is reported in victims of krait bites in northern Vietnam (*Bungarus candidus* and *B. multicinctus*). Arterial blood gases and pH may show evidence of respiratory failure (neurotoxic envenoming) and acidemia (respiratory or metabolic acidosis).

Urine examination: The color of the urine (pink, red, brown, black) should be noted and the urine should be tested by dipsticks for blood or hemoglobin or myoglobin. Standard dipsticks do not distinguish blood, hemoglobin and myoglobin. Hemoglobin and myoglobin can be separated by immunoassays but there is no easy or reliable test. Microscopy will confirm whether there are erythrocytes in the urine. Red cell casts indicate glomerular bleeding. Massive proteinuria is an early sign of the generalized increase in capillary permeability in Russell's viper envenoming and an early indicator of acute kidney injury.

Differential Diagnosis

Wounds from local flora, such as stinging nettles and puncture wounds from thorns may suggest snakebite, especially when the injury occurred at night. Bites and stings from local arthropods (e.g., Hymenoptera) and arachnids may cause local pain, swelling, and inflammation that may mimic the early stages of snake envenoming. The venomous bite of Asian centipedes (*Scolopendra* spp.) may cause severe pain and local inflammation, which may mimic that seen in the early hours of viper bites. However, the horizontally orientated chelicerae of *Scolopendra* spp. leave a distinctive chevron-shaped puncture wound. Scorpion stings and bites by Asian widow spiders (*Latrodectus* spp.) may be confused with neurotoxic envenoming by elapids; however, both of these arachnids cause local pain and muscular cramping with minimal local skin changes. Envenoming by *Latrodectus* spp. also is

associated with leukocytosis, moderate hypertension, and cramping of muscle groups, but true flaccid paralysis is most unlikely. In central and southern India, stings by the red Indian scorpion (*Hottentotta tamulus*) have been mistaken for bites by juvenile *Naja*. Important distinguishing features are that scorpion stings cause local piloerection, autonomic disturbances, and minimal local reaction, other than intense pain. Rarely, bites by Asian running spiders (*Lycosa* spp.), sac spiders (*Chiracanthium* spp.), or jumping spiders (*Phidippus* spp.) may suggest envenoming by Asian snakes. Tick paralysis is unique in presentation, appearing as symmetric, ascending, and flaccid paralysis, and is unlikely to be confused with snake venom paralysis. Nonvenomous snakebites and bites by moderately venomous NFFC snakes must be ruled out. NFFC snakes belonging to *Boiga* are pugnacious and capable of mild-to-moderate envenoming. Bite marks from these species have enlarged puncture wounds caused by the posterior maxillary teeth. Several arboreal green tree pythons (Pythonidae), which superficially resemble green *Trimeresurus*, possess elongated teeth suited for grasping birds; bites from these species may occasionally resemble the fang marks of vipers, but more commonly will leave numerous teeth marks, inconsistent with a viper bite. In the case of Krait bites during the night the patient may not be able to recollect the event. Absence of an apparent bite mark or failure to identify the bite mark may present a clinical scenario of acute flaccid paralysis mimicking Guillain Barre Syndrome (GBS). In GBS the paralysis is usually ascending and in Krait bite it is usually descending and more rapid in clinical course.

Emergency and Intensive Care

The care of a patient envenomed by an Asian elapid or viper should be viewed as a prolonged medical emergency, the intensive care management of which may last for days. A few patients are critically envenomed and present with

immediate life-threatening problems. Critical envenoming may result from IV injection of venom, envenoming by highly dangerous species, or prolonged delay in reaching medical care. After initial assessment and stabilization, severely envenomed patients need to be admitted to the ICU for continued antivenom administration, close medical and laboratory monitoring, and skilled nursing care.

Indications for ICU Admission in Asian Snake Envenoming

Any patient bitten by an elapid within 24 h who is showing symptoms of rapidly advancing paralysis (beyond ptosis and fasciculations)
 Blood loss (hemoglobin <8 mg/dL) and negative whole-blood clotting test or positive halo test
 Heart rate >120 beats/min and diastolic blood pressure <40 mmHg after fluid resuscitation
 Swelling and intracompartment pressures >35 mmHg
 Seizure, syncope, or pulseless episode
 Flaccid paralysis unresponsive to anticholinesterase treatment
 Respiratory rate >24/min with use of accessory breathing muscles
 Peak expiratory flow rate <80 L/min (adult)
 PaCO₂ > 45 mmHg and pH <7.35
 Creatine phosphokinase >10,000 U/L or serum potassium >6.5 mEq/L
 Cortisol <15 µg/dL and hypotension, hyperkalemia, or abdominal pain

In many parts of Asia, snakebite patients are managed in general medical wards along with many other incoming medical conditions. Often there is a huge caseload in the admitting ward. This may sometimes compromise the standard of emergency lifesaving care and worsen the outcome. Snakebite is an eminently treatable condition. A few hours vigilant care may completely reverse the outcome. One way to ensure this is to

establish a snakebite clinic/unit in the hospital where all the snakebite victims will be managed. This will help to create a set of health care personnel specifically trained and experienced in managing this condition. This will also help the best use of available logistics that is often in short supply. This approach has proven very rewarding in Chittagong Medical College Hospital in Bangladesh.

If the arrival of a patient is notified beforehand, personnel are assigned specific roles in patient care, coordination of laboratory tests, replenishment of IV supplies, transport and rewarming of the antivenom, and notification of the ICU. In the case of exotic bites, local antivenom repositories need to be located, institutional officers (e.g., zoo officials) contacted, and antivenom delivered to the hospital. Attempts should be made to locate an authority with experience treating envenoming by the same or a similar species. In North America and Europe, such personnel may include foreign medical graduates, who often have experience treating snakebite in their home country. Familiarity with the treatment of envenoming from one species does not translate to experience treating bites from other members of the genus or family. There is variability in the clinical syndromes resulting from envenoming by different species of Asian cobras and among Russell's vipers from different regions.

ICU Management of Asian Snake Envenoming For All Patients

Airway and ventilation support as needed
Continuous patient monitoring (cardiac, blood pressure, oximetry)
Serial neurologic examination
Monitor urinary output; place catheter if necessary (beware coagulopathy)
Repeat laboratory tests within 3 h of antivenom treatment
Repeat antivenom if coagulopathy, neurotoxicity, or local symptoms reappear
Monitor bitten extremity for thrombosis, compartment syndrome, or infection

Debridement of necrotic tissue
Early rehabilitation of damaged extremities

For Paralyzed Patients

Consider tracheostomy for krait-paralyzed cases
Atropine-neostigmine if appropriate
Sedation and analgesia
Early enteral nutrition

For Viper and NFFC Envenoming

Avoid giving blood products if coagulopathy is ongoing; treat with antivenom instead
Monitor alveolar-arterial gradient
Avoid arterial and central line placement, unless peripheral venous access is inadequate
Nephrology consultation for acute renal failure
Monitor for endocrinopathies (adrenal or pituitary insufficiency)

On arrival, patients require primary assessment to confirm a patent airway, spontaneous respirations, and adequate oxygenation and that they are not in shock. Patients with deteriorating respiratory status should be promptly intubated with a laryngeal mask airway or endotracheal tube (Figs. 37 and 39). Nasotracheal tubes should not be used for envenoming by vipers and, probably, *Rhabdophis* spp. owing to risk of bleeding and formation of compressive blood collections in the sinuses. Patients with respiratory paralysis do not require paralytics because the muscles of the upper airway are usually lax. Because patients are alert during paralysis, however, the use of benzodiazepines or other amnestic agents or haloperidol is compassionate and clinically indicated if not otherwise contraindicated by hypotension. Ketamine (1–2 mg/kg IV given over 2 min) may be used in hypotensive patients because it does not lower the blood pressure. In normotensive patients with coagulopathy, ketamine should be used with caution because it increases intracranial pressure and potentially

could increase the likelihood of an intracranial bleed.

Severely envenomed patients require fluid resuscitation. The placement of IV lines also permits blood to be drawn for the bedside evaluation of coagulation and for stat blood samples to be sent to the laboratory. At least two IV lines are needed to allow the separate delivery of antivenom, ionotropes, and IV fluids. IV lines should not be placed in the envenomed extremity, and in patients who are coagulopathic, avoid the subclavian, femoral, and jugular veins, if at all possible. Adult patients are hydrated with boluses of crystalloid as indicated by ongoing assessment of hemodynamic status. Central venous catheterization should not be attempted, unless it is found to be absolutely necessary and significant coagulopathy has been excluded. Fluid volume overload should be avoided, particularly in elderly patients and small children, because antivenom administration also requires IV fluids. In cases of envenoming with coagulopathy, saphenous vein cut-down and ligature and, in children, interosseous access are alternative hydration sites in an extreme situation. Arterial access sites not only are unnecessary but also may prove disastrous in a patient with coagulopathy. Ionotropic agents are seldom required and should be used only when 3–4 L of IV hydration has failed to relieve hypotension. Volume status may be monitored by measuring urine output.

Envenoming by Asian vipers often results in shock secondary to hemorrhagin-induced extravasation of fluid. Packed red blood cells and albumin help to offset fluid extravasation by increasing oncotic pressure. In many parts of Asia, the risk of blood-borne pathogens, such as malaria, filariasis, and viral diseases, may still exist, however, and pathogen testing of blood supplies may be either dubious or nonexistent. Reliance on synthetic colloid replaces these risks with other concerns. The IV administration of 6% hetastarch may interfere with factor VIII activity and may increase the activated partial thromboplastin time. Dextran 40 also should be avoided because it inhibits platelet aggregation, induces

fibrinolysis, and activates factor VIII [124]. In many parts of Asia, 10% pentastarch, which does not interfere with coagulation, is often available and should be considered. Many physicians favor administration of hypertonic saline; however, evidence that it is comparable to colloid fluids is lacking [125].

Criteria for ICU Discharge in Asian Snake Envenoming

Reversal of coagulopathy for >12 h

Resolution of neuromuscular symptoms for >24 h

50% improvement in creatine phosphokinase, hyperkalemia, and fibrinogen titer

Peak expiratory flow rate >100 L/min, adequate oximetry, or arterial blood gas on room air

Stable or improving urine output

Many patients are treated in the field with tourniquets, lymphatic bands, and pressure immobilization dressings. These techniques serve to compartmentalize venom and by-products of ischemia. The physician who receives patients treated with these methods (see earlier section on first aid) should remove these bands only *after* IV access is obtained, the patient is hydrated, and, ideally, antivenom therapy is started (if indicated). In the cobra bite cases, slow removal of the first aid still resulted in dramatic symptoms despite prehydration and treatment with three or more vials of appropriate antivenom (see Table 9). Significant bleeding may occur from incisions made to the fang marks, and occasionally arterial bleeding is seen. Medical care should make use of direct and indirect pressure with a sterile dressing and elevation. Wound inspection and cleaning is performed after lifesaving interventions are completed. An experienced surgeon should be consulted for convincing evidence of compartment syndrome or to identify other threats to tissue or limb. Principles of emergency care for Asian snake envenoming are summarized in Table 8.

Table 8 Emergency care of severe envenoming by Asian snakes

Assign tasks according to medical skill of personnel
In the emergency department or ICU, personnel are assigned to call the laboratory; collect IV supplies; locate, transport, rewarm, and reconstitute antivenom; and identify local snakebite experts
Airway/ventilation
Preoxygenate any patient with respiratory distress, intubate endotracheally, and provide mechanical ventilatory support. Neuromuscular blocking agents are often not necessary for venom-paralyzed patients; however, use of sedatives is appropriate, provided that caution is exercised to prevent hypotension
Fluid volume resuscitation
Place two large-gauge IV lines in the nonenvenomed extremity, and draw blood for laboratory studies and bedside clotting tests. Hydrate adult patients with 300–500 mL fluid boluses every 5 min (children 20 mL/kg) until perfusion is restored. Use of inotropes (dopamine 10–20 µg/kg/min) should be reserved for cases that fail to respond to 3–4 L hydration (packed red blood cells or other colloid should be used in hypotensive-hypovolemic patients with severe swelling). Location of cryptic bleeding should be identified by imaging studies (e.g., CT or ultrasound)
Local care
Fang marks should be inspected, retained fangs removed, and skin irrigated to remove unabsorbed venom. The bite site should not be otherwise manipulated
Patients with tourniquets or pressure dressings should be hydrated and pretreated with antivenom. The extremity should be kept immobilized in a functional position at or below heart level
Antivenom treatment
Prepare standby epinephrine (0.5 mL 1/10,000 in syringe taped to the IV bag, or alternatively mix 1 mg epinephrine in 250 mL D5W (4 mg/mL) and hang/place on IV pole or at bedside). For noncritical patients, start antivenom at low infusion rates, and adjust rate upward as tolerated by patient's symptoms
Question the patient about changes in symptoms, and reassess vital signs for 5–10 min before continuing antivenom. Stop antivenom if hypersensitivity reaction (anaphylactic reaction) develops, treat with IM or IV epinephrine (use IV route only with great caution), and resume antivenom at a slower rate
Acetylcholinesterase inhibitors
Acetylcholinesterase inhibitors should be considered in any patient with neurotoxic symptoms. Patients are first pretreated with atropine (0.6–1 mg for adult and 50 µg/kg children) and tested for edrophonium hypersensitivity. Short-acting edrophonium chloride (Tensilon) is ideal for this test but is rarely available in the region. It is given by slow intravenous injection in an adult dose of 10 mg, or

(continued)

Table 8 (continued)

0.25 mg/kg for children. Patients who respond convincingly can be maintained on neostigmine methylsulfate, 0.5–2.5 mg every 1–3 h up to 10 mg/24 h maximum for adults or 0.01–0.04 mg/kg every 2–4 h for children by intramuscular, intravenous or subcutaneous injection together with atropine to block muscarinic side effects [116]

Nasogastric tubes

Nasogastric tubes may be placed to reduce regurgitation/aspiration and in cases of extended paralysis to assist in hydration and nutrition, but are best avoided, if possible, in patients with active coagulopathy

CT computed tomography, D5W 5% dextrose in water, ICU intensive care unit, IV intravenous

Immunotherapy

Antivenom is the concentrated enzyme-refined gamma immunoglobulin (or immunoglobulin fragments) of horses or sheep which have been immunized with venom. The only definitive treatment for snake envenoming is antivenom. Antivenom does more than save lives; it also conserves blood products and reduces the attendant risk of blood-borne infection; interrupts progression of paralysis, hence conserving mechanical ventilators (or personnel needed to manually ventilate patients); and shortens hospital stay. Antivenom also reduces local injury, lessening permanent disabling sequelae. It is likely that antivenom speeds convalescence, potentially allowing wage earners to return to work faster and with fewer complications (although there is no controlled trial evidence to support this). In developing regions and in resource-rich countries, antivenom treatment is cost-effective, compassionate, and usually the most important contribution made by the health care provider.

The first decision regarding antivenom treatment is whether the patient requires antivenom at all. Many bites are dry or result in trivial envenoming. The cases most likely to challenge the physician involve bites from kraits, coral snakes, and Philippine cobras that have not yet produced neurotoxic symptoms. Envenomings from these species are also the

cases that show maximal benefit when antivenom is given early.

Antivenom should be given to any patient with symptomatic bites to the fingers or toes, severe local symptoms, rapidly progressing symptoms, or any evidence of systemic envenoming. Evidence of systemic envenoming includes coagulopathy (positive 20WBCT or prolonged prothrombin time and partial thromboplastin time; bleeding from the gums, gastrointestinal tract, or genitourinary tract); syncope; seizure; cardiac arrhythmias; perioral paresthesias; developing neurotoxic paralysis (even just ptosis), or any unusual neurologic symptom that cannot be attributed to another cause.

Indications for Antivenom

Antivenom treatment is recommended if and when a patient with proven or suspected snake-bite develops one or more of the following signs [116]:

Systemic Envenoming

1. Hemostatic abnormalities: Spontaneous systemic bleeding (clinical), coagulopathy (20WBCT or other laboratory tests such as prothrombin time), or thrombocytopenia ($<100 \times 10^9/l$ or $100\ 000/cu\ mm$) (laboratory).
2. Neurotoxic signs: ptosis, external ophthalmoplegia, paralysis, etc. (clinical).
3. Cardiovascular abnormalities: hypotension, shock, cardiac arrhythmia (clinical), abnormal ECG.
4. Acute kidney injury (renal failure): oliguria/anuria (clinical), rising blood creatinine/urea (laboratory).
5. Hemoglobinuria/myoglobinuria: dark brown urine (clinical), urine dipsticks, other evidence of intravascular hemolysis or generalized rhabdomyolysis (muscle aches and pains, hyperkalemia) (clinical, laboratory).

Supporting laboratory evidence of systemic envenoming (see above).

Local Envenoming

1. Local swelling involving more than half of the bitten limb (in the absence of a tourniquet) within 48 h of the bite. Swelling after bites on the digits (toes and especially fingers).
2. Rapid extension of swelling (for example, beyond the wrist or ankle within a few hours of bite on the hands or feet).
3. Development of an enlarged tender lymph node draining the bitten limb.

Throughout Asia, antivenom is expensive relative to the cost of other medical services. High cost, limited shelf life, and injudicious use result in frequent shortages, particularly among the rural hospitals. Appropriate species-specific antivenom is often unavailable. Ideally, nonexpired, lyophilized, monospecific antivenoms provide the best results, require the lowest dosages, and have the fewest side effects. Antivenom that has exceeded the expiration date maintains neutralizing activity, even when stored at room temperature, and should be used if no alternative is available. “Specific” antivenom means that the antivenom has been raised against the venom of the snake that has bitten the patient and that it can therefore be expected to contain specific antibody that will neutralize that particular venom and perhaps the venoms of closely related species (paraspecific neutralization). Monovalent (monospecific) antivenom neutralizes the venom of only one species of snake. Polyvalent (polyspecific) antivenom neutralizes the venoms of several different species of snakes, usually the most important species, from a medical point of view, in a particular geographical area [116]. In many parts of Asia, bivalent and polyvalent antivenoms are widely available. These antivenoms have neutralizing activity distributed across the different venoms used in the immunization process, and larger doses often are required compared with monovalent antivenoms. Bivalent and polyvalent antivenoms should be used when the identity of the snake is unknown or when monovalent antivenom is not available. When given a choice, the physician should select an antivenom prepared using venom from the same species and ideally

from the same region. When the culprit snake is unknown, the physician should select antivenom based on the constellation of local findings, the presence of systemic symptoms, the results of clotting tests, the circumstances of the bite, and the epidemiology of bites involving local venomous species. For a reference to currently available antivenom in a specific region in Asia, readers are advised to consult WHO antivenom site (<http://apps.who.int/bloodproducts/snakeantivenoms/database/>) or the Clinical Toxinology Resources Website (www.toxinology.com).

Antivenom treatment should be given as soon as it is indicated, even when systemic envenoming has persisted for several days. In case of persistent hemostatic abnormalities, it is appropriate to give antivenom for as long as evidence of the coagulopathy persists, even for two or more weeks [116] postbite. The role of antivenom in prevention of local necrosis remains controversial, but there is some clinical evidence that, to be effective in this situation, it must be administered within the first few hours after the bite [126].

Contraindications to Antivenom

There is no absolute contraindication to antivenom treatment. But patients who have a past history of reaction to horse (equine) or sheep (ovine) serum (for example, after treatment with equine anti-tetanus serum, equine antirabies serum, or equine or ovine antivenom) and those with a strong history of atopic diseases (especially severe asthma) are at increased risk of severe reactions and should therefore be given antivenom only if they have signs of systemic envenoming. In such cases, it is reasonable to consider prophylactic subcutaneous epinephrine prior to commencing antivenom.

Selection, Storage, and Shelf Life of Antivenom

Antivenom should be selected based on the specificity (paraspecificity) to the known or suspected biting snake. If a liquid antivenom becomes opaque, it should not be used. Lyophilized antivenoms (shelf life about 5 years) should be stored at below 25 °C

and liquid antivenoms (shelf life 2–3 years) should be stored at 2–8 °C and should not be frozen. If properly stored, antivenom can be expected to retain useful activity for months or even years after the stated expiry date [127]. When there is no alternative, recently expired antivenoms may be used in patients with severe envenoming.

Monovalent (monospecific) antivenom should be used when available and more importantly when the biting species is definitely known. It may be less expensive and a lower dose of antivenom may be required than with a polyvalent (polyspecific) antivenom. However, polyvalent antivenom may be more potent than a monovalent antivenom as immunization of an animal with venoms of several related species of snakes (e.g., Viperidae) may produce an enhanced antibody response to common antigens. In many parts of Asia, immuno-diagnosis of species is not possible and the offending snake often cannot be identified. In this situation, polyvalent (polyspecific) antivenoms are preferred and they can be equally effective as monovalent (monospecific) ones.

Administration of Antivenom

Antivenom should be given by the intravenous route whenever possible. Freeze-dried (lyophilized) antivenoms are reconstituted, usually with 10 ml of sterile water for injection per ampoule.

Epinephrine (adrenaline) should always be ready, drawn up before antivenom is administered.

Recommended Methods of Administration

1. Intravenous “push” injection: Reconstituted freeze-dried antivenom or neat liquid antivenom is given by slow intravenous injection (not more than 2 ml/min).
2. Intravenous infusion: Reconstituted freeze-dried or neat liquid antivenom is diluted in approximately 5–10 ml of isotonic fluid per kg body weight (i.e., 250–500 ml of isotonic saline or 5% dextrose in the case of an adult patient) and is infused at a constant rate over a period of about one hour.

Patients must be closely observed for at least one hour after starting intravenous antivenom

administration, so that early anaphylactic antivenom reactions can be detected and treated early with epinephrine (adrenaline). IV push method has the advantage that the health care personnel administering the antivenom can detect some early reactions immediately.

Local administration of antivenom at the site of the bite: It is extremely painful, may increase intracompartmental pressure, is not recommended, and should not be used.

Intramuscular injection of antivenom: Bioavailability of antivenoms are poor after IM injection (specially gluteal region) as these are large molecules ($F(ab')_2$ fragments or sometimes whole IgG) which are absorbed slowly via lymphatics. They fail to reach the desired blood levels. There is additional risk of hematoma formation in patients with hemostatic abnormalities and not to forget the pain of injection of large volumes of antivenom.

The only situations in which intramuscular administration might be considered [116]:

1. Absence of anyone capable of giving an intravenous injection
2. At a peripheral first aid station, before a patient with obvious envenoming is put in an ambulance for a journey to hospital that may last several hours
3. On an expedition exploring a remote area very far from medical care
4. When intravenous access has proved impossible

Antivenom must never be given by the intramuscular route if it can be given intravenously.

Epinephrine (adrenaline) should be kept readily available although the risk of antivenom reactions is less with intramuscular (than intravenous) administration.

If IM route is inevitable, the total dose of antivenom should be given in the upper anterolateral region of both thighs divided in a number of sites. At each site no more than 5–10 ml should be given deep intramuscularly and the site should be massaged afterwards to

aid absorption. It is particularly difficult in children as they have small muscle mass.

Dose of Antivenom

Manufacturers' recommendations may not represent the dose required to cure a human patient as these are usually based on in vitro assays. These recommendations are made based on the average venom yield of captive snakes during milking and amount of antivenom needed to neutralize that volume. In practice, the choice of an initial dose of antivenom is usually empirical. The neutralizing power of antivenoms varies from batch to batch, and any recommendation may become invalid when the manufacturers change the strength of their antivenom. Suggested initial doses of some of the available antivenoms are given in Table 9.

Children Must Be Given Exactly the Same Dose of Antivenom as Adults

For choice of antivenom, see also WHO venomous snakes and antivenoms website <http://apps.who.int/bloodproducts/snakeantivenoms/database/>.

Follow-up After Antivenom

After a dose of appropriate antivenom, the following responses should be observed:

- (a) Nausea, headache, and generalized aches and pains usually disappear quickly. The patient should feel better. But this may also be partly due to a placebo effect.
- (b) Spontaneous systemic bleeding (e.g., from gums) usually stops within 15–30 min.
- (c) Blood coagulability (as measured by 20WBCT) is usually restored in 3–9 h. Bleeding from wounds usually stops sooner.
- (d) Blood pressure may increase within the first 30–60 min in shocked patients and arrhythmias such as sinus bradycardia may resolve.
- (e) Neuroparalysis of the postsynaptic type (cobra bites) may begin to improve as early as 30 min after antivenom, but may take several hours. Envenoming with presynaptic

Table 9 Guide to initial dosage of some antivenoms for treating bites by medically important snakes in the SEARO region Species

Scientific name	Common name	Manufacturer	Recommended minimum initial dose
<i>Bungarus caeruleus</i>	Common krait	Indian manufacturers ^a polyvalent	100 ml
<i>Bungarus candidus</i>	Malayan krait	QSMI ^b Malayan Krait Antivenin ^c	50 ml
<i>Bungarus multicinctus</i>	Chinese krait	Shanghai Vaccine & Serum Institute	5 vials
		NIPM Taipei <i>Naja- Bungarus</i> antivenin	5 vials
<i>Calloselasma rhodostoma</i>	Malayan pit viper	QSMI ^b , Malayan Pit Viper (<i>Agkistrodon</i>) Antivenin monovalent ^d	100 ml
<i>Trimeresurus</i> spp. (<i>T. albolabris</i> ; <i>T. macrops</i>)	Green pit vipers	QSMI ^b Green Pit Viper(<i>Trimeresurus</i>) Antivenin ^d	100 ml
<i>Daboia russelii</i>	Western Russell's viper	Indian manufacturers ^a polyvalent	100 ml
<i>Daboia siamensis</i>	Eastern Russell's viper	Myanmar Pharmaceutical Industry monovalent viper AV	80 ml
		QSMI ^b , Russell's Viper Antivenin monovalent ^d	50 ml
<i>Echis carinatus</i>	India saw-scaled viper	Indian manufacturers ^a polyvalent	50 ml
<i>Gloydius</i> (<i>G. brevicaudus</i>)	Chinese Mamushi	Shanghai Vaccine & Serum Institute Mamushi antivenom	1 vial
Hydrophiinae	Sea snakes	CSL ^c Sea Snake Antivenom	1–10 vials
<i>Naja kaouthia</i>	Monocellate Thai cobra	QSMI ^b , monovalent ^c	100 ml
<i>Naja naja</i> , <i>N. oxiana</i>	Indian cobras	Indian manufacturers ^a polyvalent	100 ml
<i>Rhabdophis tigrinus</i> <i>R. subminiatus</i>	Japanese yamakagashi SE Asian red-necked keelback	Japanese Snake Institute, Nitta-gun Yamakagashi antivenom	1–2 vials

^aIndian Manufacturers: Bharat Serums and Vaccines, Mumbai; Vins Bioproducts, Hyderabad; Biologicals E, Hyderabad

^bQueen Saovabha Memorial Institute (Thai Red Cross Society)

^cAlso the new QSMI Neuro-polyvalent snake antivenom

^dAlso the new QSMI Hemato-polyvalent snake antivenom

^eSeqirus Ltd (formerly CSL Ltd), Parkville, Australia

toxins (kraits and sea snakes) will not respond in this way.

- (f) Active hemolysis and rhabdomyolysis may cease within a few hours, and the urine returns to its normal color.

Treating physicians should be vigilant even after an initial response to antivenom has been observed. Due to continuing absorption of venom from the “depot” at the site of the bite, and elimination of antivenom from the body [128, 129] and redistribution of venom from the tissues into the vascular

space, as the result of antivenom treatment [130], signs of systemic envenoming may recur within 24–48 h. This phenomenon has been described as **Recurrence of systemic envenoming**. This is more important in patients with coagulopathy (envenomed by vipers), though neurotoxic envenoming after cobra bite has also been implicated.

Criteria for Repeating Antivenom

1. Persistence of blood incoagulability (as measured by 20WBCT) after 6 h or recurrence of

- bleeding after 1–2 h and if patients continue to bleed briskly [116].
2. Deteriorating neurotoxic or cardiovascular signs after 1–2 h.
 3. The initial dose of antivenom should be repeated, and patient should be reevaluated for need of full supportive treatment.

Supportive/Ancillary Treatment

Antivenom needs time to act. It is expected to neutralize the circulating venom and thus prevent progression of envenoming, but already established toxicity needs to be addressed simultaneously [116]. The patient may require support of cardiovascular, respiratory, or renal function until the damaged organs and tissues recover.

There may be a situation in many parts of Asia, when antivenom is not available or specific antivenom is not available. The following conservative measures are suggested:

In case of neurotoxic envenoming with respiratory paralysis, assisted ventilation with room air or oxygen has proved effective and should be provided. Many times it has been rewarded with complete recovery, even after being maintained for more than a month. When no mechanical ventilation is available manual ventilation (anesthetic bag) by doctors, medical students, relatives, and nurses has been effective.

Anticholinesterases should always be tried. Anticholinesterase drugs have a potentially very useful, though variable, effect on neurotoxicity especially in patients bitten by cobras [85, 86, 131].

A trial of anticholinesterase (e.g., “Tensilon test”) should be performed in every patient with neurotoxic envenoming. However, this should not delay endotracheal intubation or treatment with antivenom. Patients must be observed closely while the trial of anticholinesterase is being carried out as they may deteriorate. Baseline measurements are noted against which the effectiveness of the anticholinesterase will be assessed.

First atropine sulfate (0.6 mg for adults; 50 µg/kg for children) or glycopyrronium is given by

intravenous injection followed by neostigmine bromide or methylsulfate (Prostigmin) (or distigmine, pyridostigmine, ambenonium, etc. in appropriate doses) by intramuscular injection 0.02 mg/kg for adults, 0.04 mg/kg for children. Short-acting edrophonium chloride (Tensilon) which is ideal for this test is rarely available in many parts of Asia (slow intravenous injection in an adult dose of 10 mg, or 0.25 mg/kg for children).

The patient is observed over the next 30–60 min (neostigmine) or 10–20 min (edrophonium) for signs of improved neuromuscular transmission. Ptosis may disappear and ventilatory capacity (peak flow, FEV-1 or maximum expiratory pressure) may improve.

Patients who respond convincingly to this can be maintained on intramuscular, intravenous, or subcutaneous injection of neostigmine methylsulfate, 0.5–2.5 mg every 1–3 h up to 10 mg/24 h maximum for adults or 0.01–0.04 mg/kg every 2–4 h for children together with atropine to block muscarinic side effects. Patients who are able to swallow tablets may be maintained on atropine 0.6 mg twice each day, neostigmine 15 mg four times each day, or pyridostigmine 60 mg four times each day.

In case of coagulopathy, strict bed rest and avoidance of even minor trauma should be observed. Transfusion of clotting factors and platelets, ideally, fresh frozen plasma (FFP) and cryoprecipitate with platelet concentrates or, if these are not available, fresh whole blood may be considered, but as this is a consumption coagulopathy the role of these is controversial. Any decision to administer should be clinically weighted against the situation. Intramuscular injections should always be avoided.

Hypovolemia should be corrected with colloid/crystalloids (preferably controlled by observation of the central venous pressure). In patients with generalized increase in capillary permeability vasopressor drugs (dopamine) may also be tried. Atropine should be given to patients with hypotension associated with bradycardia.

Acute kidney injury:

Oliguric phase of renal failure: Most, but not all, patients with acute renal failure are oliguric, defined as a urine output of less than 400 ml/day

or less than 20 ml/h. Conservative management may avoid the need for dialysis.

If the patient has intravascular volume depletion, indicated by supine or postural hypotension, or empty neck veins, an intravenous fluid challenge should be tried.

In adults, two litres of isotonic saline can be given over one hour or until the jugular venous pressure/central venous pressure has risen to 8–10 cm above the sternal angle (with the patient propped up at 45°). The patient should be closely observed for pulmonary edema, in which case infusion must be stopped immediately. A urethral catheter should be inserted with full sterile precautions. If the urine output does not improve, a furosemide and/or mannitol challenge may be tried, but these are not of proven benefit. In some patients it can be difficult to determine the height of the central venous pressure by clinical examination. Direct measurement of central venous (superior vena caval) pressure through a long catheter, preferably inserted at the antecubital fossa can be helpful in this circumstance. 100 mg of furosemide is injected slowly (4–5 mg/min). If this does not induce a urine output of 40 ml/h, give a second dose of furosemide of 200 mg.

No further diuretics should be given if the urine output does not improve despite these challenges. Fluid intake should be restricted to a total of the previous day's output plus "insensible losses" (500–1000 ml/day). If possible, the patient should be referred to a renal unit. Infections should be prevented or treated promptly with non-nephrotoxic antibiotics (i.e., avoid aminoglycosides). Serum potassium, urea, creatinine and, if possible, pH, bicarbonate, calcium, and phosphate should be monitored frequently. If this is not possible, the electrocardiogram (ECG) should be examined for evidence of hyperkalemia, especially following bites by sea snakes, or Sri Lankan or South Indian Russell's vipers, or if rhabdomyolysis or intravascular hemolysis is suspected (dark brown urine).

If there are tall peaked T waves, prolonged P-R interval, absent P waves, wide QRS complexes on ECG or potassium >6.0 mmol/l, give 10 ml of 10% calcium gluconate intravenously over 2 min

(with ECG monitoring if possible); this may be repeated up to three times. Give 50 ml of 50% dextrose with 10 units of soluble insulin intravenously, Sodium bicarbonate (40 ml of 8.4%) by slow intravenous infusion and a β_2 agonist aerosol by inhaler or nebulization (e.g., salbutamol 5–10 mg) may also be used. Sodium bicarbonate should also be given if the patient is hypotensive or there is signs of acidosis (deep sighing "Kussmaul" respirations, very low plasma bicarbonate concentration or very low pH – <7.10). After calculating the bicarbonate deficit it may be repeated, but it carries the risk of fluid overload in patients with no or little output and the risk of profound hypocalcemia and fits, especially in patients with rhabdomyolysis.

If there is no clinical improvement dialysis is required.

In the case of myoglobinuria or hemoglobinuria presenting with dark brown urine, correct hypovolemia with intravenous fluid. Acidosis can be corrected with a slow intravenous infusion of 50–100 mmol of sodium bicarbonate and consider a single infusion of 200 ml of 20% mannitol intravenously over 20 min. This must not be repeated as there is a chance of fluid and electrolyte imbalance.

Local necrosis, intracompartmental syndromes, and thrombosis of major vessels are more likely in patients who cannot be treated with antivenom. The risks of surgical intervention in a patient with consumption coagulopathy must be balanced against the complications of local envenoming. Prophylactic broad spectrum antimicrobial treatment should be given (see below).

Antivenom Reactions

Administration of antivenom is associated with inherent risk of reactions. Except in rare cases of presensitization (IgE-mediated Type I hypersensitivity) by previous exposure to animal serum, for example, to equine antivenom, tetanus-immune globulin, or rabies-immune globulin, the risk of reaction is mostly dose related. There are three types of reactions:

1. Early anaphylactic reactions: These usually occurs within 10–180 min of starting antivenom. It starts with an itch often over the scalp and then the patient develops urticaria, restlessness, dry cough, nausea, vomiting, fever, abdominal colic, diarrhea, and tachycardia. Physicians should be vigilant at this stage, as some of these patients may develop severe life-threatening anaphylaxis: hypotension, bronchospasm, and angioedema. In most cases, these reactions are not IgE-mediated type I hypersensitivity reactions to horse or sheep proteins as there is no evidence of specific IgE, either by skin testing or radioallergosorbent tests (RAST). The proposed likely mechanisms for these reactions are direct stimulation of mast cells or basophils by antivenom protein or complement activation by IgG aggregates or residual Fc fragments.
2. Pyrogenic (endotoxin) reactions: They are commonly reported and usually develop 1–2 h after starting infusion of antivenom. Patients usually develop chills (rigors), fever, vasodilatation, and a fall in blood pressure. Children may develop febrile convulsions. These reactions are due to the presence of pyrogenic impurities during the manufacturing process.
3. Late (serum sickness type) reactions: After 1–12 (mean 7) days of treatment with antivenom some of the patients may develop late reactions characterized by fever, nausea, vomiting, diarrhea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis, and, rarely, encephalopathy. Patients who suffer early reactions and are treated with antihistamines and corticosteroid are less likely to develop late reactions.

Prevention of Antivenom Reactions

Adrenaline (epinephrine) is the most effective treatment for anaphylactic reactions, by reducing bronchospasm and capillary permeability. However, the risks of adrenaline make it less attractive for prophylaxis, especially in children, pregnant women, and in patients with heart disease. In a large double-blind, placebo-controlled study

carried out in Sri Lanka, 1007 patients were randomized: adrenaline (0.25 ml of a 0.1% solution subcutaneously), promethazine (25 mg intravenously), and hydrocortisone (200 mg intravenously), each alone and in combinations. Adrenaline significantly reduced severe reactions to antivenom (compared with placebo) by 43% (95% CI 25–67) at 1 h and by 38% (95% CI 26–49) up to and including 48 h after antivenom administration. Adding hydrocortisone negated the benefit of adrenaline [132].

Treatment of Antivenom Reactions

Early anaphylactic and pyrogenic antivenom reactions: Severe, life-threatening anaphylaxis can evolve rapidly. At the very first sign of a reaction, even when only a few spots of urticaria have appeared or at the start of itching, tachycardia, or restlessness, epinephrine (adrenaline) should be given intramuscularly (into upper lateral thigh) in an initial dose of 0.5 mg for adults and 0.01 mg/kg body weight for children. If the patient's condition is deteriorating, dose can be repeated every 5–10 min.

Additional treatment: Antihistamine anti-H1 blocker such as chlorphenamine maleate (adults 10 mg, children 0.2 mg/kg by intravenous injection over a few minutes) should be given followed by intravenous hydrocortisone (adults 100 mg, children 2 mg/kg body weight) after epinephrine (adrenaline).

In pyrogenic reactions: Antipyretics (paracetamol by mouth or suppository). Intravenous fluids should be given to correct hypovolemia.

Treatment of late (serum sickness) reactions:

Oral antihistamine for 5 days. If no improvement after 24–48 hrs a 5-day course of prednisolone should be given.

Doses: Chlorphenamine: adults 2 mg six hourly, children 0.25 mg/kg/day in divided doses.

Prednisolone: adults 5 mg six hourly, children 0.7 mg/kg/day in divided doses for 5–7 days.

Treatment of the Bitten Part

Once the acute management of the patient is over, the treating physician should take care of the

bitten part. The bitten part which is most of the time a limb, may be painful, swollen, tender. It should be kept in the most comfortable position. There may be multiple large, tense bulae. They should be aspirated only if they seem likely to rupture. The limb should not be excessively elevated as this may reduce arterial perfusion pressure in a tensely swollen limb and increase the risk of intracompartmental ischemia. The bite site should be carefully inspected over the next few days as there may be necrosis of local tissue which may warrant surgical attention. There may also be infection due to organisms present in the snake's oral cavity and also secondary bacterial infection. Immediate broad spectrum antibiotics (e.g., amoxicillin or a cephalosporin plus a single dose of gentamicin plus metronidazole) and tetanus prophylaxis are recommended.

Compartmental Syndrome

Direct muscle injury leading to muscle swelling may result in increased pressure especially when tight fascial compartments like the digital pulp space or anterior tibial compartments are involved. An immobile, tensely-swollen, cold and apparently pulseless snake-bitten limb may suggest the possibility of increased intracompartmental pressure. Intracompartmental pressures exceeding 40 mmHg (less in children) may carry a risk of ischemic necrosis (e.g., Volkmann's ischemia or anterior tibial compartment syndrome).

Clinical features of a compartmental syndrome

- Disproportionately severe pain
- Weakness of intracompartmental muscles
- Pain on passive stretching of intracompartmental muscles
- Hypoesthesia of areas of skin supplied by nerves running through the compartment
- Obvious tenseness of the compartment on palpation

The treating physician should be very "conservative (in approach)" before taking the decision for fasciotomy. Fasciotomy should not be contemplated until hemostatic abnormalities have been

completely reversed. Even fasciotomy may not save the envenomed and swollen muscles which may already be irreversibly damaged by the direct effects of the venom [11].

Early Treatment with Antivenom Remains the Best Way of Preventing Irreversible Muscle Damage

Criteria for fasciotomy in snake-bitten limbs:

- (a) Hemostatic abnormalities have been corrected (antivenom with or without clotting factors)
- (b) Clinical evidence of an intracompartmental syndrome
- (c) Intracompartmental pressure >40 mmHg (in adults)

Rehabilitation

Measures for rehabilitation should start once the acute management is over. This starts with maintaining the affected limb in a functional position. Care should be taken to prevent deformity of the ankle and stiffness of muscles. Local tissue necrosis and development of gangrene warrant surgical consultation and management. Physiotherapy may accelerate functional recovery of the bitten limb, and it may be continued at home after the patient is discharged.

Special Populations

Pediatric Patients

In tropical Asia, children are likely to be envenomed by many species. Due to their smaller size, children seem to be at increased risk of intravenous envenoming. Also, children are uniquely subject to krait envenoming as a result of sleeping on the floor in rural houses. The symptoms of snakebite in children are often accelerated, more severe, and more resistant to treatment than in adults. In rural health clinics, pediatric-size oral airways and IV supplies are often unavailable. All children with indications for antivenom should receive the same treatment doses as adults, and the antivenom should

be volume concentrated (e.g., 100–200 mL total volume) to allow for administration of the total dose. A subset of children with apparent poor prognosis after snakebite is the malnourished. Many nutritionally compromised children are bitten while gathering food. In this group, close monitoring of serum electrolytes during treatment is an absolute necessity. After treatment, malnourished patients are likely to benefit from antihelminthic therapy, micronutrient repletion, and a high protein-calorie diet, all of which may support postenvenoming healing.

Pregnant Patients

Pregnant women occasionally may be envenomed and should be treated as nonpregnant patients with a few exceptions. The stress of envenoming can cause *ante- and postpartum hemorrhage, premature labor, abortion/stillbirth, and fetal distress*. The distribution of venom, and likely of antivenom, in pregnant women depends on the molecular weight of venom antigen and antivenom immunoglobulin. Small proteins, including several postsynaptic neurotoxins, may be capable of traversing the placenta and entering the fetal circulation. The effects of neurotoxin on a fetus residing within a paralyzed-ventilated mother are unknown. In addition, there are no data regarding the ability of whole equine or ovine IgG immunoglobulins to traverse the human placenta in a manner akin to maternal IgG. Similarities in molecular weight and amino acid sequence suggest that this movement might be a possibility. Regardless, the pregnant patient and her fetus (*uterine contractions and fetal heart rate*) should be monitored closely and treated based on the mother's symptoms. Cesarean section should not be attempted unless absolutely necessary to save the mother; it should not be undertaken unless coagulopathy has not occurred or has resolved with antivenom therapy.

Elderly Patients

The elderly and patients with comorbidities also are at increased risk of severe reactions to

snakebite. Bites by vipers may severely stress the patient's cardiac reserve [133], and many patients are unable to maintain adequate cardiac output during venom-induced hypovolemic episodes. All elderly patients and patients with heart disease, diabetes, and frail state require close cardiac monitoring and monitoring of serum creatine phosphokinase and creatinine.

Common problems in treatment of Asian snakebite

Problem	Response
Misdiagnose cobra bite as viper bite	Consider cobras in the evaluation of bites with local symptoms; follow-up for neurotoxicity
Missed krait or Philippine cobra bite	These species cause minimal local symptoms and may be dismissed as dry bites. Confirm the identity of seemingly innocuous species or admit patients with suspicious history
Sudden respiratory failure	Reassess progression of paralysis and intubate patient before respiratory failure is advanced
Missed hemolysis or hemorrhage	Extravasation leads to hemoconcentration of red blood cells, which may mask red blood cell lysis. Monitor patients with swelling, check urine output, monitor for hemoglobinuria, and obtain peripheral blood smear for evidence of hemolysis
Delayed presentation to hospital	Monitor patients envenomed by kraits and <i>Naja philippinensis</i> and treat when first symptoms appear; locate antivenom, intravenous fluids, and emergency supplies in advance of patient arrival
Insufficient antivenom	Repeat patient and laboratory assessment to determine if more antivenom is likely to be needed. Plan in advance
Incorrect antivenom	Match the culprit snake with the scientific name and region listed on the antivenom package insert. Attempt to locate more appropriate antivenom (zoos, poison control center, research center)

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Australia and New Guinea are home to the most toxic of all the world’s snakes [1]. The snake fauna is dominated by venomous species, and most snakes that measure greater than 1 m long are potentially lethal [1–4]. Snakebite is a major health issue in New Guinea, where high rates of snakebites and snakebite deaths have been reported [3]. In Australia, with an equally deadly fauna, snakebite is uncommon, however, and fatalities are uncommon to rare [1, 4, 5]. This difference reflects the urban lifestyle in Australia, the well-developed health care system, and the wide availability of intensive care units and antivenoms.

Snake Fauna

In contrast to virtually all other regions, Australia, New Guinea, and the Pacific are dominated by elapid snakes [1–3], with a smattering of non-front-fanged colubrids (NFFC) snakes [6] (► Chap. 124, “Non-Front-Fanged Colubroid Snakes”; none lethal) and no vipers.

Australia

Australia is home to seven families of snakes (Table 1), of which only three contain venomous species, and only one contains species likely to cause human fatalities [1, 2, 4, 6].

Non-front-Fanged Colubroid Snakes

There are only a few NFFC [6] species in Australia, mostly confined to northern and eastern continental Australia, and only one of these is significantly venomous, the brown tree snake, *Boiga irregularis* (Colubridae; Fig. 1) [1, 2, 4]. Even this species does not pose a threat to human life, although infants bitten by immigrant snakes on Guam may occasionally develop significant envenoming [6]. Few bites are recorded from Australia, however, none significant [6]. The NFFC “backfanged” homalopsids (Homalopsidae; notably *Cerberus australis*, *Fordonia leucobalia*, *Myron* spp., *Pseudoferania*

Table 1 Snake families in Australia and the Pacific Islands

Family	Common name	Distribution
Typhlopidae	Blind snakes	Australia, New Guinea, some Pacific islands
Boidae	Pythons and boas	Australia, New Guinea, Samoa, Fiji, Solomon islands
Acrochordidae	File snakes	Australia, New Guinea
Colubridae	Colubrid NFFC snakes [6]	Australia, New Guinea (including Bougainville), Solomon islands, Guam, Fiji
Natricidae (Note that Cogger, 2014, still lists this as a subfamily of Colubridae) [2]	Natricine NFFC snakes	Australia, New Guinea, and beyond
Homalopsidae	Homalopsid NFFC snakes	Australia, New Guinea and beyond
Elapidae (includes Hydrophiinae)	Elapid (cobra type -) snakes (includes sea snakes)	Australia, New Guinea (including Bougainville), Solomon islands, Fiji. Sea snakes found throughout Pacific adjacent to islands, plus one pelagic species

polylepis), though venomous, are not considered a risk to humans [2, 6].

Elapids

Elapids dominate the terrestrial and aquatic Australian snake fauna [1, 2]. Sea snakes of numerous species (about 36 species) abound in the waters of coastal Australia except southern waters [2]. On land, elapids account for 97 of the 126 species of terrestrial (excluding blind snakes; Typhlopidae) and freshwater snakes [2]. Although all elapids are venomous and possess fangs, only

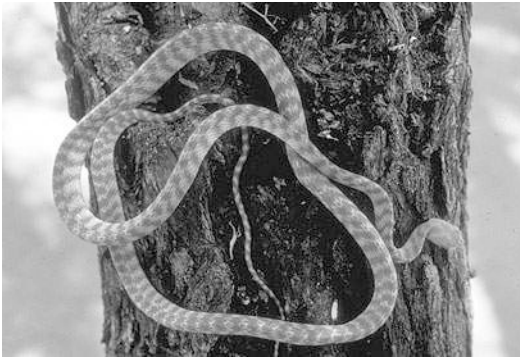


Fig. 1 Brown tree snake, *Boiga irregularis* (Copyright © Dr. Julian White)

about 33 terrestrial species are large enough or toxic enough to pose a significant threat to humans [1, 2, 4, 5]. This latter group is divided into five distinct groups (Table 2) [1, 4].

Brown Snakes. The brown snakes, genus *Pseudonaja*, occupy all of mainland Australia and are currently the most common cause of snakebites and fatalities [1, 2, 4, 5, 7, 8]. These snakes are adapting to urban habitats and are now common in many cities. They vary widely in color and size; some exceed 2 m in length (Figs. 2, 3, 4, 5, 6, 7, and 8) [1, 2, 4].

Tiger Snake Group. The tiger snake group includes the tiger snakes, genus *Notechis* (Figs. 9, 10, 11, 12, and 13); the rough-scaled snake, *Tropidechis carinatus* (Figs. 14 and 15); the copperheads, genus *Austrelaps* (Figs. 16, 17, and 18); the broad-headed snakes, genus *Hoplocephalus* (Figs. 19, 20, 21, and 22); and technically, several genera of smaller elapids of little medical significance [1, 2, 4, 5]. These snakes range from northeastern mainland Australia, down the east coast, across the southern mainland, to southern islands, including Tasmania, and are the second most important cause of snakebites and fatalities [1, 2, 4]. Note that the nonvenomous Natricid freshwater snake, *Tropidonophis mairii*, is sympatric with *Tropidechis carinatus*, and to the nonexpert looks very similar.

Black Snake Group. The black snake group, genus *Pseudechis*, contains a group of larger snakes, collectively ranging across almost all of Australia and responsible for numerous

snakebites but few deaths (Figs. 23, 24, 25, 26, 27, and 28) [1, 2, 4, 5]. Principal species include the mulga snake and the red-bellied black snake.

Death Adders. Death adders, genus *Acanthophis*, are restricted to parts of mainland Australia; are unique in appearance, with a viper-like form (Figs. 29 and 30), but have fared poorly since European settlement and are increasingly uncommon as a cause of snakebites and fatalities [1, 2, 4, 5].

Taipans. The two taipan species, genus *Oxyuranus*, represent the most dangerous of all snakes, combining large size (3 m), big fangs, copious amounts of toxic venom, and a rapid strike (Figs. 31, 32, and 33). These snakes are restricted to northern and parts of eastern coastal Australia (common taipan) and sparsely populated parts of inland Australia (inland taipan) and cause relatively few snakebites and only occasional deaths [1, 2, 4, 5]. Untreated taipan bites carry a lethality rate of greater than 70% [9].

New Guinea

The New Guinea fauna reflects historic land bridges with Australia. Most of the venomous snake fauna is shared (see Table 2) [3].

Non-front-Fanged Colubroid Snakes

Information about NFFC [6] snakes in New Guinea is essentially similar to Australia.

Elapids

Death Adders. Death adders are still common in New Guinea and are a major cause of snakebites and fatalities, particularly in highland areas [3].

Taipans. The New Guinea subspecies of taipan is a major cause of snakebites and fatalities in the southern plains regions [3].

Black Snake Group. The endemic Papuan black snake and the mulga snake are found in southern plains regions but are no longer considered a common cause of bites [3].

Small-Eyed Snake. Unique to New Guinea and nearby islands, the small-eyed snake, *Micropechis ikaheka*, is now thought to cause significant numbers of bites and a few fatalities within its range [3].

Table 2 Medically Important Groups of Australian and Pacific Terrestrial Venomous Snakes, Including Species of Uncertain Medical Importance. Where distribution is listed as “Australia,” this does not imply occurrence throughout Australia, but rather that it occurs at least somewhere within Australia

Scientific name	Common name	Distribution
Colubridae		
<i>Boiga irregularis</i>	Brown tree snake	Northern Australia, New Guinea, adjacent Pacific islands
Homalopsidae		
<i>Cantoria</i> , <i>Enhydria</i> , <i>Foronidia</i> , <i>Myron</i> , <i>Cerberus</i> , <i>Pseudoferania</i> , <i>Heurnia</i> spp.	Water snakes (not sea snakes)	Northern Australia, New Guinea, adjacent Pacific islands
Elapidae		
Brown Snake Group		
<i>Pseudonaja affinis</i>	Dugite	Australia
<i>Pseudonaja aspidorhyncha</i>	Patch nosed brown snake	Australia
<i>Pseudonaja guttata</i>	Spotted brown snake	Australia
<i>Pseudonaja ingrami</i>	Ingram’s brown snake	Australia
<i>Pseudonaja inframacula</i>	Peninsular brown snake	Australia
<i>Pseudonaja mengdeni</i>	Western brown snake or gwardar	Australia
<i>Pseudonaja nuchalis</i>	Tropical brown snake	Australia
<i>Pseudonaja textilis</i>	Eastern brown snake	Australia, New Guinea
Tiger Snake Group		
<i>Notechis scutatus</i>	Common tiger snake, black tiger snake (several subspecies)	Australia
<i>Tropidechis carinatus</i>	Rough-scaled snake	Australia
<i>Austrelaps superbus</i>	Lowland copperhead	Australia
<i>Austrelaps ramsayii</i>	Highland copperhead	Australia
<i>Austrelaps labialis</i>	Pygmy copperhead	Australia

(continued)

Table 2 (continued)

Scientific name	Common name	Distribution
<i>Hoplocephalus bungaroides</i>	Broad-headed snake	Australia
<i>Hoplocephalus bitorquatus</i>	Pale-headed snake	Australia
<i>Hoplocephalus stephensi</i>	Stephen’s banded snake	Australia
<i>Paroplocephalus atriceps</i> ^a	Lake Cronin snake	Australia
<i>Cyrtophis</i> (<i>Rhinoplocephalus</i>) <i>nigrescens</i> ^b	Eastern small-eyed snake	Australia
Black Snake Group		
<i>Pseudechis australis</i>	Mulga snake or king brown	Australia, New Guinea
<i>Pseudechis butleri</i>	Butler’s mulga snake	Australia
<i>Pseudechis colletti</i>	Collett’s snake	Australia
<i>Pseudechis guttatus</i>	Spotted black snake	Australia
<i>Pseudechis papuanus</i>	New Guinea black snake	New Guinea
<i>Pseudechis porphyriacus</i>	Red-bellied black snake	Australia
<i>Pseudechis rosignolii</i>	Papuan dwarf mulga snake	New Guinea
<i>Pseudechis weigeli</i>	Pygmy mulga snake	Australia
Death Adder Group		
<i>Acanthophis antarcticus</i>	Common death adder	Australia
<i>Acanthophis hawkei</i>	Barkly tableland death adder	Australia
<i>Acanthophis cryptamydros</i>	(New species – not yet allocated)	Australia
<i>Acanthophis laevis</i>	New guinea death adder	New Guinea
<i>Acanthophis praelongus</i>	Northern death adder	Australia
<i>Acanthophis pyrrhus</i>	Desert death adder	Australia
<i>Acanthophis rugosus</i>	Papuan death adder	New Guinea, Australia
<i>Acanthophis wellsei</i>	Pilbara death adder	Australia

(continued)

Table 2 (continued)

Scientific name	Common name	Distribution
Taipan Group		
<i>Oxyuranus scutellatus</i>	Common taipan	Australia, New Guinea
<i>Oxyuranus microlepidotus</i>	Inland taipan	Australia
<i>Oxyuranus temporalis</i>	Central ranges taipan	Australia
Miscellaneous		
<i>Micropechis ikaheka</i>	New Guinea small-eyed snake	New Guinea, including Bougainville
<i>Toxicocalamus loriae</i> ^c	Loria forest snake	New Guinea
<i>Salomonelaps par</i> ^c	Solomons coral snake	Islands North of Bougainville, Solomon islands
<i>Loveridgelaps elapoides</i> ^c	Solomons small-eyed snake	Solomon islands
<i>Parapistocalamus hedigeri</i> ^c	Hediger's coral snake	Bougainville Island
<i>Aspidomorphus</i> spp. ^c	New Guinea crowned snakes	New Guinea, Moluccas
Sea snakes		
	Numerous species	Throughout Indo-Pacific waters, near land or reefs; one pelagic species

^aThe medical significance of envenoming by this rarely encountered snake is based on a single case report, where the patient developed procoagulant (defibrination) type coagulopathy, similar to envenoming by the closely related *Hoplocephalus* spp.

^bThere is one reported fatal case of envenoming by this species. The patient developed severe systemic myolysis, and myotoxins were subsequently found in the venom. This is not a rare snake, but no other cases of envenoming are reported

^cThese snakes are generally small; little or nothing is known of their venom; and for most species, no bites are recorded. They are of uncertain medical importance and are not included in subsequent tables. Of the species for which bites are recorded, none were fatal, and local swelling was the most common effect. This does not exclude the possibility, however, that a large specimen might cause severe envenoming, especially in a child

Brown Snakes. A few specimens of Australian brown snakes are reported from southern New Guinea, but they are not a major cause of snake-bites at present. It is unclear if they are native or if they were accidentally introduced [3].

Other Species

Several other species of lesser or uncertain medical significance occur in New Guinea (see Table 2).

Pacific

Most Pacific islands are without terrestrial snakes, or the snake fauna is limited to minor colubrid species, but sea snakes abound in most areas.

Non-front-Fanged Colubroid Snakes

The most important NFFC snake in the Pacific, the Australian brown tree snake, *Boiga irregularis*, was accidentally introduced to islands such as Guam during World War II [6]. Although this snake is not lethal, lack of predators has resulted in a population explosion, a consequence of which is a far higher rate of bites than seen in New Guinea or Australia. Human infants, in particular, may develop significant nonlethal envenoming when bitten [6].

Elapids

Apart from the presence of death adders and the small-eyed snake on a few islands near New Guinea and a few lesser species (see Table 2), medically significant elapids in the Pacific are restricted to the abundant sea snakes.

Venoms

As with other snakes, the medically significant snakes of the Australian and Pacific region possess complex, multicomponent venoms with a variety of clinical effects [1, 4, 5, 9–11]. These effects are overwhelmingly systemic rather than local, however. A summary of activities for each snake is given in Table 3.

Fig. 2 Distribution of Australian brown snakes, *Pseudonaja* spp. (Copyright © Dr. Julian White)



Fig. 3 Eastern brown snake, *Pseudonaja textilis* (Copyright © Dr. Julian White)



Fig. 4 Juvenile eastern brown snake. Note classic black markings on the back of the head and adjacent neck (Copyright © Dr. Julian White)

Neurotoxins

Neurotoxins are the classic toxins of elapid snakes, and they are well represented within the Australian and related fauna [1, 5, 9]. They are all paralytic neurotoxins active at the neuromuscular junction [12].

Presynaptic Neurotoxins

Presynaptic neurotoxins are phospholipase A_2 toxins of variable size, ranging from approximately 10 to 88 kd [1, 5, 9]. Some have myotoxic activity in addition to causing progressive damage to the terminal axon of the neuromuscular junction. They initially cause acetylcholine release, then destruction of synaptic vesicles and



Fig. 5 Western brown snake, *Pseudonaja aspidorhyncha* (Copyright © Dr. Julian White)

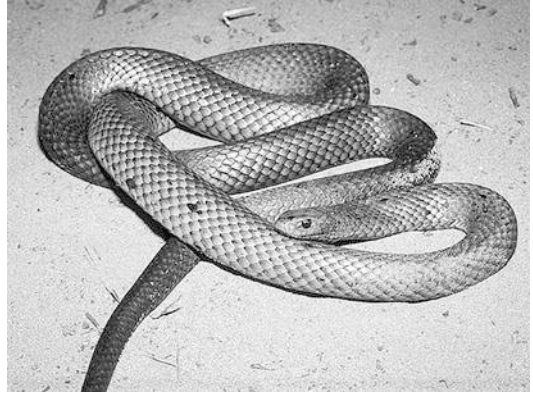


Fig. 8 Peninsular brown snake, *Pseudonaja inframacula* (Copyright © Dr. Julian White)

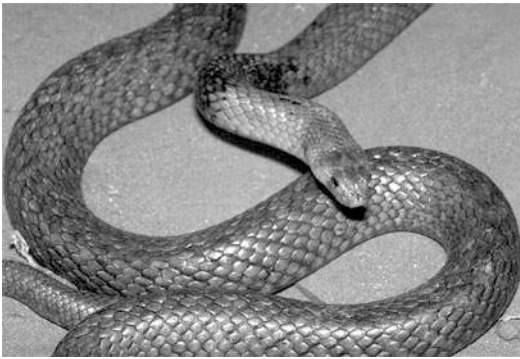


Fig. 6 Western brown snake, different coloring (Copyright © Dr. Julian White)



Fig. 7 Dugite, *Pseudonaja affinis* (Copyright © Dr. Julian White)

mitochondrial structures, causing irreversible cessation of signal function [9].

Postsynaptic Neurotoxins

Most venoms containing presynaptic neurotoxins also contain postsynaptic toxins [9]. These toxins competitively bind to the acetylcholine receptor on the muscle end plate, blocking signal reception and causing paralysis, which is potentially reversible.

Myotoxins

The myotoxic activity in Australian snake venoms is mediated by modified phospholipase A₂ toxins, a few of which are also presynaptically active [9, 12]. Only skeletal muscle is affected to any significant degree, and the effect is predominantly systemic rather than local in the bitten area.

Procoagulants, Anticoagulants, and Hemorrhagins

Australian snake venoms are a rich source of potent procoagulants, mostly prothrombin converters, causing a brief period of thrombosis, followed by prolonged profound defibrination [1, 4, 9, 13]. Only a few species have clinically

Fig. 9 Distribution of tiger snakes, *Notechis spp.*, in Australia (Copyright © Dr. Julian White)

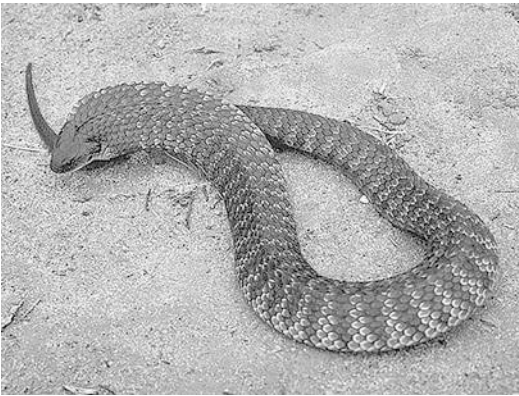


Fig. 10 Common tiger snake, *Notechis scutatus scutatus* (Copyright © Dr. Julian White)

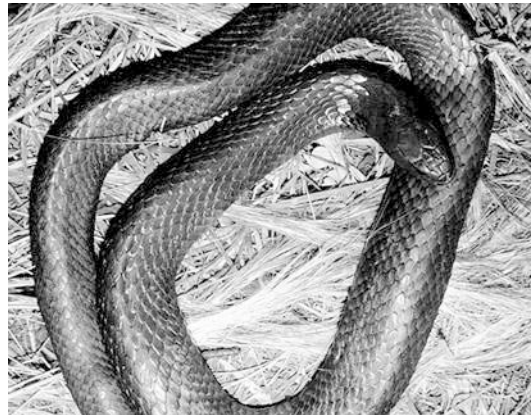


Fig. 11 Common tiger snake, unbanded brown color phase, *Notechis scutatus scutatus* (Copyright © Dr. Julian White)

apparent anticoagulants [9, 13]. Hemorrhagins, although suspected for some species, have not been definitively isolated so far. The massive hemorrhagic effect seen with some viper venoms is not apparent with these elapid venoms.

Procoagulants

The potent prothrombin converters in some Australian snake venoms are extraordinarily

potent coagulants in vitro, but in vivo they usually are not associated with detectable thrombosis [1, 4, 9, 12, 13]. Rather, they are associated with rapid, often complete defibrination and hyperfibrinolysis, resulting in potentially lethal bleeding from any damaged vessels. These procoagulants are of Group C and D, varying in size from about 58 kd to greater than 200 kd [13].



Fig. 12 West Australian tiger snake, *Notechis scutatus occidentalis* (Copyright © Dr. Julian White)

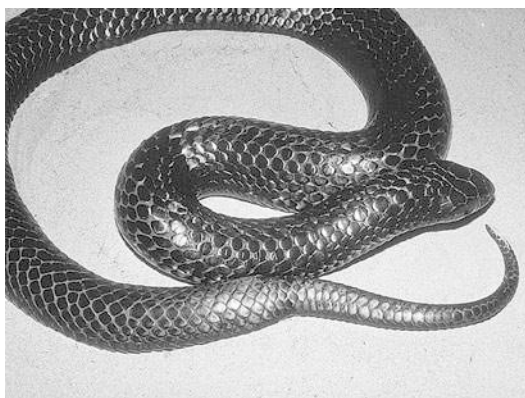


Fig. 13 Black tiger snake (Flinders Ranges), *Notechis scutatus ater* (Copyright © Dr. Julian White)

Anticoagulants

Still poorly characterized, true anticoagulants of clinical significance are restricted to only some *Pseudechis* spp. and are only rarely associated with major bleeding [4, 12, 13].

Hemorrhagins

Hemorrhagins are unproven for any Australian venom, although they have been clinically suspected for at least the New Guinea taipan venom [1]. However, another explanation for the gingival bleeding often seen with taipan envenoming in New Guinea is that poor oral hygiene leaves numerous small potential oral bleeding points that become obvious once

defibrination and hyperfibrinolysis occurs, preventing effective hemostasis at these otherwise minor areas of gingival damage.

Nephrotoxins

Nephrotoxins are unproven for any Australian snake venom, although they have been clinically suspected for at least brown snake venom [1]. Nephrotoxicity is more likely a secondary effect of the disseminated microangiopathic hemolytic anemia that can occur in some envenomed patients [4, 8, 12]. The latter condition is characterized by intravascular hemolysis, anemia, thrombocytopenia, and renal failure, similar in presentation to thrombotic thrombocytopenia and hemolytic uremic syndrome, but the etiology of this condition in envenoming remains uncertain, since it appears more frequently following bites by species with low hemolytic potential in their venom [12–18].

Necrotoxins

There is no evidence of significant necrotoxic activity in any Australian snake venom, although a few, notably *Notechis* spp., may cause minor local tissue injury in certain circumstances [9].

Pathophysiology of Envenoming

Route and Onset

Most cases of snakebite follow subcutaneous injection of venom through one or two fangs, the quantity of venom injected being highly variable within a species and between species and genera (Table 4) [10]. Major venom components are generally of moderate to large size, mostly greater than 10 kd, and seem to be transported principally from the bite site via lymphatics [19]. Pressure immobilization first aid may effectively retard venom movement completely and delay onset of systemic envenoming until removed [20], whereupon rapid, severe systemic envenoming may

Fig. 14 Distribution of rough-scaled snake, *Tropidechis carinatus* (Copyright © Dr. Julian White)

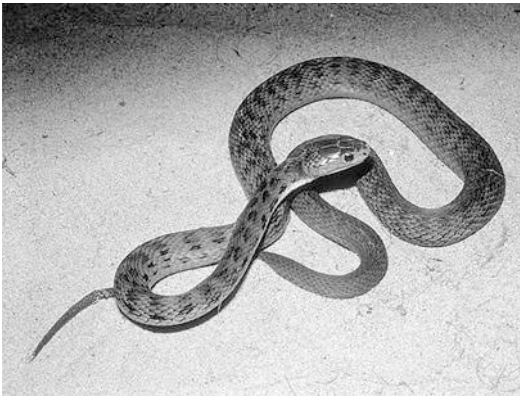


Fig. 15 Rough-scaled snake, *Tropidechis carinatus* (Copyright © Dr. Julian White)

ensue in less than 30 min [1, 4, 5]. Without effective first aid, envenoming usually manifests within 30 min, although certain effects take longer to appear. In adults particularly, potentially life-threatening systemic envenoming, notably coagulopathy, may occasionally develop in the absence of major symptomatology and may only be detected by laboratory testing [11]. Occasionally, envenoming may be delayed by many hours, however, even without first aid.

Mechanisms

Paralysis

Presynaptic and postsynaptic flaccid paralysis is mediated through effects at the neuromuscular junction [1, 11, 12]. The neurotoxins first must traverse from the bite site to the circulation, via the lymphatics, then exit into the extravascular space to reach their target sites, a process easily subject to delays. For presynaptic neurotoxins, there is a latency period of at least 60 min from the time the neurotoxin reaches the target site (terminal axon cellular membrane, NMJ) and binds, to the time neurotransmission ceases [9]. This may explain why paralysis is unlikely to be evident in the first 60 min after the bite and is often apparent only several hours later.

When paralysis has been established, the half-life of the neurotoxins, generally unknown, may have little influence anyway, particularly for pre-synaptic neurotoxins. When these have caused damage to the terminal axon at the neuromuscular junction, recovery depends on cell regeneration, a process that may take days, weeks, or months [9, 11].

Fig. 16 Distribution of Australian copperheads, *Austrelaps* spp. (Copyright © Dr. Julian White)

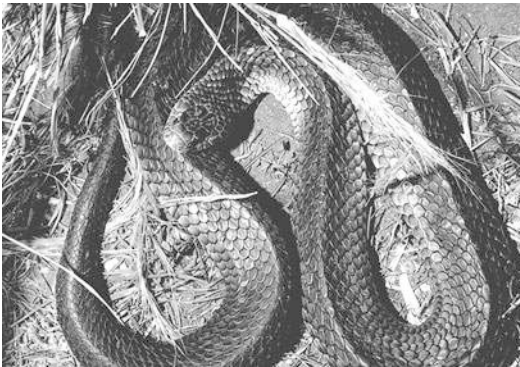


Fig. 17 Common copperhead, *Austrelaps superbus* (Copyright © Dr. Julian White)



Fig. 18 Pygmy copperhead, *Austrelaps labialis* (Copyright © Dr. Julian White)

Myolysis

The precise mechanism of myolysis induced by Australian snake venom toxins is poorly understood, but experimentally these toxins rapidly cause muscle cell damage when they have reached their target site, a process that, as with the neurotoxins, may be delayed for 1 or more hours [1, 9, 11]. Complete destruction of affected muscle cells occurs within 24–72 h, but the

basal lamina is unaffected, and myoblasts quickly begin the rebuilding process, resulting in progressive muscle reconstitution over about 4 weeks [9]. There is experimental evidence that only slow-twitch muscle fibers regenerate [9].

Fig. 19 Distribution of broad-headed snakes in Australia, *Hoplocephalus* spp. (Copyright © Dr. Julian White)

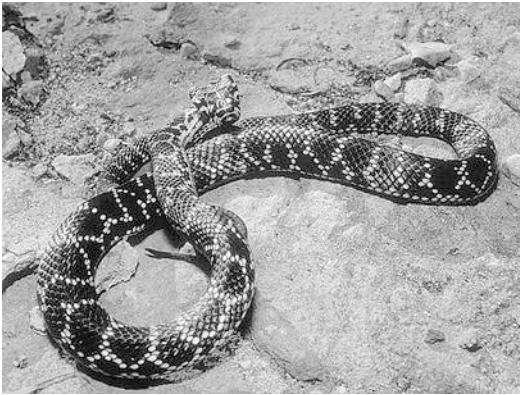


Fig. 20 Broad-headed snake, *Hoplocephalus bungaroides* (Copyright © Dr. Julian White)

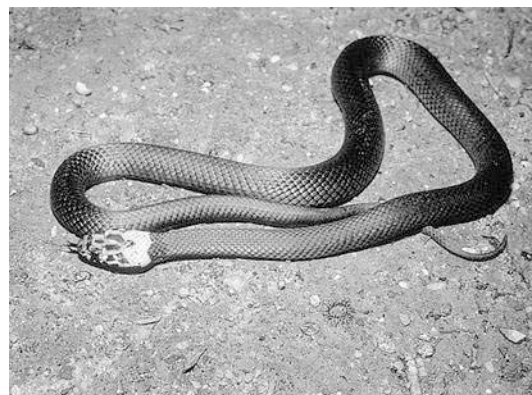


Fig. 21 Pale-headed snake, *Hoplocephalus bitorquatus* (Copyright © Dr. Julian White)

Coagulopathy

The prothrombin converters reach their target as soon as they enter the circulation, a process that may occur within 10–20 min of the bite, unless effective first aid is used [1, 9, 11, 13, 21]. Coagulopathy, in this case defibrination, occurs in less than 30 min in some cases [11]. Research in dogs suggests that with high venom loads, there may be a brief but significant period of

thrombosis, before onset of prolonged and profound defibrination [22]. Fibrinolysis takes several minutes to become established after onset of fibrin formation. During this time, significant thrombi may form, potentially occluding crucial vessels, such as coronary arteries; this may explain the apparent early, often lethal cardiac collapse associated with some severe brown snake bites [4]. By the time an autopsy is

performed, hyperfibrinolysis will have ensured removal of all thrombi.

The duration of the prolonged defibrination phase is variable. For tiger snakes, even without treatment, it may last only 15–18 h, but for brown snakes and taipans, it may persist for more than a day if not treated [4]. Untreated coagulopathy is associated with sometimes severe, persistent bleeding from all wounds, including iatrogenic wounds, such as venipuncture sites and

intravenous line insertions [4, 11]. Lethal intracranial hemorrhages occur, although infrequently [4, 23]. The addition of external coagulation factors (e.g., fresh frozen plasma or cryoprecipitate) as treatment can worsen the coagulopathy if active venom procoagulant is still circulating. This may occur if insufficient antivenom has been given [1, 4].

The true anticoagulant venoms rarely cause severe effects, although they can rapidly produce gross abnormalities in clotting tests [1, 4]. Because their effect is purely inhibitory, however, without destruction of clotting factors, reversal of anticoagulation is rapid after antivenom therapy. The duration of the anticoagulant effect, if left untreated, is not known, although it is unlikely to extend more than 24–48 h.

Renal Damage

Although a primary nephrotoxic effect is suspected for brown snake venom, most cases of renal damage after Australian snakebite are probably secondary to some other process, such as myolysis with myoglobinuria, severe coagulopathy, intravascular hemolysis, or a hypotensive episode [1, 4]. The depth and duration of

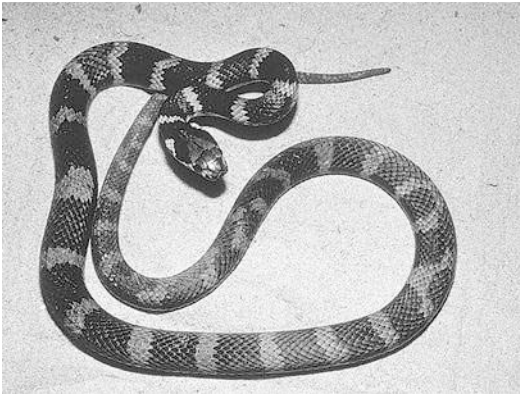


Fig. 22 Stephen's banded snake, *Hoplocephalus stephensi* (Copyright © Dr. Julian White)

Fig. 23 Distribution of mulga snakes, *Pseudechis australis* and *Pseudechis butleri* (Copyright © Dr. Julian White)



renal damage are highly variable, ranging from a mild-to-moderate increase in serum creatinine levels and normal urine output to oliguric or anuric renal failure, often associated with acute tubular necrosis, to rare instances of permanent renal damage, renal cortical necrosis. Only renal cortical necrosis routinely results in long-term problems.

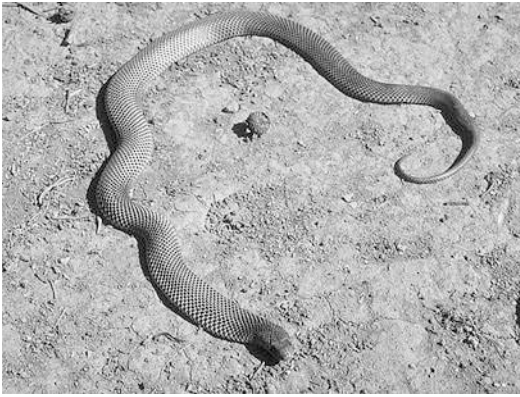


Fig. 24 Mulga snake, *Pseudechis australis* (Copyright © Dr. Julian White)

Clinical Presentation of Envenoming

The rate of envenoming is highly variable (Table 5); many, if not most, Australian snakebites result in no or minimal envenoming and do not require antivenom therapy [1, 4]. It is difficult to determine initially, however, if the bite will be minor or major because the local effects of envenoming, in contrast to snakebite in other parts of the world, are often minor and give no indication of forthcoming systemic problems. It follows that all suspected snakebites in the Australian region should be assumed to be major until clearly shown to be otherwise [1, 4].

Local Effects

Local effects vary from nil to minimal (e.g., brown snakes); to local pain, bruising, and mild edema (e.g., tiger snakes); to extensive local pain and edema (e.g., mulga and black snakes) (Table 6) [1, 4, 11]. Bite marks vary from invisible tiny punctures or scratches to obvious single or multiple fang punctures or scratches (Figs. 34, 35, and 36).

Fig. 25 Distribution of Collett's snake, *Pseudechis colletti* (Copyright © Dr. Julian White)



Fig. 26 Collett's snake,
Pseudechis colletti
(Copyright © Dr. Julian
White)

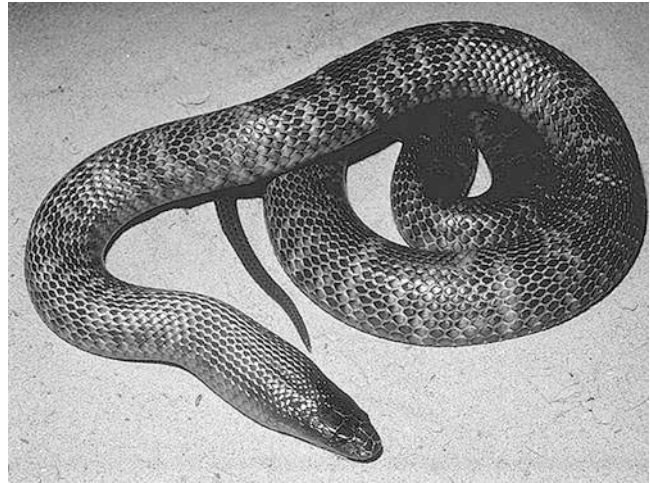


Fig. 27 Distribution of
Australian black snakes,
Pseudechis porphyriacus
and *Pseudechis guttatus*
(Copyright © Dr. Julian
White)



General Systemic Effects

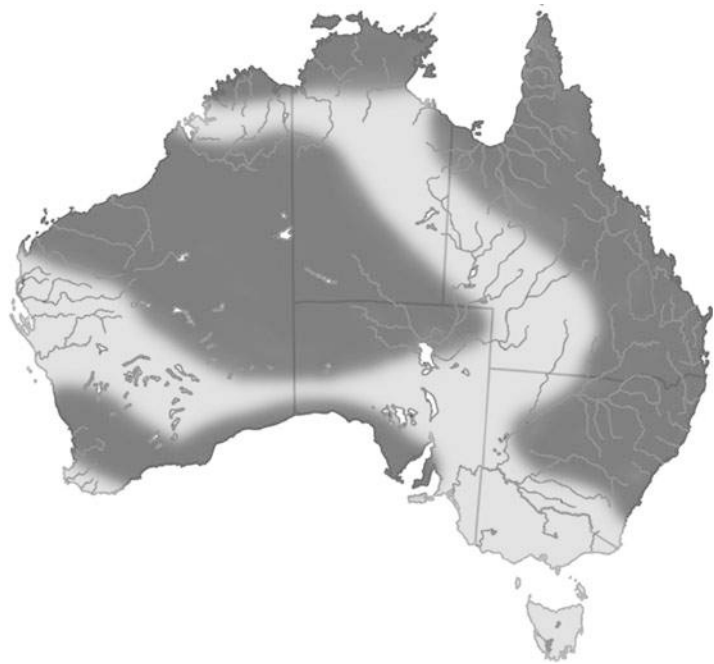
The general effects of systemic envenoming are easily confused with the effects of anxiety, itself a likely response to suspected snakebite [1, 4, 11]. When venom has been absorbed and traverses the lymphatics, draining lymph nodes may become enlarged or tender. The patient may

develop a severe headache, nausea, persistent vomiting, abdominal pain, dizziness, blurred vision, and nonspecific (i.e., nonneurotoxic) weakness [1, 4, 11]. Early collapse is common, usually associated with spontaneous recovery after only a few minutes [1, 4, 11]. Particularly in children, generalized convulsions may occur [1, 4].

Fig. 28 Red-bellied black snake, *Pseudechis porphyriacus* (Copyright © Dr. Julian White)



Fig. 29 Distribution of Australian death adders, *Acanthophis* spp. (Copyright © Dr. Julian White)



Specific Systemic Effects

Australian snakebite is strongly associated with potentially lethal-specific systemic effects (Table 7).

Neurotoxic Paralysis

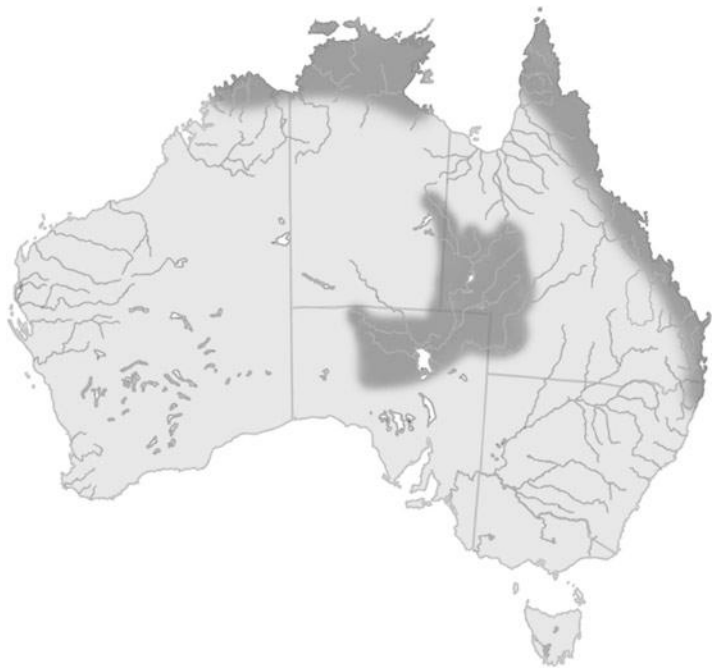
Progressive flaccid paralysis, ending after 18–30 h in complete respiratory paralysis and death due to respiratory failure, previously was the classic cause of snakebite death [11]. With modern

intensive care unit facilities, such respiratory deaths should now be rare. The first signs of flaccid paralysis are seen in the cranial nerves, at least 1 h (sometimes many hours) postbite [1, 4, 11]. Ptosis usually is seen first (Fig. 37), followed by partial ophthalmoplegia (diplopia) (Fig. 38), then complete ophthalmoplegia with fixed forward gaze, often with fixed dilated pupils. Ophthalmoplegia is accompanied by dysarthria, dysphagia, tongue weakness, slack facies, and drooling. Loss of airway protection at this stage

Fig. 30 Common death adder, *Acanthophis antarcticus* (Copyright © Dr. Julian White)



Fig. 31 Distribution of Australian taipans, *Oxyuranus* spp. (Copyright © Dr. Julian White)



may force early intubation. Untreated, the paralysis may extend to encompass limb weakness to complete paralysis, with loss of deep tendon reflexes. Paralysis of respiratory muscles, particularly the diaphragm, may take 18–30 h postbite to develop (Fig. 39).

Myolysis

Myolysis takes 1 or more hours postbite to become evident, as development of muscle pain, tenderness, and nonspecific weakness, usually

with some degree of myoglobinuria (Fig. 40) and always with a major rise in plasma creatine phosphokinase (CP) [1, 4, 11]. Occasionally, myolysis becomes evident only 1–2 days postbite. Major myolysis is sometimes associated with secondary renal failure and severe hyperkalemia, with concomitant, potentially lethal cardiac problems, but severe myolysis and myoglobinuria can occur without evidence of renal damage.

An intriguing single case of apparently localized myolysis in the bitten limb of a previously

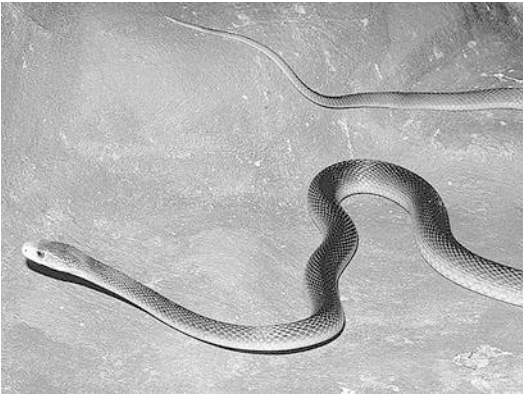


Fig. 32 Common taipan, *Oxyuranus scutellatus* (Copy-right © Dr. Julian White)

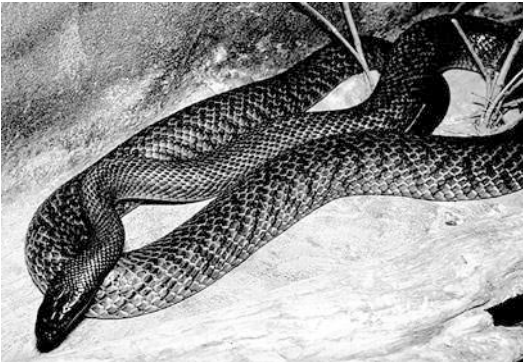


Fig. 33 Inland taipan, *Oxyuranus microlepidotus* (Copy-right © Dr. Julian White)

bitten keeper of death adders (*Acanthophis* spp.), reaching a peak CK of about 4,900IU/l, has been reported [24]. No systemic effects developed, other than the rise in CK and there was marked pain and swelling of the bitten limb. IgG antibodies to death adder venom had been detected after a previous bite (not treated with antivenom), and no circulating venom was detected on this subsequent bite. It is unclear if circulating antibodies against the venom prevented systemic envenoming in this case, but clearly did not prevent significant local envenoming.

Coagulopathy

Coagulopathy, even complete defibrination, although usually found in association with

Table 3 Summary of principal venom activities for each group of snakes^a

Snake group	Venom activity
Colubridae	
Brown tree snake	Partially characterized; no neurotoxic, myotoxic, or procoagulant activity in mammals reported
Elapidae	
Brown snake group (<i>Pseudonaja</i> spp.)	Procoagulants, pre- and postsynaptic neurotoxins, possible nephrotoxin
Tiger snake group (<i>Notechis scutatus</i> , <i>Tropidechis carinatus</i>)	Procoagulants, pre- and postsynaptic neurotoxins, myotoxins
Copperhead subgroup (<i>Austrelaps</i> spp.)	Pre- and postsynaptic neurotoxins, anticoagulants, myotoxins (uncertain clinical significance)
Broad headed snake subgroup (<i>Hoplocephalus</i> spp., <i>Paroplocephalus atriceps</i>)	Procoagulants
Black snake group (<i>Pseudechis</i> spp.)	Anticoagulants, myotoxins, neurotoxins (Papuan black snake)
Death adder group (<i>Acanthophis</i> spp.)	Pre- and postsynaptic neurotoxins
Taipan group (<i>Oxyuranus</i> spp.)	Procoagulants, pre- and postsynaptic neurotoxins, myotoxins
New Guinea small-eyed snake (<i>Micropechis ikaheka</i>)	Anticoagulant, myotoxin, postsynaptic neurotoxin
Sea snakes	Postsynaptic neurotoxins, myotoxins

^aNot all species in each group display all activities listed for that group

obvious general symptoms, such as headache and vomiting, may develop silently, particularly in adults, becoming apparent only when clotting tests are performed or when major bleeding manifests unexpectedly [1, 4, 11]. Some authors have labeled this venom-induced consumptive coagulopathy [8, 15, 18]. The classic sign of coagulopathy is a persistent oozing of blood not only from the bite site but also from venipuncture and intravenous insertion sites and from any recent wound (Fig. 41). Gingival bleeding can occur, notably in patients with poor oral hygiene.

Table 4 Average venom yields for selected major snake groups^a [10]

Snake group	Average venom yield (mg)
Colubridae	
Brown tree snake	1–10
Elapidae	
Brown snake group	2– > 20
Tiger snake group	5– > 50
Black snake group	30– > 180
Death adder group	80
Taipan group	>120
New Guinea small-eyed snake	Not well characterized
Sea snakes	2– > 30

^aAverages vary among species within group; average milked venom in dry weight

Table 5 Estimated average rate of medically significant Envenoming for Medically Important Snake Groups^a

Snake group	Average rate of envenoming (%)
Colubridae	
Brown tree snake	Infants, <20; all others, <1
Elapidae	
Brown snake group	<20
Tiger snake group	>50
Black snake group	>50
Death adder group	>60
Taipan group	>80
New Guinea small-eyed snake	Not well characterized
Sea snakes	<20

^aFigures are only approximate and may vary among species in group

Intracranial bleeds or bleeds into major organs manifest as with any other cause of such bleeding. The clinician should beware of injudicious venous or arterial line insertions if coagulopathy possibly could be present and should avoid insertion or sampling from the subclavian, femoral, or jugular vessels (Fig. 42) [4]. Extended coagulation tests, repeated frequently, are the most useful determinant of coagulopathy [1, 4, 19]. The abnormalities detected depend not only on the severity of the envenoming but also on the type of snake and its venom constituents. Thrombocytopenia is not common and usually occurs either as an isolated

Table 6 Local effects at bite site for Medically Important Snake Groups

Snake group	Local effect of bite
Colubridae	
Brown tree snake	Mild-to-moderate swelling, ± blistering, without necrosis
Elapidae	
Brown snake group	Nil or minimal local pain, swelling, or erythema. Even severe bites may be virtually invisible and the patient unaware of bite
Tiger snake group	Tiger snakes and rough-scaled snakes generally cause painful bites with local erythema, ecchymosis, and swelling. Copperhead bites are less locally severe. Broad-headed snakes usually cause few local effects
Black snake group	Locally painful, usually with moderate-to-marked local, occasionally regional swelling. Papuan black snake causes less marked local swelling
Death adder group	Locally painful, but usually little local swelling or other visible effects, though at least 1 case reported with significant local swelling, pain and local myolysis despite absence of systemic envenoming [24]
Taipan group	Variable from minimal local effects to local pain, swelling, erythema, and slight ecchymosis
New Guinea small-eyed snake	Not well characterized
Sea snakes	Minimal local reaction

finding, or in patients developing a microangiopathic hemolytic anemia (triad of thrombocytopenis, intravascular hemolysis with anemia, and secondary renal failure), but secondary disseminated intravascular coagulation may occasionally occur [1, 4, 5, 11, 13–18].

Renal Damage

Renal damage usually is symptomatically silent. It is first announced by either a rising blood creatinine or by a falling urine output.

Other

Cardiac abnormalities are not common with Australian snakebite and when present are always



Fig. 34 Minimal local reaction at the bite site, as seen with brown snake bites. Minimal local effects can be associated with life-threatening systemic envenoming (Copyright © Dr. Julian White)



Fig. 35 Local erythema and bruising at the bite site, typical of tiger snake bites (Copyright © Dr. Julian White)

Fig. 36 Extensive local swelling, typical of mulga snake bites (Copyright © Dr. Julian White)



secondary, either to coagulopathy (early temporary thrombosis) or to myolysis (hyperkalemia). Although hypotension may occur, systemic envenoming usually is associated with hypertension. However, particularly for bites by brown snakes (*Pseudonaja* spp.), early collapse and cardiac arrest can occur and may be the commonest cause of snakebite fatality in Australia [4]. The etiology of this cardiac collapse remains uncertain. If adequate cardiopulmonary resuscitation (CPR) is provided, patients generally then respond and recover. An absolute lymphopenia is a common, although not universal, accompaniment of major systemic envenoming [25].

Diagnosis of Envenoming

The diagnosis of envenoming may be simple or difficult. The latter applies in children, who may not be able to give a history of a bite, and in adults, who may be bitten unawares, presenting later with general symptoms that could imply a wide array of diagnoses. The often trivial sometimes invisible bite marks may make correct diagnosis difficult, unless a high index of suspicion is maintained for snakebite.

History

The crucial points in history are the following:

Geographic location where a bite might have occurred

Table 7 Principal systemic effects for Medically Important Snake Groups

Snake group	Systemic effect
Colubridae	
<i>Boiga irregularis</i>	In infants only (Guam cases), mild flaccid paralysis (ptosis, lethargy, impaired standing/walking), rarely respiratory distress
Elapidae	
Brown Snake Group	
<i>Pseudonaja spp.</i>	Defibrination coagulopathy, \pm renal damage, only rarely paralysis, never myolysis
Tiger Snake Group	
<i>Notechis spp.</i>	Defibrination coagulopathy (resolves untreated after 15–18 h), pre- and postsynaptic flaccid paralysis (severe), severe myolysis, \pm renal damage
<i>Tropidechis carinatus</i>	As for <i>Notechis</i> spp.
<i>Austrelaps spp.</i>	Poorly defined; flaccid paralysis dominant feature
<i>Hoplocephalus spp.</i>	Defibrination coagulopathy only
<i>Paroplocephalus atriceps</i>	Defibrination coagulopathy only
<i>Rhinoplocephalus nigrescens</i>	Myolysis only, \pm secondary renal damage
Black Snake Group	
<i>Pseudechis australis</i> , <i>Pseudechis butleri</i> , <i>Pseudechis colletti</i>	Anticoagulant coagulopathy, severe myolysis, rarely mild flaccid paralysis (ptosis only)
<i>Pseudechis papuanus</i>	Coagulopathy, thrombocytopenia, flaccid paralysis
<i>Pseudechis guttatus</i> , <i>Pseudechis porphyriacus</i>	Anticoagulant coagulopathy (not all cases), mild-to-moderate myolysis (rarely severe). Recurrent severe vomiting is particularly prominent with significant systemic envenoming by these snakes
Death Adder Group	
<i>Acanthophis spp.</i>	Predominantly postsynaptic flaccid paralysis only, but some presynaptic paralysis may

(continued)

Table 7 (continued)

Snake group	Systemic effect
	occur in a minority of cases. In New Guinea, mild anticoagulant coagulopathy may occur. Though apparently localized to the bitten limb, systemic rise in CK (to $\sim 4,900$ IU/l) detected in a single reported case, without other evidence of systemic envenoming [24]
Taipan Group	
<i>Oxyuranus spp.</i>	Defibrination coagulopathy, hemorrhage, pre- and postsynaptic flaccid paralysis (rapid, severe), occasionally moderate myolysis, \pm renal damage
Miscellaneous	
<i>Micropechis ikaheka</i>	Poorly defined due to paucity of reported cases, but expect anticoagulant coagulopathy, bleeding, flaccid paralysis, possibly myolysis, \pm secondary renal damage
Sea Snakes	
	Varies with species, but flaccid postsynaptic paralysis and/or myolysis, \pm secondary renal damage

Circumstances surrounding definite or suspected bite

Number of bites

Activity before applying first aid

Type and effectiveness of first aid

Timing of onset and nature of any symptoms that might reflect envenoming

Past medical history, including any past exposure to antivenom

Medications, particularly those affecting blood clotting

Examination

The crucial points in examination are the following:



Fig. 37 Early ptosis, the first sign of developing paralysis (tiger snake bite) (Copyright © Dr. Julian White)



Fig. 38 Partial ophthalmoplegia with divergent squint and diplopia. Ptosis is also present (death adder bite) (Copyright © Dr. Julian White)

Fig. 39 Complete flaccid paralysis, requiring prolonged mechanical respiratory support (on ventilator for 5 weeks; taipan bite) (Copyright © Dr. Julian White)



Local bite site – presence of bite marks (especially multiple bites), persistent bleeding, edema, and bruising

Tender or swollen draining lymph nodes

Presence of signs of paralysis, myolysis, or coagulopathy

Laboratory Tests

The crucial laboratory tests are the following:

Snake venom detection (Australia and New Guinea only)

Extended coagulation studies (prothrombin time or international normalized ratio [PT/INR]), activated partial thromboplastin time [aPTT], fibrinogen level, and fibrin degradation products/D dimer (FDP/XDP) [1, 4, 26]. Note that point of care INR testing may give erroneous results with snakebite coagulopathy, potentially indicating a normal INR and therefore absence of coagulopathy in a patient with severe defibrination coagulopathy [4, 27, 28].

Complete blood count (platelet count, absolute lymphocyte count)

Electrolytes and renal function

CK

In a country hospital without ready access to a laboratory, a reasonable assessment can be made with the following tests:



Fig. 40 Red urine indicative of myoglobinuria (mulga snake bite) (Copyright © Dr. Julian White)



Fig. 41 Persistent blood ooze from venous line site, indicating coagulopathy (inland taipan bite) (Copyright © Dr. Julian White)

Snake venom detection

Whole-blood clotting time (preferably 20 min whole-blood clotting test, using a glass vessel)

Dip-stick urine analysis



Fig. 42 Extensive hematoma extending from failed jugular line insertion in the neck, in a patient with severe coagulopathy (taipan bite) (Copyright © Dr. Julian White)

If initial tests are normal, they must be repeated to eliminate delayed envenoming. As a general rule, tests should be done on presentation prior to removing and first aid (except for arterial tourniquets which require urgent removal in most cases) and if normal and the patient is asymptomatic and shows no physical evidence of envenoming (e.g. no neurotoxic signs), then remove first aid and retest 1 h later and if normal and no clinical evidence of envenoming, again at about 6 and 12 h postbite [4, 26] (Grade II-2 recommendation). If tests are abnormal, a different test regimen is required (see later in treatment section).

Interpreting Laboratory Tests

Laboratory tests can be crucial in determining if systemic envenoming is present or if snakebite is likely, and it may assist in determining the type of snake.

Snake Venom Detection Interpretation of snake venom detection tests is discussed subsequently.

Coagulation Tests Significantly prolonged PT/INR (INR 2 to >12) and activated partial thromboplastin time (aPTT) plus decreased fibrinogen (often undetectable) and increased FDP/D-dimer (often grossly increased) usually with normal platelet count indicate defibrination coagulopathy (brown snakes, tiger snakes,

rough-scaled snakes, broad-headed snakes, taipans) [1, 4].

Significantly prolonged PT/INR (INR 2 to >12) and/or prolonged activated partial thromboplastin time; and normal fibrinogen, FDP/D-dimer, and platelets indicates anticoagulant coagulopathy (mulga snake, Collett's snake, Papuan black snake) [1, 4].

If a laboratory able to perform coagulation tests is not available, such as in a small country hospital, then a potential alternative is the 20-min whole blood clotting tests (20WBCT) [4, 29]. This simple test requires a clean glass vessel in which is placed about 2–3 ml of the patient's venous blood. This is gently inverted once, then left to stand for 20 min, after which it is again gently inverted looking for a clot. If the blood remains fluid, without a clot, the test is positive, indicating a coagulopathy may be present. It is always advisable to perform a control at the same time with an identical second container and blood from a presumed normal person (relative or staff member). The 20WBCT is the standard for detecting snakebite coagulopathy in many high risk regions of the world and has been considered reliable [29], despite a recent study questioning reliability (this study was not using Australian snakebite cases) [30].

Absolute Lymphocyte Count Absolute lymphopenia is a feature of significant systemic envenoming by potentially all Australian dangerous snakes, but particularly tiger snakes. It is seen usually in the first 12 h after onset of envenoming [25].

Electrolytes and Renal Function Rising serum creatinine and urea indicate developing renal damage.

Hyperkalemia usually indicates severe myolysis, mostly in association with secondary renal failure [4].

Creatine Phosphokinase CPK elevation may indicate myolysis; values greater than 5,000 U/L almost always are due to myolysis in a snakebite patient. Values greater than one million U/L may occur. Peak myolysis may not be seen for 72 h, occasionally longer [4].

Venom Detection

The bioCSL Ltd. (now Seqirus) Snake Venom Detection Kit (SVDK) is an enzyme-linked sandwich immunosorbent assay-based test, unique to Australia and New Guinea, capable of detecting nanogram-quantities of major snake venoms in samples from the bite site or urine (blood is not as reliable) [4, 5, 31]. The SVDK contains five separate wells, each one corresponding to a snake venom immunotype, corresponding to the five types of monospecific antivenoms. The best sample is a swab from the bite site, first moistened with the SVDK fluid, but in the presence of systemic envenoming, urine also may be used [4]. A positive result indicates that snake venom is probably present in the sample and indicates the most likely type of snake venom immunotype, but it is not an indication to use antivenom; it merely indicates which is the most appropriate antivenom, should this be required on clinical or laboratory grounds [4]. A negative result indicates only the test was negative; it does not exclude snakebite [4]. Thus, the purpose of the kit is to choose the most appropriate monospecific antivenom to use in an envenomed patient. It is not a screening test for snakebite. The SVDK is not readily available in New Guinea.

Diagnostic Algorithms

Diagnostic algorithms have been developed for Australia to assist in determining the most likely snake in cases with significant systemic envenoming (Figs. 43 and 44) [4]. These algorithms are useful when venom detection has failed or is not available, or when the result is suspect, but more commonly and importantly they help support the SVDK result. If the algorithm and the SVDK give a similar result, then the type of snake can be confidently assumed, but if they give disparate results expert advice should be sought via bioCSL Ltd. (now Seqirus) [4]. Similar to all such diagnostic algorithms, these cannot cater to all eventualities and should be used with wisdom and caution.

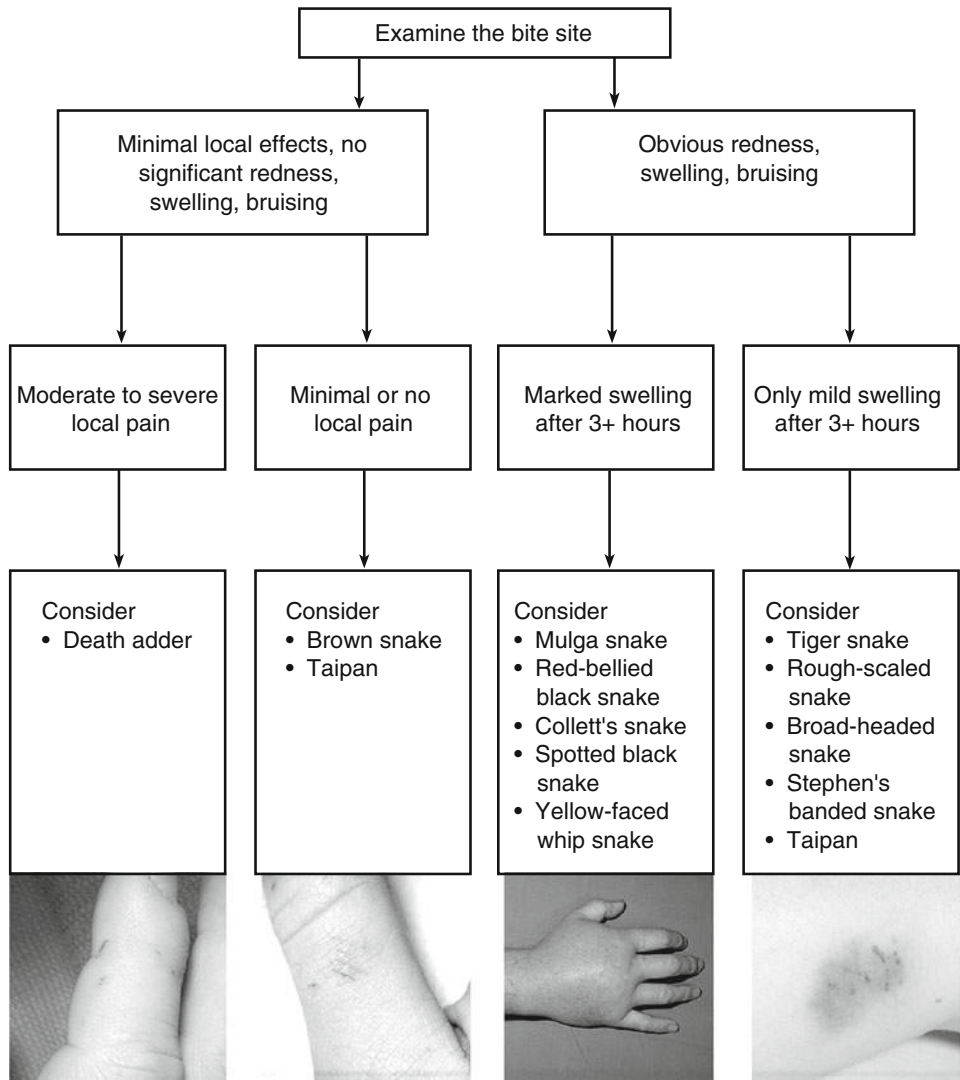


Fig. 43 Diagnostic algorithm for Australian snakebite, based on local effects (Copyright © Dr. Julian White)

Differential Diagnosis

Snakebite should be considered in the differential diagnosis of any unexplained flaccid paralysis, myolysis, coagulopathy, unexpected major hemorrhage, renal failure, cardiac collapse, general collapse, or convulsions, where snakebite is a possibility, even if there is no history of exposure to a snake [1, 4]. Snakebite is not limited to rural areas or outside buildings; dangerous snakes regularly enter gardens and homes in even the largest Australian cities.

Treatment of Envenoming

Indications for ICU Admission in Australian and Pacific Snake Envenoming
Every case of significant systemic envenoming with any of the following:

Any degree of flaccid paralysis beyond simple ptosis

(continued)

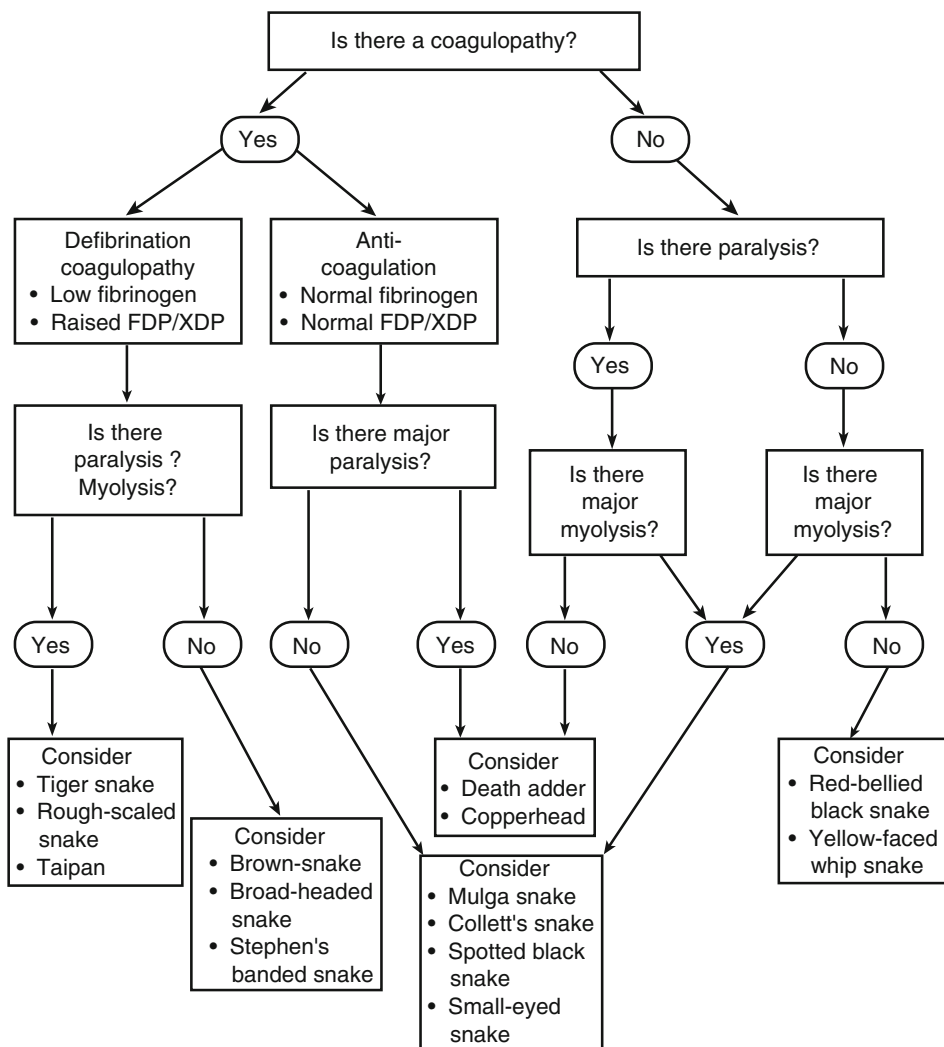


Fig. 44 Diagnostic algorithm for Australian snakebite based on systemic effects. FDP/XDP, fibrin degradation product/D dimer (Copyright © Dr. Julian White)

Any established defibrination or anticoagulant coagulopathy

Any major secondary problems, such as major bleeding or anuric renal failure

The following cases are best managed in an emergency department short stay ward, or high-dependency unit setting or, if unavailable, in an intensive care unit:

Any case of suspected snakebite, even if initially no evidence of systemic envenoming

Although most snakebites in Australia are likely to prove minor, this cannot be reliably predicted within the first few hours. All cases of definite or suspected snakebite should be considered potentially major and lethal until clearly shown to be otherwise [1, 4].

First-Aid Considerations

First aid for snakebite in Australia and New Guinea is the pressure bandage and immobilization method (PBI), designed to retard venom

movement via the lymphatics [4, 20] (Grade II-2, 3 recommendation). It has been shown to be effective in a monkey model and anecdotally in human cases of envenoming, although the method remains unproven by clinical trial [4, 5, 11, 20]. Nevertheless, the pressure bandage immobilization method appears comparatively safe and effective compared with the alternatives used in most other parts of the world. The technique involves the application of a broad bandage over the bitten area, at about the same pressure as used for a sprain. The bandage is extended to cover as much of the limb as possible, then the limb is immobilized using a splint. Correctly applied, this first aid can be left on for several hours, until the patient is in a hospital and can be treated with appropriate antivenom, if required. Recent research has suggested that an elastic bandage is more likely to provide effective pressure than the crepe bandage originally used in development of the technique [32]. Because of venom detection, the bite would should not be cleaned or moistened. A modified method using just a local pressure pad has been tested and recommended in Myanmar, but not tested or recommended in Australia; therefore, the reliability of this method remains uncertain for Australian snakebite [33]. A further additional technique using pharmacological methods, applied topically, to slow lymphatic flow, has been tested experimentally with success, but remains unproven clinically [34].

However, given that most snakebite fatalities in Australia are now due to prehospital cardiac collapse and arrest, with inadequate CPR, it could be argued that the most critical first aid for snakebite is CPR (where indicated), the application of PBI.

When the patient is already in the hospital, the issues with first aid are when to apply it in the hospital and, more commonly, when to remove it. First aid should be applied in a hospital only if the following apply (Grade III recommendation) [4]:

1. It is less than 15 min postbite.
2. There are no facilities to give antivenom, and the patient will be transferred elsewhere.
3. The patient already has severe, life-threatening envenoming.

First aid should be removed in the hospital only when the following have been done:

1. An intravenous line has been inserted, with an initial intravenous fluid load.
2. The bandage over the bite site has been cut away, the wound has been inspected, and the wound has been moist-swabbed (swab stick moistened with diluent) for venom detection.
3. Blood has been taken for relevant tests (coagulation, complete blood count, electrolytes, renal function, CPK).
4. A relevant history has been obtained.
5. The patient has been examined for signs of envenoming.
6. The results of venom detection and blood tests have been received and evaluated.
7. An expert in envenoming has been consulted (if appropriate).
8. Initial antivenom therapy has been started, if required (it is not required in most cases).

The first aid should not be left on when the above-listed requirements are fulfilled. Prolonged use of first aid may cause local skin injury (notably with tiger snake bites).

Basic Treatment

As noted earlier, after vital functions are secured (rarely an issue), initial management is based on obtaining intravenous access; ensuring adequate hydration; establishing a firm diagnosis, including assessment of the extent of any envenoming; and starting specific treatment if required [4] (Grade III recommendation). Because most cases of snakebite in Australia do not result in significant envenoming, initial tests are likely to be normal. Because delayed envenoming can occur, it is essential both that repeat tests be performed (as noted earlier) and that vital signs be assessed frequently, including checks for early paralysis, coagulopathy, and myolysis [4] (Grade III recommendation). Renal output should be monitored; if the output is in question, the patient should be catheterized, but otherwise avoid catheterization, especially if there may be coagulopathy.

Snakebite in New Guinea is different because a higher proportion of cases show significant envenoming, correct first aid is less likely to have been used, laboratory testing and antivenom may be unavailable except in a few major centers, and patients frequently present many hours postbite with major problems already evident.

Antivenom

The key decision in managing snakebite is if and when to give antivenom, then which type and how much. All cases with significant envenoming should be considered for antivenom therapy [1, 4, 5, 19] (Grade III recommendation). It is required in nearly all such cases, often proving lifesaving.

When to Use Antivenom

Antivenom should be used only in the presence of significant systemic envenoming, which may be defined as the presence of one or more of the following [1, 4, 19]:

- Flaccid paralysis (even just ptosis, unless this is the only sign and has been present >12 h)
- Myolysis (usually a CK >1,500 U/L or a rapidly increasing CK early after envenoming)
- Coagulopathy (usually any degree of defibrination, such as an INR >2, or any degree of true anticoagulation)
- Renal damage (an elevated and rising creatinine, even if still normal urine output)
- A clear history of collapse or convulsions after a witnessed snakebite by a dangerous species of snake (e.g., not a python bite).

General symptoms, such as headache, nausea, vomiting, and abdominal pain, although raising suspicions of significant envenoming, also may be due to anxiety and are not alone an indication that antivenom is required [1, 4]. Certain snakes, notably some or all *Pseudechis* spp. (mulga snakes, black snakes), can cause severe intractable vomiting that may be unresponsive to antiemetics, but responsive to antivenom [4]. A positive SVDK result from either the bite site or urine in

isolation is not an indication that antivenom is required (Grade III recommendation) [4]. Antivenom should be given as soon as safely possible when there is an indication that it is required [4].

Choosing the Right Antivenom

In contrast to some other regions, the choice of snake antivenom, although limited to one producer (bioCSL Ltd, Melbourne; now Seqirus), encompasses a variety of “monospecific” antivenoms, in addition to a polyvalent antivenom [4]. The latter covers all species but is the highest volume (increased risk of adverse reactions) and the highest cost and generally is used only if the type of snake is unknown and it is not practical to cover all possible species by mixing two monospecific antivenoms [4]. The available antivenoms and the species they cover are listed in Table 8. Because envenoming by some species may require the equivalent of multiple ampules of antivenom as an initial dose, the disadvantages of routinely using polyvalent antivenom are apparent. The dose of antivenom used in Australia has reduced substantially in recent years, and the high doses previously recommended [1] are no longer used [4], but there is ongoing controversy over how low the dose should be [4], with one group recommending a single vial is always sufficient, in every case [35], though even this group is now reporting cases which challenge the “one vial” recommendation [36]. Others, including the antivenom producer, consider such a restrictive minimal dose policy unwise and recommend slightly higher dose for certain antivenoms [4]. The reasoning for this is that it is best to cover for more severe outlier cases in selecting initial doses as it is these patients who are at highest risk and antivenom is most likely to be effective when given early. It is also known that some subspecies or races of particular snakes (notably some types of black tiger snake) require significantly increased doses of antivenom to cover their higher venom yield [1, 4].

Identifying which type of snake is responsible for the bite is the principal function of the SVDK [4]. This identification may be supported by the use of diagnostic algorithms, as discussed earlier [4]. Because color is variable and an unreliable

Table 8 Recommended doses of antivenom for patients with significant envenoming, based on type of snake^a

Snake	Starting dose of antivenom ^b
Colubridae	
<i>Boiga irregularis</i>	No AV available
Elapidae	
Brown Snake Group	
<i>Pseudonaja spp.</i>	1–2 vials CSL Brown Snake AV
Tiger Snake Group	
<i>Notechis scutatus</i> and most <i>Notechis ater</i> subspecies	1–2 vials CSL Tiger Snake AV
<i>Notechis ater serventyi</i> , <i>Notechis ater humphreysi</i>	2–4 vials CSL Tiger Snake AV
<i>Tropidechis carinatus</i>	1–2 vials CSL Tiger Snake AV
<i>Austrelaps spp.</i>	1 vial CSL Tiger Snake AV
<i>Hoplocephalus spp.</i>	1 vial CSL Tiger Snake AV
<i>Rhinoplocephalus nigrescens</i>	1 vial CSL Tiger Snake AV
Black Snake Group	
<i>Pseudechis australis</i> , <i>Pseudechis butleri</i> , <i>colletti</i>	1 vial CSL Black Snake AV
<i>Pseudechis guttatus</i> , <i>Pseudechis porphyriacus</i>	1–2 vials CSL Tiger Snake AV OR 1 vial of CSL Black Snake AV
Death Adder Group	
<i>Acanthophis spp.</i>	1 vial CSL Death Adder AV
Taipan Group	
<i>Oxyuranus spp.</i>	1 vial CSL Taipan or Polyvalent AV
Miscellaneous	
<i>Micropechis ikaheka</i>	1+ vials CSL Polyvalent Snake AV
Sea Snakes	
	1–3 vials CSL Sea Snake AV, or if unavailable, 3+ vials CSL Tiger Snake AV or CSL Polyvalent Snake AV

^aAll listed antivenoms (AV) are produced by bioCSL Ltd, Melbourne, Australia

^bFor all snakes, if insufficient specific AV is available, consider using bioCSL Polyvalent Snake Antivenom at the same dose (i.e., same number of vials) as for the specific antivenom. Dose given is initial dose only. Severe cases may require higher initial doses and possibly may require further doses after the initial dose, though repeat dosing is now uncommon to rare

indicator of species, the patient's identification of the snake, if offered, should be used only with great caution [4, 19]. An exception is a herpetologist bitten by a captive snake or a wild specimen during the course of capture; however, not all herpetologists are as reliable at identifying snakes as their confidence might suggest.

In New Guinea, assuming that antivenom is even available, the range of antivenoms is often limited to Death Adder and Polyvalent [37]. A new antitaipan antivenom is undergoing clinical trial and if successful may be approved [38–40]. Because death adders are distinctive snakes, a patient's confident assertion that the assailant was a death adder is usually correct. In all other circumstances, polyvalent antivenom should be used. In Indonesian New Guinea (Irian Jaya) and a few islands to the east, where death adders occur, Seqirus (bioCSL) antivenoms may be unavailable. Instead, local Indonesian antivenoms may be present. These are essentially useless for the snakes discussed in this chapter and should not be used, unless it is certain that the bite was from an Indonesian cobra (not likely in Irian Jaya, unless a captive specimen).

In Pacific islands with terrestrial snakes, envenoming does not warrant antivenom, or none is available (e.g., brown tree snake bite to an infant in Guam). For all areas where sea snakes are present, the optimal choice of antivenom is Seqirus (bioCSL) Sea Snake [4]. If it is unavailable, Seqirus (bioCSL) Tiger Snake or Polyvalent should be tried, at a ratio of 3 ampules for each ampule of Sea Snake antivenom that would have been indicated [4]. However, earlier research indicating these antivenoms may be effective against sea snake envenoming is no longer valid because of changes in the method of producing these antivenoms [4]. Currently it is unclear how effective, if at all, these antivenoms may be against sea snake envenoming, reinforcing the preferential use of specific Seqirus (bioCSL) Sea Snake AV [4].

Correct Dose

The initial dose of antivenom depends on the type of snake and the degree of envenoming. Although there are no absolutes in determining dose,

suggested guidelines are given in Table 8. Giving too low an initial dose is a common reason for failure of antivenom therapy [4, 19]. In New Guinea, where antivenom is in restricted supply, optimal doses may not be achievable. Often a single dose of one ampoule is all that is possible, though this does appear to be generally effective. Children require the same dose as adults [4].

How to Give Antivenom

Antivenom for snakebite should always be given intravenously, preferably diluted 1:10 in saline, Hartman's, or a similar solution (Grade III recommendation) [4, 19, 35]. The degree of dilution achievable is determined by the volume of antivenom and the size of the patient. Significant dilutions may be difficult to achieve with pediatric patients, with elderly patients with preexisting cardiac problems, or with high-volume antivenoms such as Polyvalent. The infusion should be started slowly, aiming to give the whole dose (even multiple ampoules) over 15–20 min (Grade III recommendation) [4, 35]. The clinician should always have epinephrine (adrenaline) ready to give, in case an anaphylactic/anaphylactoid reaction occurs. If available, a prepared epinephrine infusion may be suitable, with an infusion pump [4, 19].

When to Give More Antivenom

The initial dose may not be enough, but determining when and how much more antivenom to give is not always straightforward and repeat dosing is now uncommon to a rare event [4, 35]. For defibrination coagulopathy, enough antivenom has been given when fibrinogen levels start to rise, indicated by either an increase in the absolute value or by a decrease in the PT/INR [4]. However, this may take at least 6 h post antivenom, sometimes longer. Giving further antivenom prior to this is generally not justified [4]. It is not necessary to wait for return to normal values. In general, coagulation tests should be repeated at 1 h and 3 h and 6 h after completion of the initial dose of antivenom [4]. The first and second tests are to indicate trends, and the third test is to decide if further antivenom is needed. If the 6-h test

shows no change from complete defibrination, expert consultation should be sought to help guide whether further antivenom should be given in a dose similar to or slightly less than the initial dose (Grade III recommendation) [4]. Some authors consider that antivenom may be ineffective at reversing defibrination coagulopathy with Australian elapid snakebite and advocate that no antivenom should be given after the initial dose [35, 41–46]. While this view is not accepted by all experts in clinical toxinology, it is accepted that the high doses of antivenom previously used to treat defibrination coagulopathy are no longer appropriate and that repeat dosing should be the exception, not the rule [4]. Even if there is no change in laboratory clotting parameters 6 h post antivenom, if the patient is no longer showing evidence of active coagulopathy (failure to clot at venipuncture sites, continued oozing from all bleeding points such as gums, IV sites), then it is advisable to hold off on giving more antivenom and repeat coagulation testing again 1–3 h later (Grade III recommendation) [4]. Fresh frozen plasma or cryoprecipitate should not be given while there is active coagulopathy except if an uncontrolled and catastrophic hemorrhage is occurring [1, 4, 19]. The use of FFP after giving antivenom has been studied, and if given within 6 h of the bite it may make the coagulopathy worse, while if given more than 6 h post bite, it is not associated with improved patient outcomes, even though coagulation tests may return towards normal more rapidly [35, 47].

For myolysis, laboratory tests are less helpful in guiding further therapy. If there is a persistent significant increase in CPK after initial antivenom therapy, then giving further antivenom at a similar dose may be considered. However, evidence is equivocal about effectiveness of delayed antivenom in managing myolysis. One study indicated that for bites by high risk species for myolysis (black and mulga snakes, *Pseudechis* spp.), giving antivenom early (within first 6 h post bite) was associated with low incidence of myolysis, while antivenom given after 6 h had no effect on incidence or severity of myolysis [48,

49]. A more recent report indicates that use of early antivenom at a low dose may not protect against myolysis, in contrast to the earlier studies [36]. The author has had case experience indicating that late antivenom is associated with temporal improvement in both symptomatology and laboratory measures of myolysis and therefore generally recommends antivenom be considered in cases with ongoing severe myolysis (Grade III recommendation).

For postsynaptic paralysis, giving further antivenom may be considered if the initial dose fails to cause adequate reversal of signs [1, 4]. For presynaptic paralysis, there is little likelihood that antivenom would reverse established paralysis, so further antivenom therapy is pointless [1, 4].

For renal damage, the role of antivenom is uncertain. Because most renal damage is mediated through secondary effects, further antivenom is unlikely to result in benefit.

Antivenom Therapy Complications

If the patient develops an early reaction of significance, such as hypotension or bronchospasm, the clinician should halt the antivenom infusion, treat the reaction, then cautiously restart the antivenom infusion, if necessary titrating the antivenom rate against the epinephrine rate (if using an IV epinephrine infusion, via a pump), to maintain blood pressure (Grade III recommendation) [1, 4, 5, 19, 35]. After a short while, it may be possible to reduce the epinephrine rate, as any reaction subsides. Antivenom therapy should not be abandoned just because the patient has an adverse reaction.

The major delayed reaction to antivenom is serum sickness [4, 5]. Although unproven by clinical trial, it often is recommended that patients receive a 5–7-day course of prophylactic oral steroids to reduce the incidence of serum sickness [4]. This complication may increase in rate with increased volumes of antivenom [4, 5], though some studies have questioned this [50]; any patient receiving greater than 25 mL of antivenom probably should be considered for a course of prophylactic steroids [4].

Criteria for ICU Discharge in Australian and Pacific Snake Envenoming

Evidence of resolution of significant effects of envenoming (coagulopathy, myolysis, flaccid paralysis, renal failure) to the point that major risk is no longer present.

In cases of suspected snakebite that develop no evidence of systemic envenoming, 12–24 h post bite.

Other Treatments

Even though tetanus rarely occurs after snakebite, it remains a risk and tetanus immune status should be reviewed (Grade III recommendation) [4]. No injection should be given, however, until venom-induced coagulopathy is fully resolved [4]. Routine antibiotic therapy is inappropriate because bite wound infections are uncommon [4]. For patients with mostly postsynaptic paralysis (e.g., most death adder bites), neostigmine may be a useful adjunct to antivenom therapy [4].

Special Populations

Pediatric Patients

Young children, owing to their smaller size, are at greater risk of severe envenoming and so require even greater vigilance. Antivenom dosage is the same as for adults. Intravenous fluid therapy needs to be monitored carefully to prevent overload.

Pregnant Patients

There are few records of snakebite in pregnancy, and it is unclear which, if any, venom components might cross the placenta. Antivenom poses far less risk than envenoming in pregnancy, and there should be no reluctance to start antivenom treatment. Where practical, fetal well-being should be monitored.

Elderly Patients

The elderly are more likely to die as a result of major envenoming because they are at greater risk of secondary problems, such as renal damage and fluid overload.

Other Special Populations

The most important special population is the amateur and professional herpetologist community, whose members are at risk of repeated bites, with potential for severe allergy to antivenom and venom [4]. Venom may cause lethal anaphylaxis within minutes of the bite, long before hospital care can be accessed. Because of the potential to develop major allergies to antivenom, its use in herpetologists should be slightly more conservative than in the general population, but even so, antivenom should never be withheld when clearly indicated.

Common Misconceptions about Australian and Pacific Snake Envenoming

1. All snakebites require antivenom therapy.
2. A positive Snake Venom Detection Kit result indicates antivenom therapy is required.
3. Coagulation factor replacement is required to treat coagulopathy.
4. Antivenom is more dangerous than envenoming.
5. Intensive care unit (ICU) management of airway and respiratory function is sufficient to keep the patient alive, and antivenom is unnecessary.
6. ICU specialists can manage snakebite alone, as with other emergencies.

Key Points in Australian and Pacific Snake Envenomation

1. Most Australian snakebites ultimately prove to be minor, or “dry” bites, not requiring antivenom therapy.

2. Most New Guinea snakebites are major, requiring antivenom therapy.
3. Diagnosis is based on presence of specific systemic effects (as above), determined by examination and appropriate laboratory tests.
4. A positive Snake Venom Detection Kit on either bite site or urine indicates only that venom has been detected and the type of snake that has bitten. The requirement for antivenom is based on clinical and laboratory evidence of significant systemic envenoming.
5. Antivenom is the most important treatment. It should always be given intravenously. Always be prepared to treat an anaphylactic adverse reaction.
6. If there is major presynaptic paralysis with established airway or respiratory compromise, antivenom is unlikely to reverse this, and ICU skills are essential, but the effects of coagulopathy, myolysis, and secondary renal failure are the major causes of snakebite fatalities, and at least for the first two, antivenom is the cornerstone of treatment.
7. Antivenom (correct type in sufficient quantity) effectively abolishes general symptoms, may reverse at least some types of coagulopathy, may reduce myolysis, can reverse predominantly postsynaptic paralysis (e.g., death adders), but cannot reverse established severe presynaptic paralysis.
8. The type of envenoming and the most appropriate antivenom and initial dose requirements are largely determined by the type of snake; identifying the snake using venom detection plus diagnostic algorithms is important.
9. The clinically important effects of snakebite in Australia and New Guinea are systemic, not local: flaccid paralysis, defibrination or anticoagulant coagulopathy, myolysis, and renal damage.

(continued)

10. The extent of envenoming is not reflected in the local bite site reaction, which may be trivial despite life-threatening envenoming.
11. Snakebite is a potentially complicated illness that is seen infrequently in most ICUs. It is always sensible to seek outside expert assistance in managing snakebite, particularly if there is severe envenoming.
12. Coagulopathy of the consumptive variety (defibrination) may be reversible with antivenom therapy or by waiting for all venom to be cleared (the latter option prolongs the risk of lethal hemorrhage); use of coagulation factor replacement therapy (fresh frozen plasma, cryoprecipitate, whole blood) while procoagulant is still circulating merely “adds fuel to the fire,” making matters worse, not better and heparin has not been demonstrated as being beneficial.
13. Antivenom is *not* more dangerous than envenoming. Several people die each year from snakebite envenoming, many more in New Guinea, but deaths from adverse reactions to antivenom are rare and generally occur when no provision has been made to treat anaphylactoid reactions.

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Snakebites are a major public health problem in a number of African, Asian, and Latin American countries, and thousands of deaths are reported every year [1]. By comparison, this risk of venomous snakebite is much lower in Europe, where native species are less dangerous and the number of snakebite cases is low. Recent epidemiologic studies [1, 2] based on a meta-analysis of medical literature showed that with a population of 750 million inhabitants, Europe (including European regions of Turkey and Russia up to the Caucasus and Ural Mountains) records 7500 cases of snakebite per year. Approximately 1000 of these bites are associated with signs of severe envenomation requiring prolonged hospitalization. Fewer than five deaths are recorded every year in the old continent. In spite of these reassuring findings, several recent studies have been carried out in Europe and have allowed development of specific treatments and protocols for management of envenomed victims [3, 4].

European Vipers

Zoology and Distribution

Apart from a few toxicologically less important non-front-fanged *colubrid* species (see special paragraph), all naturally occurring venomous snakes in Europe are so-called vipers (family Viperidae, subfamily Viperinae, mainly genus *Vipera*; but species of the genus *Macrovipera*

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Fig. 1 Distribution map of *V. berus* (Courtesy of, and copyrighted by, Julian White)



and the genus *Montivipera* are also naturally present in continental Greece, Cyclades Archipelago, and European Turkey) [1].

Several species of the *Vipera* genus living in Europe are considered harmless to humans, i.e., the Basque viper (*Vipera seoanei*) and the meadow viper (*Vipera ursinii*) have never been implicated in serious envenomation [5, 6]. Both are small snakes living within a limited area and are not medically significant. Other smaller-sized species like the snub-nosed viper (*Vipera latastei*) in Spain are able to induce moderate envenoming with local symptoms, mild systemic symptoms, and, very rarely, severe or lethal envenoming [7]. Three species are larger snakes that range from 40 to 60 cm in length and can be the origin of envenomations with possible and frequent life-threatening situations, i.e., the adder (*Vipera berus*), the asp viper (*Vipera aspis*), and the long-nosed viper (*Vipera ammodytes*) [3].

Vipera berus is adapted to cold regions and can be found in Scandinavian countries beyond the Arctic polar circle. The common European adder occupies more land area than any other venomous snake. It occurs throughout Europe except for

Ireland, the southern parts of the continent, and the larger Mediterranean islands. Its range extends eastward through Asia to the Pacific Ocean. Northern France and the mountainous regions of central France mark the southernmost extension of the habitat of this species that is common in Sweden and England (Fig. 1).

Vipera aspis, which requires sun and warm temperatures, is mostly found in northern Spain, Switzerland, Italy, and France where it can proliferate in suitable environments. Pattern markings are highly variable, even within the same population (Fig. 2).

The larger *Vipera ammodytes* is widespread in Southeastern Europe, Northern Italy, Austria, and Turkey. All of these snakes are divided into subspecies in certain areas, and variations of clinical toxicities are seen (Figs. 3 and 4).

Circumstances

Bites generally occur outdoors when people incidentally come across the snakes in their natural habitat. Also, careless handling of snakes by

Fig. 2 Adult *V.ammodytes* (Courtesy of, and copyrighted by, Julian White). Distribution map of *V. aspis* (Courtesy of, and copyrighted by Julian White)



Fig. 3 Distribution map of *V. ammodytes* (Courtesy of, and copyrighted by, Julian White)





Fig. 4 Adult *V. ammodytes* (Courtesy of, and copyrighted by, Julian White)

private collectors may result in bites and envenomation. Bites mostly strike the extremities but also may impact the trunk, neck, and head (e.g., during swimming or when lying on the ground). *V. latastei* may stay in trees, which explains the occurrence of bites to the head and trunk in farmers harvesting fruits.

Venom

Composition and Pathophysiology

Although the European vipers differ in appearance and size, they are closely related in terms of venom composition and clinical effects of envenomation [3, 8]. The main components of the venom are proteins with enzymatic and toxic properties, such as hyaluronidase, proteolytic enzymes, peptide hydrolases, phospholipases A₂, and phosphodiesterases. Amino acids, polypeptides, carbohydrates, and metalloproteins are also present in the venoms.

The onset of venom enzyme activity is more or less immediate. Subcutaneous tissues, muscles, capillary endothelium, and basement membranes are damaged, with subsequent extravasation of plasma and erythrocytes, leading to progressive tissue swelling and discoloration of the skin. This process may not peak for 72 h after the bite.

A wide range of systemic effects is initiated through the activity of venom enzymes. Common acute effects, such as hypotension, gastrointestinal upset, angioedema, and bronchospasm, are due to an enzyme-mediated release of potent endogenous substances, such as histamine, bradykinin, prostaglandins, and serotonin. Local and systemic hemolysis and coagulopathies can be induced by venom enzymes.

The venom likely also contains components with more specific toxic properties. This explains the cranial and peripheral nerve disorders observed after bites by several populations of *V. ammodytes*, *V. aspis*, and *V. berus* suggesting neurotoxic components [9–11]. Similarly the early occurrence of hematuria and proteinuria in some populations of *V. berus* envenomation [12] indicates a specific nephrotoxicity. The presence of a cardiotoxic ingredient cannot be ruled out either, with numerous reports of electrocardiogram changes observed after bites by European vipers [12].

Toxicokinetics

Venom normally is injected intracutaneously or subcutaneously. Bites by the larger-fanged species (*V. ammodytes*, *V. aspis*, and *V. berus*) occasionally may result in intramuscular deposition of the venom and, in rare instances, intravenous injection.

Venom has been detected in blood 30 min after the bite and with a peak concentration observed at approximately 2 h [13]. Plasma venom concentrations decline slowly over 1–2 days, but venom has been detected up to 1 week after the bite [12].

Venom spreads rapidly in the local tissues, where its distribution is facilitated through the action of hyaluronidase. The venom is transported further to the systemic circulation through the lymphatic system. This transport is enhanced by simultaneous muscular activity, making immobilization and rest important first-aid measures.

Clinical Presentation

Severity

The severity of envenomation varies. Anything from just fang marks – with no signs of envenomation – to severe systemic reactions and extensive swelling is possible. The larger species in Southern and Southeastern Europe are often claimed to cause more pronounced symptoms, but this is not confirmed convincingly in existing reports.

The great variation in toxic response to bites is related to several factors. The most important is the *dose of injected venom*. Of snakebites, 30–50% are considered to be “dry,” meaning no injection of venom; this has led to the misconception that the venom is not dangerous. The *age and weight* of the patient are also crucial, explaining why small children are especially susceptible. Other important factors for the response are the *location of the bite* (bites on the head and neck could pose higher risk), *previous health state*, and *physical activity* after the bite. There are two reports of cardiovascular collapse following strong physical activity directly after a viper bite [3, 14].

Clinical Features and Gradation

Since the beginning of the 1990s, a European grading scale based on clinical features (Table 1) has been validated for evaluation of viper envenomation [8, 15]. The utility of this scale has been confirmed in several clinical series [4, 14, 16, 17], and it is now used in several European countries [1–3].

Vipers inject venom under pressure with the bite lasting only a few tenths of a second. In some cases there may be only one fang mark. When there are two punctures, the distance between them may be a few millimeters initially but then increase to over 1 cm as swelling develops. In grade 0, pain is moderate and limited to the injection site due to fang puncture. If symptoms do not progress with time, it is safe to assume that no venom was injected (grade 0).

Table 1 Clinical gradation table of envenoming by European vipers

Grade 0 = no envenomation or “dry bite”
Fang marks
No swelling
Grade 1 = minimal envenomation
Local swelling around the site of bite
No systemic symptoms
Grade 2 = moderate envenomation
2a with regional swelling (most of the bitten limb) and/or hematoma, adenopathy
2b = 2a + moderate general clinical effects such as mild hypotension, vomiting, diarrhea, neurotoxic symptoms, and/or biological criteria for severity (thrombocytes < 150G/L, leukocytes > 15G/L, INR > 1.5, fibrinogen < 2 g/L)
Grade 3 = severe envenomation
Extensive swelling spreading to the trunk and/or severe general symptoms (Table 2)

The hallmark of grade 1 envenomation is immediate severe pain, likely due to proteases, biogenic amines, and other venom components. Pain is followed within a few minutes by inflammatory edema and sometimes blistering at the bite site. Most envenomings stabilize at grade 1 and then regress spontaneously within 24–72 h.

Grade 2 envenomations are observed in only 15–20% of viper bite cases in Europe, though the percentage varies from place to place depending on the snake populations. Grade 2 symptoms can develop either rapidly (early grade 2) with the appearance of low blood pressure in the first 30 min after the bite or over a period of 6–16 h (classic grade 2) with extensive swelling and sometimes general symptoms (vomiting, abdominal pain, and malaise). Systemic manifestations such as diarrhea or arterial hypotension not resolved with fluid or colloid resuscitation are unfavorable prognostic signs. For grade 2, laboratory findings may show asymptomatic hemostatic disturbances (Fig. 5).

Grade 3 envenomation is defined as grade 2 effects lasting for several hours with development of extensive swelling of the trunk due to the absence of specific treatment (Fig. 6). Persistent general clinical manifestations are associated with

Fig. 5 The first captured neurotoxic specimen of *Vipera aspis aspis* in Southern France in 1991 (Photography of the Marseilles' Poison Centre)

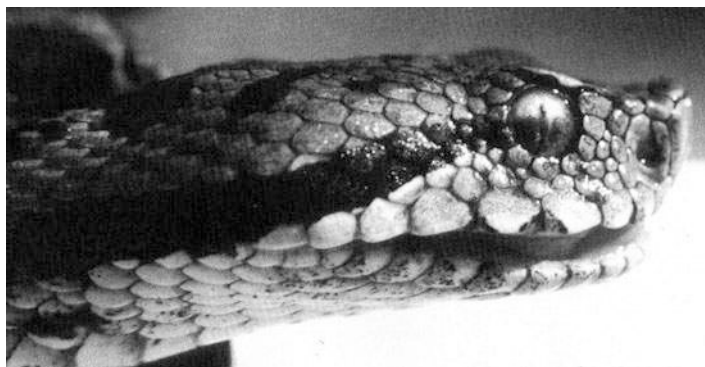


Fig. 6 Typical locoregional aspect of a grade 3 envenomation by *Vipera aspis* in Western France with a giant blistering with blood and swelling plus hematoma of the trunk of a young envenomed girl (Photography of the Angers' Poison Centre)



numerous complications that can lead to multiple organ failure, e.g., renal insufficiency due to tubulopathy or glomerular nephropathy and hypoxia with variable bleeding due to pulmonary lesions related to edema, occasionally with pleural effusion, multiple episodes of digestive or respiratory bleeding, etc. Laboratory tests in grade 3 envenomings often reveal severe abnormalities including thrombocytopenia, hyperleukocytosis, and hypofibrinogenemia, severe water-electrolyte imbalance, or coagulation disturbances.

Serologic studies in viper bite victims confirm a close link between blood concentration of venom and severity of envenomation. The use of ELISA to measure venom blood levels has been shown to predict short-term clinical course [15, 17]. However, this technique is still experimental and is not yet adapted to emergency situations.

Some populations of the three dangerous European vipers have neurotoxins that cause special clinical manifestations characterized by low-grade local or regional effects immediately after venom injection and appearance of general

neurologic signs within 4–12 h [9, 10, 18]. The most frequent effect is ptosis, but other signs have been reported including ophthalmoplegia, diplopia, dysarthria, paralysis of the orbicularis oris, and difficulty in swallowing and focusing. In some cases, more extensive neurological manifestations with drowsiness, vertigo, dyspnea, and diffuse paresthesia have been observed [10, 14, 19]. This unusual envenomation pattern has been described not only in a small area of Southern France [10] and Italy [19–21] with asp vipers but also in Hungary [22, 23] and Bulgaria [24] with adders and in the Balkans with the long-nosed viper.

The grading system used for typical envenomation (Table 1) is also applicable to viper envenoming involving neurotoxins (Table 2) [3, 10]. Neurologic manifestations should be considered as general signs and are associated with grade 2. A recent study described a case of proven Guillain-Barré syndrome after a *Vipera aspis aspis* bite. The asp viper came from the southern French Alps and had no neurotoxins in its venom

Table 2 Indications for antivenom in bites by European vipers

Grade 2 or grade 3 envenomation with extensive swelling. General symptoms as potential evidence of venom diffusion must always be considered as an indication for antivenom infusion:
Circulatory instability that responds poorly to symptomatic treatment or recurs
Protracted or recurring gastrointestinal symptoms
Mucous membrane swelling with the risk of airway obstruction
Diarrhea
Fluctuating level of consciousness, peripheral or cranial nerve paresis
In “borderline” cases, one or more of the following may support the indication:
Leukocytosis $>15\text{--}20 \times 10^9/\text{L}$
Metabolic acidosis
Hemolysis
Coagulation disturbances
ECG changes
Persistent severe pain

[25]. The neurological clinical feature was the consequence of an autoimmune reaction (cross-reaction between GM2 ganglioside and glycosidic epitopes of the concerned asp viper venom) of the patient who was not treated with specific antivenom despite suffering grade 2 envenomation.

Diagnosis

Diagnosis relies on confirming the bite and assessing the severity. In most cases, the diagnosis is obvious from the actual circumstances. One to four fang punctures may be observed.

In many European regions, there is just one naturally occurring viper species. Even if more than one indigenous species is present in a certain region, a precise identification is seldom necessary. The different vipers in Europe are closely enough related to respond to the same treatment – including antivenom. There seems to be an acceptable amount of cross-reactivity for most species.

Severity is categorized by careful assessment of the clinical evolution of the bite. Early signs of

severe envenomation are hypotension, impaired consciousness, intense or long-lasting gastrointestinal symptoms, respiratory distress, and rapid progression of local swelling. The degree of pain does not correlate with the severity of the bite. Leukocytosis greater than $15\text{--}20 \times 10^9/\text{L}$, pronounced hemoconcentration, metabolic acidosis, hemolysis, and coagulation disturbances similarly indicate high venom dose and a risk of further serious effects.

Based on ELISA results for detection of venom, there is evidence for a good correlation between clinical signs and the blood concentrations of venom antigen in patients bitten by *V. aspis* and *V. berus* [8, 13]. This correlation has been confirmed further in a study of patients envenomed by *V. aspis* and *V. berus* [6, 17]. In the average clinical setting, clinical evolution, rather than venom antigen levels, provides treatment guidance.

Treatment

Medical management of viper envenomation must follow strict rules [3, 14].

What to do at the bite scene (first aid): Immobilize the bite site and stay as quiet as possible to keep venom from spreading. Call for assistance as quickly as possible. If the bite takes place in a remote area and it is necessary to seek a means of communication, the victim can be carried (e.g., children) or left at the scene (preferably with another person). Provide rescuers precise details about the location of the patient. While waiting for assistance, remove tight clothing and jewelry (watches, bracelets, rings, etc) before swelling starts and, if possible, disinfect the wound.

What not to do at the bite scene: Do not restrict circulation by applying tight bands or tourniquets. Do not promote spreading by giving drinks that increase heart rate (coffee or tea). Do not perform mutilating acts such as wound incision, suctioning, or cauterization. Do not give alcoholic beverages or recreational drugs. Do not administer antivenom without medical supervision.

What to do during transportation to the hospital: The presence of any local manifestations indicates grade 1 envenomation and requires hospitalization. Placement of an intravenous line is a necessary precaution to allow immediate treatment of arterial hypotension. Nonsedating analgesics such as paracetamol should be administered in cases of severe pain.

What is not useful during transportation to the hospital: Administration of heparin or its derivatives is unnecessary and unhelpful. Injection of low-molecular weight heparin may promote spreading of venom. Administration of corticosteroids is also unnecessary. Aspiration devices, e.g., pumps, cannot extract venom injected deep within tissue and are not recommended.

At the hospital: Prompt clinical assessment with interview, examination, and grading is necessary upon arrival at the hospital (Table 1) [17]. Thorough laboratory testing should also be carried out including hemogram, hemostasis (platelets, prothrombin time, INR, aPTT, fibrinogen, and fibrin degradation products), and kidney functional testing (creatinine, urea, plus testing urine for hematuria, proteinuria).

For patients with grade 0 envenomation: A 4-h surveillance period in the emergency room may be proposed. However, the need for surveillance is controversial since the absence of pain rules out injection of venom and makes progression of symptoms unlikely.

For patients with grade 1 envenomation: hospitalization is required for at least 24 h since venom has been injected and outcome is unpredictable. The bitten extremity should be immobilized in an elevated position and appropriate supportive treatment should be administered including analgesics, such as paracetamol, or on the hospital, if necessary, opioids. Antibiotics should be administered only if bacterial infection is suspected. In this regard, oozing of purulent material from puncture sites is a common early indicator of contamination.

For patients with grade 2 or 3 envenomation: intravenous immunotherapy with antivenom must be undertaken. Several antivenoms are available, but some are preferentially used in certain countries.

Viperfav*

Viperfav* is the current antivenom used in France and Italy. It contains equine F(ab')₂ fragments obtained from antibodies produced in response to venoms from *Vipera berus*, *Vipera aspis*, and *Vipera ammodytes* (500LD₅₀, 1000LD₅₀, and 1000LD₅₀, respectively, per 4 mL bottle). Viperfav* has been approved for marketing and use only in a hospital setting. The required dose of antivenom depends less on the victim than on clinical features related to the quantity and quality of the venom which are linked to the snake's physiologic state and on the circumstances under which the bite occurs. The dose of antidote is the same in children and adults, but the volume of saline used to dilute the antivenom is adapted to patient weight.

Approval of Viperfav* in France was obtained based on studies showing good tolerance [16] and excellent effectiveness [17] in envenomed patients. Since it contains heterologous proteins, it must be administered under medical supervision. Preventing life-threatening effects of envenomation outweighs the risk of anaphylactic reaction that is usually manageable in a properly equipped hospital setting. Thanks to techniques now available for purification of antivenom, as well as to current levels of viral security, recent products like Viperfav* are considered as safe medicines. Toxicokinetic studies have shown that the intravenous route provides prompt neutralization of venom antigens in the bloodstream and tissue and is now the only recommended route [3, 13].

European Viper Venom Antiserum (Serum Antiviperinum)

European viper venom antiserum (serum antiviperinum) is made from purified equine F(ab')₂ fragments (Institute of Immunology, Zagreb, Croatia). The typical dose is one vial (10 mL) diluted in 200 mL of physiologic saline and given as an infusion over 60 min. The same dose is given to adults and children, though the total volume of the infusion may be adjusted. Additional doses may be required depending on the clinical course.

ViperaTab

ViperaTab is made from affinity-purified ovine Fab fragments (Protherics Ltd., London, UK). The typical dose is 200 mg (the contents of two ampuls) dissolved in 10 mL of sterile water (two ampuls of 5 mL), then diluted in 100 mL of physiologic saline, and given as an infusion over 30 min. The same dose is given to adults and children. Additional doses may be required depending on the clinical course [26]. A recent article suggests that this antivenom may be a valuable therapeutic antidote for treating snakebite by a variety of European vipers found throughout the continent [27].

Neurotoxins: Phospholipase A₂ neurotoxins in the venom of some French asp vipers are similar to vipoxin and ammodytoxins of *Vipera ammodytes* [10, 11]. *Vipera ammodytes* venom is used to immunize horses for production of Viperfav*. Antibodies against *Vipera ammodytes* neurotoxins are effective in treating neurotoxic symptoms induced by asp vipers in Southern France and Northern Italy [3, 10]. For this reason Viperfav* is recommended for neurotoxic envenomation (level of evidence II-3) with recent discussions concerning possible changes in antidote dosage [28].

Other treatments: Infection after snakebite is a non-negligible risk regardless of toxic manifestations. However, the need for systemic antibacterial therapy in Europe remains controversial. Unlike many tropical countries, infection after snakebite is uncommon in Europe. Close monitoring of the wound site is necessary to ensure prompt treatment if necessary. Tetanus has never been observed following snakebite in Europe, but immunization status should be checked and, if necessary, updated, preferably after any coagulopathy has substantially resolved.

Anticoagulant treatment using heparin or low-molecular weight derivatives provides no direct benefit for initial management of envenomation. A recent study in Western France showed that anticoagulant treatments are associated with longer duration of hospitalization for envenomed patients [4]. However, two indications may warrant its use. The first is to prevent possible venous

thrombosis in snakebite victims requiring prolonged decubitus due to extensive edema in the lower extremities.

The role of surgery is also limited and controversial. In the past, fasciotomy was recommended to relieve pressure and avoid peripheral compressive ischemia in cases of extensive edema. Current experience shows that immunotherapy using antivenom leads to prompt reduction in edema. Peripheral ischemia has not been reported in any recent European series describing viper envenomation treated with or without antivenom immunotherapy. Thus, fasciotomy is generally considered unnecessary for viper envenomation in Europe [3, 14] but is still used in rare cases after bites by species of the genus *Crotalus* in which elevated compartment pressures are documented and not relieved by appropriate antivenom therapy [29].

Criteria for ICU Discharge in Envenomation by European Snakes

Vital functions stabilized

Signs of ongoing systemic envenomation ceased

Local swelling not progressing

Further antivenom treatment not anticipated

Special Populations

Pediatric Patients

Small children constitute a special risk group and are overrepresented in hospital populations. All children who have been bitten by a viper should be observed for at least 24 h. The threshold for giving small children antivenom should be lower than in adults.

Pregnant Patients

Few data are available on snakebites in pregnancy, which might indicate that snakebite does not represent a particular risk to pregnancy. However, intrauterine death of the fetus has occurred in late pregnancy in two women after *V. berus* bites

(Swedish Poisons Information Centre, unpublished data). In both cases, there was significant envenomation with systemic and local effects. It seems logical to recommend prompt antivenom therapy for pregnant women to neutralize possible toxic effects of circulating venom on the placenta and fetus when signs of systemic envenomation are present.

Elderly Patients

Elderly patients may be more vulnerable, especially if they have cardiovascular disease.

Common Misconceptions about Envenomation by European Snakes

1. Viper venom is only moderately toxic because some people do not react at all.
2. Onset of severe symptoms is always early and rapid.
3. Corticosteroids have a neutralizing effect on the venom.
4. Antivenom treatment is more dangerous than the bite itself.
5. Antivenom has no effect on the local reactions.

Key Points in Envenomation by European Snakes

1. Immobilization and rest are essential.
2. Continuous observation is mandatory.
3. Life-threatening signs (circulatory shock, airway obstruction) may appear abruptly.
4. Onset of serious signs symptoms may be delayed up to 24 h after the bite.
5. Symptomatic and supportive care should be started immediately and given as required.
6. Indications for antivenom treatment must be considered carefully.
7. Antivenom should be given early for optimal efficacy.

European Non-front-fanged Colubrids

There are numerous non-front-fanged colubrid species in Europe. The only one currently considered as venomous is the Montpellier snake (*Malpolon monspessulanus*), which lives on the French Mediterranean coastline, most parts of the Iberian Peninsula, and the Maghreb. It is the largest snake in the continent, growing up to 2 m long. The neurotoxic venom has not been extensively studied, but is powerful enough to rapidly paralyze prey. However, the snake cannot normally inject venom into humans because its fangs are located toward the back of the mouth and cannot easily be brought into contact with the skin. Most cases of human envenomation involving the Montpellier snake have occurred under special circumstances. A few cases have been reported in Spain and one case from Southern France was published [30]. In at least some cases, the bite victim had introduced his/her finger into the snake's mouth so that it was able to chew the skin and inject venom. It should be noted that of more than 70 reported cases of Montpellier snake-bite, accurate identification of the snake can only be assured in a very few instances. The main clinical manifestations are local reaction at the injection site (moderate pain and limited edema) that disappears within 1–2 h. Cranial nerve disturbance can occur 2–6 h after injection including ptosis, ophthalmoplegia, swallowing difficulty, speech impairment, and accommodative dysfunction. These symptoms can be associated with extreme weakness and drowsiness, though full respiratory paralysis has not been reported. Bites by these snakes have been recently reviewed. [31]. No specific treatment exists. As colubrid venom is completely different than viper venom, antivenom for viper bites is ineffective. Care is provided, including analgesics and antibiotics, if necessary. Neurotoxic signs can last for 2–6 days.

Although all other colubrid species in Europe are fangless [32], this feature does not exclude the possibility that their saliva is venomous as the Duvernoy's glands can produce toxins even

though there is no physical venom apparatus [33]. In this regard, clear-cut differences have not been established in ophidians between venom and saliva. One case of envenomation by the green and yellow colubrid (*Coluber viridiflavus*) that has only conventional teeth was reported in a drunken man who wrapped the animal around his neck and was bitten repeatedly [34]. The circumstances of this case are exceptional, and a single colubrid bite is usually considered harmless, requiring only wound disinfection. It is noteworthy that colubrids are much more active than vipers and may bite more often.

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Non-Front-Fanged Colubroid Snakes 124

Scott A. Weinstein

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“Colubrid” Snakes and the Functional Morphology of “Rear-Fanged” Snakes

The world’s living snake fauna consists of approximately 3580 species, and the majority belongs to the superfamily Colubroidea, the “advanced snakes” (e.g., those with derived anatomical traits), that evolved during the Oligocene-Miocene periods of the Cenozoic Era. It should be noted that some authors utilize a more segregated but complex phylogeny in which the advanced snakes are all included in the infraorder Caenophidia with the families Elapidae and Lamprophiidae as part of the superfamily Elapoidea. The recognition of up to 11 inclusive families in this phylogeny is dependent on a given author’s cladistics interpretation. Therefore, although the Colubroidea is used here for convenience, it should be noted that the dynamic nature of squamate reptile taxonomy might alter the usage/taxonomic accuracy of this particular phylogeny.

Approximately 700 colubroid snake species (roughly some 19.5%) are front-fanged (front-fanged colubroids, FFC) and possess either relatively “fixed” (family Elapidae) or distensible front fangs (family Viperidae and two genera of the family Lamprophiidae) in the maxilla that have variable morphology, but all have an enclosed lumen (canal) and orifice, which superficially resemble a hypodermic needle (Fig. 1). In general, elapid fangs may be considered “fixed,” meaning relatively immobile and in a permanently erected position in the maxilla; there are a number of species (e.g., Australian coastal taipan, *Oxyuranus scutellatus*) that have significant fang mobility. The term “fixed” is primarily used in order to grossly distinguish elapid fangs, which are frequently called “proteroglyphous,” from the generally more mobile fangs, often termed, “solenoglyphous,” of viperids and atractaspidine lamprophiids. The variability and embryological origins of ophidian dentition in the posterior maxillae renders the firm categorization of “fangs” as somewhat artificial, and the terminology is largely used for general convenience because it lacks precise accuracy.

The medical risks of many species of FFC have been formally recognized for several centuries, and envenoming inflicted by numerous clinically important taxa has been documented with increasing medical accuracy since the late nineteenth century. Of the extant FFC belonging to the families Viperidae (Old World vipers, subfamily Viperinae, and New and Old World pit vipers, subfamily Crotalinae) and Elapidae (cobras, mambas, coral snakes, sea snakes, and their allies), probably about 50% (some 300–350 species) are known to inflict medically significant bites on humans [1].

In addition, as noted above, two unusual genera (*Atractaspis* spp. [mole vipers, burrowing asps, or stiletto snakes, arguably about 21 species] and *Homoroselaps* spp. [African dwarf garter or harlequin snakes, 2 species]) of the primarily African family Lamprophiidae, subfamily Atractaspidinae (on occasion contracted to Atractaspinae), also have evolved front fangs, and those of *Atractaspis* spp. have notable mobility. Therefore, 55/57 genera and 286/309 species of the Lamprophiidae are non-front-fanged, and this may suggest that the front-fanged state arose in these two genera of robustly closely allied African snakes, independent to the evolutionary process that selected the front-fanged state in elapids and viperids. Although their medical importance has often been incorrectly underestimated, several *Atractaspis* spp. are medically important in sub-Saharan Africa and the Middle East, but there are also a number of lesser-known front-fanged species (including the aforementioned *Homoroselaps* spp.) of uncertain medical significance. This is partly due to the infrequent contact of these species with humans (e.g., many of these snakes are fossorial and/or are found in ecosystems in which contact with humans is rare), as well as the common lack of formal medical review of bites that may occur in isolated locales among remote human populations [1].

In reality, a relative handful of FFC species are responsible for most of the global annual snakebite-related human mortality and morbidity, which has been roughly approximated to include 45,000 – >100,000 deaths [8, 9]. This figure is

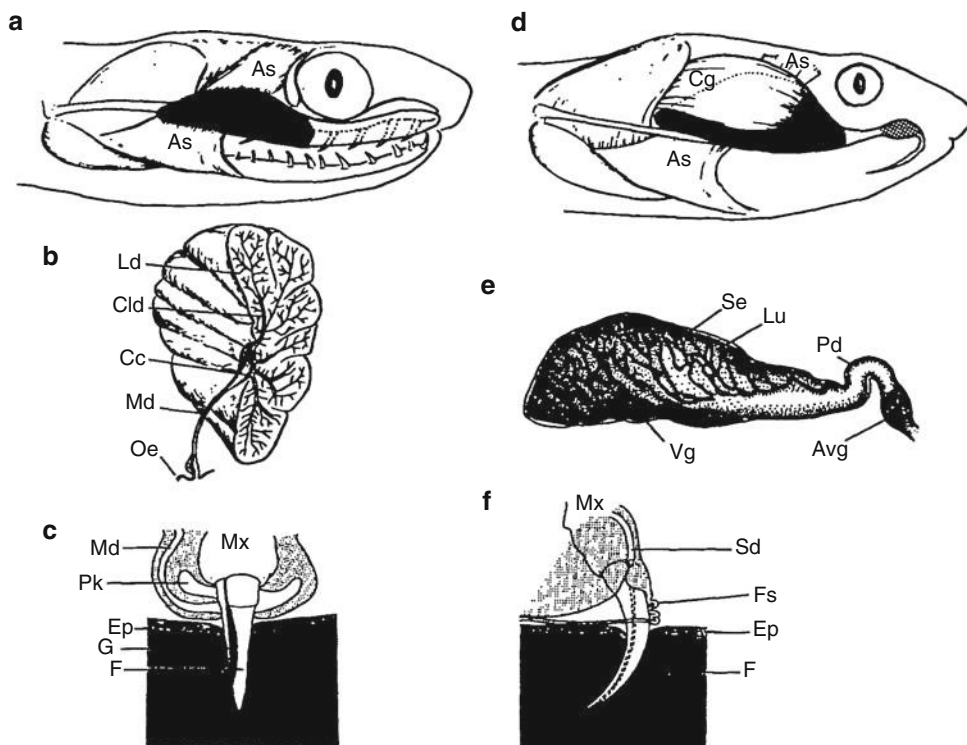


Fig. 1 Comparison of the venom delivery systems in a representative front-fanged colubroid (FFC) and a non-front-fanged colubroid (NFFC). (a) In the NFFC, the Duvernoy's gland (DG) or, "low-pressure venom gland", Duvernoy's venom gland, indicated by cross-hatching) is located in the temporal region. Although adjacent striated muscles are medially proximal to the gland fundus, they typically do not attach directly to it. (b) An enlarged cross-sectional view of the DG that depicts the internal duct system, which drains the relatively dense parenchyma. A single duct departing from a small central cistern delivers the newly synthesized contents to a cuff of buccal mucosa that surrounds the posterior or mid-maxillary tooth. (c) Infliction of a wound in the integument of the prey by the maxillary tooth shown in (b) causes the mucosal cuff to remain on the surface while receiving the gland secretion (venom) that flows around the tooth that may or may not be grooved. This is an open, low-pressure system. (d) The venom gland (*shaded*) of this FFC (most closely resembling that of a "proteroglyphous" species, e.g., an elapid) includes the main venom gland with a main duct, an accessory gland (that mainly secretes mucosal secretions), and a secondary duct that empties into the base of the

canaliculated, or hollow, fang. Striated muscle fibers insert directly onto the venom gland fundus thereby raising the intraglandular pressure and send a bolus of stored venom from the gland to the canaliculated fang. (e) A sagittal view of the venom gland showing the secretory epithelium and extensive storage reservoir of the gland. The typical DG has no comparable extent of storage volume. (f) When the canaliculated fang penetrates the integument of the prey, or unfortunate human, the attachment of the venom duct to the fang maintains the relatively high pressure head, and venom passes unobstructed through the lumen of the fang and is delivered deeply into the integument. Abbreviations: *adductor mandibulae externus superficialis* (AS), *compressor gloandulae* (Cg); accessory venom gland (Av), central cistern (Cc), common lobular duct (Cld), prey integument (Ep), fang/maxillary tooth (F), lobular duct (LD), lumen with secretory product (Lu), main duct (Md), maxillary bone (Mx), oral epithelium/buccal mucosa (Oe), buccal mucosal cuff around tooth (Pk), primary venom duct (Pd), secondary venom duct (Sd), secretory epithelium (Se), main venom gland (Vg) (After Weinstein and Kardong [9], used with permission)

probably an underestimate, and these envenoming also result in an inestimable number of significant chronic injuries that adversely affect the victims' activities of daily living. Several examples of

these most medically important FFC species include *Echis* spp. (the saw-scaled, or carpet, vipers, Viperidae, Viperinae), *Naja naja* and *N. kaouthia* (respectively, the common Asian

cobra and the monocled, or monocellate, cobra, Elapidae), *Oxyuranus scutellatus canni* (Papuan taipan, Elapidae), *Bitis arietans* (the puff adder, Viperidae, Viperinae), Russell's viper (*Daboia russelii*, *D. siamensis*, Viperidae, Viperinae), *Bungarus* spp. (various species of kraits, Elapidae), and *Bothrops asper* and *B. atrox* (respectively, the terciopelo, and barba amarilla, or common lance head; both are occasionally called "fer-de-lance," Viperidae, Crotalinae). These species collectively account for a large proportion of the global human mortality and/or morbidity from snakebite.

As briefly mentioned earlier, all of the known FFC possess a canaliculated (hollow or lumenate) venom apparatus located on the anterior maxillae that is associated with a venom gland whose contents are ejected under high pressure by compression of the gland through contraction of skeletal muscle fibers inserted in the gland fundus. In general, the venom glands of most front-fanged species have a pre-stored bolus of venom that is produced by slowly cycling columnar cells present in the venom gland, which synthesize and secrete multiple classes of venom components (primarily polypeptides and peptides). The stored venom bolus is thereby available for immediate injection under pressure (Fig. 1).

The larger number of colubroid species are non-front-fanged species (non-front-fanged colubroids, NFFC). Historically, many NFFC were inaccurately grouped in an amorphous and thus somewhat artificial family, the Colubridae, a group first defined in 1758 by the Swedish natural historian and founder of systematic zoology/taxonomy, Carl Nilsson Linnaeus (Carl von Linné or Carolus Linnaeus; 1707–1778). The name, "Colubridae," is derived from the rather non-descript Latin, *coluber*, the general term for "snake" or "serpent." Under the previous definition of the Colubridae, about 65–70% of extant snake species (e.g., about 2,350 taxa) were included in this poorly defined family. On the basis of several morphological and/or molecular systematic investigations (some conflicting), the number and identities of previous subfamilies included under the Colubridae have been redefined. Several have been raised to full family status and some have

been rendered artificial, while others have been retained within the original family that now comprises an estimated 1,800 species (about 75% of the previous assemblage). Although the majority of these snakes are still in the family Colubridae, they are now collectively, and more accurately, termed NFFC. As currently defined, these snakes are represented by taxa with wide distribution, but geographically variable abundance in the Neotropics, North America, Mexico, Africa, Asia and Southeast Asia, the Indian subcontinent, New Guinea, Europe, and with the least representation in Australia [1].

A general accounting of the Colubridae and newly defined families that previously were included as "colubrids" includes a diverse assortment of widely distributed species (Table 1) [1]. Some of these snakes have often been called "rear-fanged," "opisthoglyphous," or "aglyphous," referring to their posterior or mid-maxillary dentition that may or may not be enlarged and/or quite variably modified with external grooves and/or lateral ridges, but are not hollow and thus lack a fully enclosed internal lumen or canal (Figs. 1 and 2) [1, 3, 10]. As mentioned earlier, the notably variable position of the modified teeth in the maxilla contradicts the accuracy of the popular term, "rear-fanged," because these teeth in some of these snakes are not located in the "rear" (posterior) of the maxilla.

In some NFFC species (the precise number is unclear), this dentition is associated with a gland that is often considered distinctive from that of FFC and has been variously called "Duvernoy's gland" [11–14], "low-pressure venom gland" [1, 3], or "Duvernoy's venom gland" [15]. However, some investigators do not distinguish this gland from the viperid and elapid venom gland and thus also simply call it a "venom gland" [16]. An unknown number of NFFC possess these glands that produce variably toxic secretions released under low pressure due usually to a general lack of any significant skeletal muscle fiber insertion in the gland fundus [11, 16–18]. The differing terminology for these glands has resulted from investigator interpretation of functional morphology and/or glandular roles or assignment of identity

Table 1 Overview of the superfamily Colubroidea¹ and their medical significance

(Commonly used familial name) ²	Subfamilies [Number of medically relevant NFFC species identified from evidence-based analysis ³]	Approximate number of total genera and species ⁴	Comments
Colubridae ("Typical" snakes; "harmless egg-laying snakes") Natricidae Dipsadidae Pseudoxenodontinae [IC]	Colubrinae [12], Grayiinae [IC], Calamariinae [IC] Sibynophiinae [IC] None [3] None [28] ⁵ None [IC]	250 [1,750]	Cases not included in the summarized tally here featured mild, transient local effects. Six taxa have caused life-threatening effects or fatalities (see text). There is a lack of any information about the possible medical risks posed by the potential bites of a number of species that are entering the commercial trade (e.g., bamboo snake, <i>Pseudoxenodon bambusicola</i> , Pseudoxenodontidae). Some taxa are very rarely encountered (e.g., the two taxa of <i>Scaphiodontophis</i> , Sibynophiinae, and many others), and, in numerous cases, there is no substantial/reliable clinical information about the effects of bites from a given species
Lamprophiidae (sometimes collectively called, "African nocturnal snakes," although a single species, <i>Psammophis indochinensis</i> , Psammophiinae, occurs in Southeast Asia), and others (e.g., <i>Malpolon</i> spp.) range into Europe	Aparallactinae [1] ⁶ Atractaspidinae [NA] ⁷ Lamprophiinae [IC] Prosymninae [IC] Psammophiinae [6] Pseudaspidinae [IC] Pseudoxyrhophiinae [5]	61 [300]	One species has inflicted a single well-documented case of systemic envenoming featuring cranial nerve palsies (see text). To date, most well-documented cases feature mild, transient local effects. However, bites from larger specimens of some species may be capable of producing more significant effects. Currently, there is no clinical information that supports common speculation of the hypothetically more serious effects of bites from large specimens of <i>Psammophis</i> spp. ("sand snakes," Psammophinae) Although envenoming cases are not included in the tally because they are front-fanged, all of the <i>Atractaspis</i> spp. must be considered medically important as their bites have caused fatalities, and some species are significant causes of snakebite within their respective ranges
Homalopsidae (Australasian mud snakes)	----- [IC]	11 [38]	Mostly anecdotal information; the few medically well-documented reports indicate mild, transient local effects. Larger specimens of some species may be capable of inflicting a bite with more significant local effects
Pareatidae (Asian slug-eating snakes)	----- [IC]	3 [15]	Ibid
Xenodermatidae ("strange-scaled snakes"; see comments)	----- [IC]	5 [17]	Rarely encountered and reportedly reluctant to bite, there is no available relevant clinical information. Several specimens of these unusual snakes were briefly maintained by the author, and none attempted to bite, but rarely handled due to their fragile nature
Viperidae (vipers and pit vipers)	Azemiopinae, Crotalinae Viperinae [NA]	39 [300]	The medically serious, life-threatening and/or fatal bites of a large number of species have been thoroughly documented. However, the medical risks of some species are unestablished due to their remote habitats, infrequent contact with human populations and/or lack of medically qualified documentation of their bites

(continued)

Table 1 (continued)

(Commonly used familial name) ²	Subfamilies [Number of medically relevant NFFC species identified from evidence-based analysis ³]	Approximate number of total genera and species ⁴	Comments
Elapidae (sometimes collectively called, “fixed-front-fanged snakes”; see comments)	Hydrophiinae ⁸ [NA]	65 [350]	Ibid There is very limited or a lack of information about the medical risks that may be posed by some small fossorial species (see the previous entry)

¹The taxonomy of the Colubroidea is fluid and under continuing review and reassignment. The taxonomy included here follows that of Pyron et al. [2]

²Traditionally used by some authors, these common names do not accurately encompass the diverse members of this large family because some are viviparous (some previously termed, ovoviviparous) and some are not “harmless,” or “typical” (see text)

³Based on the critical analysis of Weinstein et al. [3], and is limited to only those species for which available clinically relevant information is sufficient for risk assessment. This tally is limited to a summarized number of species that have inflicted bites that have included some clinically significant pathological effects, for example, ranging from some locally progressive but minor edema to bites with a fatal outcome. Bites resulting in simple puncture wounds and lacerations with reactive erythema are not included in the summarized figure. There are very likely a number of other NFFC that may have medical significance under some multifactorial circumstances

⁴This approximate number estimates the number of genera and species (in brackets) contained in the family listed

⁵This summarized number includes a single entry for some species such as the South American burrowing snakes, *Apostolepis* spp., a genus with some 26 taxa. The single number reflects the results of a collected series of reported bites that provide documentation of some significant uncomplicated local effects of bites from members of this genus without individual species identification

⁶The single taxa included here is the Natal black snake, *Macrelaps microlepidotus*, a monotype that is considered a provisional member of either the Atractaspidinae or the Aparallactinae, depending on author. Therefore, the taxonomic status of this species remains unconfirmed. Purely for the sake of the medically relevant discussion here, it is included with the Aparallactinae here in order to separate it from the front-fanged atractaspidines (see next footnote)

⁷This subfamily is provisionally recognized by some investigators, and not by others who still consider Atractaspididae as a full family. *Atractaspis* spp. and the other allied genus, *Homoroselaps* spp., grouped with *Atractaspis* spp. on robust morphological grounds, are the only front-fanged colubroids assigned to what otherwise is a NFFC clade. See Pyron and Burbrink [4], Vidal et al. [5, 6] and Zaher et al. [7] for detailed information about the problematic taxonomy of some of these assignments

⁸Most taxonomists no longer recognize this subfamily or several others that were previously proposed or used (e.g., Micrurinae, Laticaudinae, Elapinae, etc.). The Hydrophiinae is included only because it appears in some of the relevant literature

Figure after Weinstein et al. [1]; used with permission

Abbreviations: NFFC Non-front-fanged colubroid snakes, NA not applicable, IC insufficient information/lack of documented case reports

based primarily on phylogenetic relationships [1, 3].

Delivery of the oral product, venom, or other products with potential toxicity to the animal (including human) recipient is an important consideration when evaluating potential medical risks of a given ophidian species. Compressed high-pressure FFC venom glands release a bolus of stored venom and facilitate its injection into prey or a human victim. The pressure of injection may exceed 30 psi, which is similar to a typical automobile tire pressure [19]. In contrast, NFFC

inoculate their secretions under low pressure (the few studied species produce ≤ 5 psi [19]) into wounds produced by maxillary teeth that may be variably grooved. Those with surface grooves may have shallow grooves that in some species may resemble superficial indentations or may be deeply etched with a longitudinal groove that extends over almost the entire dentary surface. A small assortment of studied species have partially enclosed grooves, but these still remain part of a low pressure, open system [1]. The medically important colubrine colubrid, *Dispholidus typus*

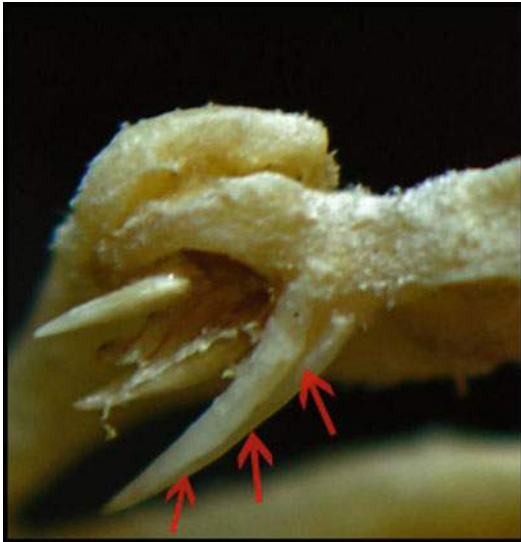


Fig. 2 Posterior grooved (arrows), enlarged maxillary tooth of the brown tree snake, *Boiga irregularis* (Colubridae, Colubrinae) (Photo copyright to Scott A. Weinstein)



Fig. 3 Boomslang (*Dispholidus typus*, Colubridae, Colubrinae). This Hazard Index 1 species has medical importance in East Africa and South Africa. It has a wide gape, multiple, deeply grooved posterior maxillary teeth, and some limited striated muscle attachment on the venom gland fundus, which likely partially pressurizes the gland. This aids delivery of highly potent procoagulant venom that exerts its clinically important effects by a combination of prothrombin activation and rhexic hemorrhagic action of metalloproteases (Photo copyright to David Warrell)

(boomslang, Fig. 3), and possibly other members of the tribe, Dispholidini, as well as perhaps a few other unrelated taxa, have limited striated muscle insertion into the gland resulting in a partially pressurized venom delivery system [1, 3].



Fig. 4 At least two species of the African twig, bird, or vine snakes, *Thelotornis* spp. (Colubridae, Colubrinae), have inflicted fatal envenoming that is very similar to that caused by *Dispholidus typus*, as it features consumptive coagulopathy and hemorrhagic diathesis. Treatment of serious envenoming by any of these snakes is limited to replacement therapy and careful supportive management including hemodialysis in some patients with AKI. Pictured is the Eastern twig, vine, or bird snake, *T. mossambicanus* (Photo copyright to David A. Warrell)

However, even these species very likely generate significantly lower intraglandular pressures than that of NFFC and, also unlike medically important FFC, do not have appreciable capacity for a stored venom bolus. Nevertheless, this intraglandular pressure deficit does not preclude the risk of a medically significant envenoming from a quick bite and release delivered by *D. typus* and possibly other medically important dispholidines and natricids (see ahead).

Toxins and Other Components of NFFC Venoms and Other Oral Products

Modern snake venom research has spanned a relatively short period (approximately 80 year), and detailed investigations have largely focused on medically important FFC species. The venoms and other oral products of NFFC have received far less attention [1, 3]. Although early twentieth century South African researchers were aware of the human lethal potential of boomslangs (*Dispholidus typus*, Colubridae, Colubrinae), wider interest in the biomedical properties of the African dispholidines (*Dispholidus typus* and the African twig, bird, tree, or vine snakes, *Thelotornis* spp., Fig. 4) was stimulated by the tragic and publicized deaths of two distinguished herpetologists, Karl P. Schmidt (in 1956) and Robert F.W. Mertens (in 1976). Similarly, the



Fig. 5 Another Hazard Level 1 species, the tiger keelback, or Yamakagashi (*Rhabdophis tigrinus*, Natricidae), has caused multiple fatal envenoming in Japan. There is effective antivenom against this taxon, and it has been used successfully to treat life threatening envenoming by this species (Photo copyright to Dr. S. Mishima)



Fig. 6 The red necked keelback (*Rhabdophis subminiatus*, Natricidae) has inflicted serious coagulopathic envenoming, but unlike its congener, *R. tigrinus*, has not caused any human fatalities. So far no envenoming by this species has been treated with *R. tigrinus* antivenom, although it is likely to have clinically important paraspecific neutralizing capacity. This antivenom should be used in life-threatening envenoming by this species (Photo copyright to Taksa Vasaruchapong)

potentially fatal effects of tiger keelback or yamakagashi (*Rhabdophis tigrinus*, Natricidae, Fig. 5) envenoming were long known to some Japanese investigators, but the life-threatening bite from a privately owned red-necked keelback, *Rhabdophis subminiatus* (Fig. 6), in London in 1978 also sparked wider interest in the venoms of these species, as well as those of other NFFC that might have medical importance [3]. Contemporary biochemical and pharmacological investigations are greatly expanding knowledge of the Duvernoy's gland secretions and venoms of NFFC. However, advances in this subdiscipline are greatly hindered by an almost complete lack of active research funding and disinterest by relevant "mainstream" biomedical disciplines, as, aside from *D. typus*, there is limited demonstrable medical importance attributed to most NFFC [1, 3, 10].

Biochemistry

The composition of NFFC venoms and other oral secretions is similar to that of venoms of viperids, elapids, and *Atractaspis* spp. [1, 3] although some NFFC venoms/oral secretions are less complex than venoms of viperids and elapids (e.g., those

from the homolopsid, *Cerberus rynchops* [dog-faced water snake, Fig. 7] [20], and the dipsadid, Lichtenstein's green racer [*Philodryas olfersii*, Fig. 8] [21]). A handful of biologically active components present in the oral secretions/venoms and glands of NFFC have been characterized. Some of these belong to the known classes of snake venom components (Table 2). Recent proteomic, genomic, and transcriptomic investigations have identified some of the components detected during early chromatographic studies of NFFC venoms and secretions [1, 3] and/or have reported the presence of previously undetected classes of biologically active constituents including cysteine-rich secretory proteins, multiple enzymes and isozymes (e.g., metalloproteases, phospholipases A2, fibrinogenases, Factor X and prothrombin activators, and others), mycotoxins, as well as postsynaptic neurotoxins (see Table 2 for representative examples). To date, the few well-characterized neurotoxins [three-finger-fold toxins] have shown greater specificity for the saurian and/or avian motor end plate (Table 2).

Assessment of NFFC venom/other oral secretion biomedical activities should include essential consideration of their biological functions, as

Fig. 7 Although most studied venoms from NFFCs show complexity similar to that of FFCs, the venoms of some NFFC such as this Australasian homolopsid, the dog-faced watersnake, *Cerberus rynchops*, are less complex. The few documented bites by this species have featured only minor puncture wounds and mild reactive edema/erythema (Photo copyright to Eng Wah Teo)



Fig. 8 Lichtenstein's racer, *Philodryas olfersii* (Dipsadidae), is gaining recognition as a species with some occasional medical importance in South America (especially Brazil). This Hazard Index 2/3 species can occasionally inflict systemic envenoming so far characterized by widespread ecchymoses (see Figs. 27 and 28). Although there are anecdotal reports of coagulopathic envenoming from this species, to date there are no well-documented reports that establish consumptive coagulopathy after a bite from this species. There are also anecdotal reports of fatal envenomings, but these are unsubstantiated and unsupported. There is no antivenom that is effective for treating bites from these snakes, and serious envenoming is managed supportively with meticulous wound care (Photo copyright to Pedro H. Bernardo)

this can help the construction of a medical hazard profile for the species. Therefore, it should be noted that the majority of NFFC produce oral products have unknown biological properties and/or functions [1, 3, 22]. Consequently, one can view that many of these oral products are

“assumed” to be venom, as they are identified as such solely on the detection of classes of proteins/toxins that are described from elapid and/or viperid venom components and without quality evidence of their function, e.g., their possible role in the subjugation of prey, and/or the facilitation of prey capture, or role in self defense, as these are traditional roles used to define snake venoms [22]. Therefore, using a strict scientific standard, a relatively small number of these snakes can be considered to meet the traditional biological criteria defining them as “venomous,” although there is current debate concerning the definition of “venom” and the “venomous condition” [3, 22–25]. Snakes evolved venoms long before humans appeared on Earth, and the *most likely* primary impetus for their evolution was (and remains) prey capture/subjugation [1, 3, 22]. Therefore, it is important to recognize that the medical effects of snake venoms are a circumstantial result of the interaction of humans with snakes whose venoms or oral products coincidentally have a medically significant effect, and therefore these effects should not be used as criteria for defining snakes as “venomous” or not [1, 3, 17, 22, 26].

For the purposes of broad discussion of this large grouping of snakes, it is reasonable to generally use the term “venom” for their oral products with the understanding that the traditional biological criteria assigning the term is unknown for a significant number of taxa.

Table 2 Representative components isolated from venoms/oral secretions of non-front-fanged colubroid snakes (NFFC)

NFFC taxa ^a	Isolated/ characterized component(s)	Reference	Comments
Family, Subfamily [1]			
Colubridae, Colubrinae			
Mangrove snake, or ringed cat snake, <i>Boiga dendrophila</i>	Three-finger fold postsynaptic neurotoxin [3FTX] ("denmotoxin")	[34, 61]	Primarily avian-specific postsynaptic neurotoxin; Mr 8.5 kDa that contains five disulfides. Aside from a conserved leader signal sequence, its basic genetic organization (e.g., arrangement of untranslated and translated sequences) differs from that of elapid three-finger toxins. This toxin is unlikely to have clinical importance
Brown tree snake, <i>Boiga irregularis</i>	Unusual three-finger fold postsynaptic neurotoxin ("irditoxin")	[61]	Novel 17.1 kDa disulphide-linked, heterodimeric structure; approximately threefold more active in vitro at the avian neuromuscular junction than in the rat phrenic nerve preparation; selective toxicity for lizards and birds. This toxin is unlikely to have clinical importance
Brown tree snake, <i>Boiga irregularis</i>	"Myotoxic fraction" (containing 2 proteins)	[62]	Fraction contained two proteins, 14.5 kDa and 17 kDa; i.p. injection into mice caused myoglobinuria due to multifocal myofiber degeneration and necrosis. There is currently no evidence supporting medical importance of these proteins
Radiated ratsnake, copperhead ratsnake, <i>Coelognathus radiatus</i>	Three-finger fold postsynaptic neurotoxin ("colubritoxin")	[63]	An 8.5 kDa 3FTX; notable structural homology with elapid 3FTX; produces reversible antagonism in the chick biventer cervicis muscle preparation. There is currently no evidence supporting medical importance of this toxin
Boomslang, <i>Dispholidus typus</i>	"Coagulant principle"	[64, 65]	The ≈ 67 kDa "procoagulant principle" reported by Hiestand and Hiestand [29] is probably the same or a similar molecular species noted by Guillin et al. [28] with powerful prothrombin-activating activity. This toxin very likely plays an important role in the life-threatening clinical envenoming that can follow bites by this species
Boomslang, <i>Dispholidus typus</i>	P-III/P-IV snake venom metalloprotease [SVMP] ("dispholysin A")	[66]	The 65 kDa species cross-reacted with the P-III hemorrhagic SVMP from <i>Bothropoides (Bothrops) jararaca</i> (Oliveira et al. [31]) venom. This toxin very likely plays an important role in the life-threatening clinical envenoming that can follow bites by this species (see the previous entry)
Kirtland's twig, vine or bird snake, <i>Thelotornis kirtlandii</i>	Procoagulant	[68]	The ≈ 85 kDa procoagulant (pI 5.25) was partly characterized from a "venom gland" extract and found to be a direct prothrombin activator. This fraction, as well as other similar procoagulant components in combined action with metalloproteinases, causes the life-threatening clinical effects in patients after being bitten by this species
Sonoran lyre snake, <i>Trimorphodon biscutatus lambda</i> [<i>Trimorphodon lambda</i> DeVitt et al., 2008]	Phospholipase A ₂ [PLA2] ("trimorphin")	[69]	Some conserved structural features of the Group IA PLA2 were present in this 13.99 kDa PLA2 and suggested that there was a close relationship with some hydrophiine elapid PLA2. There is currently no evidence supporting medical importance of this PLA2, but, to date, there are also very few well-documented bites by this species, and none are medically significant

(continued)

Table 2 (continued)

NFFC taxa ^a	Isolated/ characterized component(s)	Reference	Comments
Dipsadidae			
Puerto Rican racer, <i>Borikenophis</i> [<i>Alsophis</i>] <i>portoricensis</i>	P-III metalloproteinase ("alsophinase")	[70]	α -fibrinogenolytic 56 kDa polypeptide with hemorrhagic activity in mice that has 67% primary sequence homology with metalloproteinase from <i>P. olfersii</i> venom; of unknown clinical significance
Mountain keel back, <i>Helicops angulatus</i>	Cysteine-rich secretory protein [CRISP] ("helicopsin")	[71]	The 20 kDa CRISP was toxic to mice. There is currently no evidence supporting medical importance of this toxin, but there are also very few well-documented bites by members of this genus
<i>Philodryas olfersii</i>	Myotoxin	[72]	The 20 kDa (pI 4.8) toxin produced myolysis and extensive widening of the intercellular spaces with partial or total loss of transverse muscle striations in the muscle periphery. See above entry for additional comments regarding possible medical importance of this toxin
Patagonian racer, <i>Philodryas</i> <i>patagoniensis</i>	Hemorrhagic, α - fibrinogenolytic metalloprotease ("patagonifibrase")	[73]	An acidic 53.2 kDa SVMP that can directly cleave fibrinogen. The venom/oral secretion of this species also contains other metalloproteases, CRISPs, 3FTX, and a rich complement of other biologically active proteins. Although several authors relate these and similar toxins of <i>Philodryas</i> spp. to clinical effects in bitten victims, to date, there is no clear evidence of this linkage
Natricidae			
Tiger keel back, or Yamakagashi, <i>Rhabdophis tigrinus</i>	Metalloproteinase ("38 kDa metalloproteinase")	[74]	The authors noted that the regulatory mechanism of this novel proteinase suggested that it was more likely a matrix metalloproteinase, rather than a SVMP. The venom of this species and that of the congener <i>R. subminiatus</i> (red-necked keel back) has several medically important toxins such as prothrombin activators, and these combined with the action of metalloproteinases likely result in the life-threatening hemorrhagic effects observed in patients after being bitten by these species
Homalopsidae			
Dog-faced watersnake, <i>Cerberus</i> <i>rhynchops</i>	"Ryncolins" (unconfirmed/ unknown function)	[20]	Based on their structural homology with mammalian ficolins, OmPraba et al. [21] hypothesized that ryncolins may act as platelet aggregators and/or complement activators
Lamprophiidae, Psammophinae			
Montpellier snake, <i>Malpolon</i> <i>monspessulanus</i>	Hemorrhagic toxin ("Fraction CM-6")	[13]	This 24 kDa component produced pulmonary hemorrhage in mice but did not cause local hemorrhage when administered intradermally. Currently, there is no evidence that this toxin is medically important
African beaked snake, <i>Rhamphiophis</i> <i>oxyrhynchus</i>	Postsynaptic neurotoxin, 3FTX ("rufoxin")	[75]	Novel toxin (molecular mass \approx 10–12 kDa) lacking N-terminus homology with elapid 3FTX; produces reversible antagonism in the chick biventer cervicis muscle preparation. As with most NFFC toxins characterized to date, there is currently no evidence that "rufoxin" has any medical importance, but there are also no well-documented clinically significant bites by this species

^aTable modified after Weinstein et al. [1], and used with permission

Medical Risks Posed by Most NFFC Species Have a Notably Limited Evidence Base

There is much confusion and disseminated incorrect information about the known and possible medical risks posed by some NFFC. This includes premature theorized risk assignment suggested by wholly incomplete or inapplicable information such as chromatographic detection of toxin classes in limited venom samples, inaccurate comparisons between experimental murine lethal potency studies of venoms from FFC and NFFC, and unsupported propagation of anecdotal and second- or thirdhand, as well as blatantly false reports of medically significant, even fatal, bites from various NFFC taxa [1, 27]. This incorrect and often misleading information is increasingly found on the Internet, in popular publications, as well as in some sensationalist television documentaries, and even in the scientific and medical literature.

When considering only the well-documented medical literature (meaning, high-quality

evidence-based clinical reports prepared and reported by medically qualified authors), to date, four species of NFFC have caused human fatalities, while three others have inflicted bites capable of causing serious and potentially life-threatening systemic pathology (Table 3). However, most well-documented bites from NFFC cause only minor medically insignificant, local effects (Fig. 9). Nonetheless, most taxa are of unknown medical significance because there have been no adequately documented cases delineating the clinical symptoms and pathophysiological effects of their bites. Previously, only a limited number of published cases have been subjected to medically qualified review, and these tended to be regionally focused [28, 29]. A recent comprehensive analysis of the available evidence for medical significance of NFFC found a limited database with few well-documented cases containing detail sufficient for assignment of risk to a relatively small number of NFFC [1, 3]. Thus, medically reliable risk assessments and envenoming management recommendations can only be provided for a relative handful of NFFC species. Many published

Table 3 The medical significance of some representative non-front-fanged colubroid snakes (NFFC)^{a,b}

NFFC taxa (family, subfamily)	Hazard index ^c	Basic medical management strategy ^d	Evidence level ^e
Boomslang, <i>Dispholidus typus</i> (Colubridae, Colubrinae) Cape twig or vine snake, <i>Thelotornis capensis</i> (Colubridae, Colubrinae) Kirtland's twig or vine snake, <i>T. kirtlandii</i> (Colubridae, Colubrinae) Tiger keel back or Yamakagashi, <i>Rhabdophis tigrinus</i> (Natricidae) Red-necked keel back, <i>R. subminiatus</i> (Natricidae) Sri Lankan keelback, "blossom" or "flower krait," or "flower blossom" snake (<i>Balanophis ceylonensis</i> , Natricidae)	1	<i>Effective antivenoms are available for D. typus and R. tigrinus. Antivenom raised against R. tigrinus venom should be used to treat serious envenoming by R. subminiatus as it probably provides paraspecific protection. Due to a robustly close taxonomic relationship, it would be reasonable to use R. tigrinus antivenom for a potentially life-threatening envenoming by B. ceylonensis, while remaining cognizant that there is no evidence base to specifically support its efficacy There is no antivenom for envenoming by Thelotornis spp. and there are no antivenoms that provide paraspecific protection (including those mentioned above). Treatment consists of replacement therapy^f only. Replacement therapy may also be needed for the aforementioned species in addition to antivenom on a case-by-case basis. Significant bites from any of these species must be considered life threatening The use of heparin, antifibrinolytics, vitamin K, corticosteroids, etc. is positively contraindicated due to an unfavorable risk vs. benefit profile</i>	Level III Antivenom for <i>D. typus</i> and <i>R. tigrinus</i> envenoming IE <i>R. tigrinus</i> antivenom for <i>R. subminiatus</i> or <i>B. ceylonensis</i> envenoming IE Replacement therapy for treatment of <i>Thelotornis</i> spp.

(continued)

Table 3 (continued)

NFFC taxa (family, subfamily)	Hazard index ^c	Basic medical management strategy ^d	Evidence level ^e
Monpellier snake, <i>Malpolon monspessulanus</i> (Lamprophiidae, Psammophinae) Brown tree snake, <i>Boiga irregularis</i> ^g (Colubridae, Colubrinae) Lichenstein's racer, <i>Philodryas olfersii</i> (Dipsadidae)	2–3	Closely monitor neurological signs in those bitten (especially pediatric patients) by <i>M. monspessulanus</i> and <i>B. irregularis</i> and coagulation panels in those bitten by <i>Philodryas</i> spp. Consider the use of neostigmine if paralytic features (e.g., ptosis, dysphagia) develop. <i>Do NOT give antivenom of any kind</i> . Carefully scrutinize the wound and provide early wound treatment if clinically indicated	IE
False water cobra, <i>Hydrodynastes gigas</i> (Dipsadidae) Western hognose snake, <i>Heterodon nasicus</i> (Dipsadidae) Mangrove snake, <i>Boiga dendrophila</i> (Colubridae, Colubrinae)	3	Any patient presenting with a clinically significant bite should be observed in a well-equipped facility. <i>Do NOT give antivenom of any kind</i> . Carefully scrutinize the wound and provide early wound treatment if clinically indicated. There is no current convincing evidence of systemic effects occurring after the bites of any of these taxa, but patients should be carefully assessed and bites from large specimens may produce moderate local “envenoming”	Level III
Garter and ribbon snakes, <i>Thamnophis</i> spp. (Natricidae) and many other taxa of diverse taxonomic affinities	4	Minor local wound care only	Level III

IE insufficient information to provide an evidence ranking

^aThis list contains only some representative species, and risk assignment can only be accomplished for relatively few NFFC. This is due to the absence of acceptably documented clinical information, species identification, and/or other criteria that would constitute a basis for accurate assessment and Hazard Index assignment, as suggested by Weinstein et al. [3]. The presence in ophidian oral secretions/venoms of toxins and/or their transcripts are insufficient criteria for assessment of possible medical significance of a given species as these may be prey-specific and/or may have no medical relevance due to multifactorial influences relevant to both the snake and human victim. There are very likely a number of other NFFC that may have medical significance under some multifactorial circumstances

^bTable after that in Weinstein et al. [1]

^cHazard index is defined as: Level 1 – Serious and potentially fatal envenoming is possible; Level 2 – Systemic envenoming is possible, but uncommon; Level 3 – Usually mild-moderate local effects and usually associated with a protracted bite; Level 4 – Most commonly medically insignificant; larger specimens may inflict minor local effects [3]

^dThis only lists the essential basic management approach; specific cases may require additional interventions. See Weinstein et al. [3] for a detailed discussion of diagnosis, laboratory investigations, and management of medically significant NFFC bites

^eLevels of evidence are defined as follows: I. Evidence obtained from at least one properly randomized controlled trial; II-1. Evidence obtained from well-designed controlled trials without randomization; II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group; II-3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled could also be regarded as this type of evidence; III. Opinions of respected authorities based on clinical experience, descriptive studies and case reports, or reports of expert committees. IE – there is insufficient quality information to provide an evidence ranking. All of the included current information determining evidence levels for diagnosis and management of NFFC envenoming is derived from case reports, low-powered, small series, respected opinion, and personal experience

^fReplacement therapy consists of provision of packed erythrocytes, platelets, cryoprecipitate or fresh frozen plasma, etc. The use of these in coagulopathic envenoming carries risk and remains controversial. Therefore, this should be considered per clinical need (e.g., bleeding risk) on a case-by-case basis

^gThis hazard assignment applies only to the nonnative *B. irregularis* populations that were introduced on Guam and several other Micronesian islands during World War II. These snakes generally reach larger size than that of most *B. irregularis* found in their natural range (coastal New South Wales, Queensland and Northern Territory, Australia; New Guinea, Sulawesi, Togian Islands, Indonesia)



Fig. 9 A typical example of a medically insignificant bite from a NFFC. The effects are limited to minor puncture wounds, slight erythema, and minor bleeding. Some bites also cause mild, transient edema localized to the wound site. The pictured bite was caused by a Kenyan specimen of the speckled sand racer, *Psammophis punctulatus* (Lamprophiidae, Psammophiinae) (Photo copyright to David A. Warrell)

cases of bites by NFFC contain low-quality evidence, and the poor documentation complicates the assessment of evidence-based risk of many species.

This chapter will provide a brief overview of medically important information about those selected NFFC for which there is some reasonable quality evidence.

Clinical Presentation and Evidence-Based Assessment of Medical Risks of NFFC

The medical significance of the majority of NFFC taxa is unknown, and a recent comprehensive analysis of this question emphasized the paucity of well-documented medically significant bites, or “envenoming,” inflicted by NFFC in the literature [3]. Aside from several NFFC that have been carefully observed to inflict serious, life-threatening, and/or fatal envenomings (e.g., *R. tigrinus* [Fig. 5], *R. subminiatus* [Fig. 6], *D. typus* [Fig. 3], *Thelotornis* spp. [Fig. 4], *Balanophis ceylonensis* [Fig. 10]), bite cases ascribed to NFFC predominantly are poorly documented, rely on anecdotal



Fig. 10 The rare Sri Lankan flower blossom krait, *Balanophis ceylonensis* (Natricidae), a Hazard Index 1 species that is closely allied with *Rhabdophis* spp. A recent index case documented the potentially life-threatening coagulopathic effects that may occur from an envenoming by this species. Although there is no clinical evidence that

antivenom against *R. tigrinus* has efficacy in treating envenoming by this snake, any life-threatening envenoming by this taxon should be treated with this antivenom because the benefit to risk ratio is likely favorable, and it could have good therapeutic efficacy (Photo copyright to Daniel E. Keyler)



Fig. 11 The false water cobra, *Hydrodynastes gigas* (Dipsadidae), is a large, heavy bodied species that is popular in private collections particularly in the USA and Europe. These snakes can inflict a painful bite, which can include some locally progressive edema. A published report that described much delayed more serious effects has been critically analyzed, and it was concluded that the

victim experienced somatosensory amplification and/or panic disorder. However, even small specimens such as the juvenile pictured here can inflict painful, edematous bites and should not be taken lightly. Management is restricted to supportive care and meticulous wound management (Photo copyright to David P. Richards)

information, and/or are authored/analyzed by nonmedically qualified contributors, often by the victim himself/herself with highly subjective impressions. Partly as a result of unsupported speculation, a number of taxa have acquired an unwarranted reputation for inflicting potentially fatal bites or have been prematurely viewed as hazardous [1, 3, 27]. Conversely, other NFFC may be prematurely dismissed as “harmless,” when in fact their medical significance is unknown [3, 27]. Many NFFC are popular in private collections, and speculation (especially on the Internet) about their possible ability to inflict medically significant bites is often replete with incorrect information and assumption. Mouse lethal potency studies of venom/oral secretions of NFFC have been used as a basis for such predictions (e.g., that of the false water cobra, *Hydrodynastes gigas*, Dipsadidae; 2.0 [i.p.]–9.4 [s.c.] mg/kg [30]; see Figs. 11 and 12) by comparison with medically important front-fanged species such as the timber rattlesnake (*Crotalus horridus*, Viperidae, Crotalinae) (2.63–3.31 [i.p.]–9.15 [s.c.] mg/kg [31–33]) [1, 18]. There are also other inappropriate and misleading pharmacological comparisons such as neurotoxic potency based on in vitro nerve twitch electrophysiological



Fig. 12 Another member of the genus *Hydrodynastes* is *H. bicinctus* (Herrmann's water snake); this species is infrequently illustrated and, although sought by collectors, is uncommon in private collections. Medical professionals treating bites from privately maintained NFFC must remain cognizant of the occasional acquisition by collectors of species that are often infrequently displayed in zoological parks (Photo copyright to Pedro H. Bernardo)

preparations testing powerful elapid venoms (e.g., that of the common death adder, *Acanthophis antarcticus*, Elapidae) directly compared with those of some NFFC. This is misleading as it simply relates the magnitude of antagonism observed from in vitro nerve-muscle preparation

assays to potential lethal potency in vivo. Such observations can reflect the medical importance of highly potent venoms that contain a high proportion of medically important toxins in a potentially large volume of venom delivered under high pressure with canaliculated fangs, but it is misleading to compare these with NFFC toxins [3, 18]. Aside from the differences in delivery systems and glandular storage/secretion characteristics, another contributing factor to such an inappropriate comparison is the receptor specificity of some colubroid toxins (e.g., greater affinity for avian- or lizard-specific cellular targets as mentioned previously). Most NFFC venoms/oral secretions that have been assayed to date exhibit modal or low lethal potencies in the murine model (see Weinstein and Kardong [10] and Weinstein et al. [3] for comparison of lethal potencies). However, whenever possible, laboratory investigation of NFFC venom lethal potency or other biological activities should consider prey preferences of the species of interest, as some do have high toxicity and potency in some avian and lizard models [34–36], a concern that is also often unaddressed in some studies of FFC venoms.

Verified identification of snake taxa responsible for a given medically significant snakebite is often challenging, but, with bites inflicted by NFFC, this can be a major issue, as it can confuse the assignment of medical risk to the correct species. Aside from the common problem of correct identification even to genus, a significant number of NFFC species may appear similar to FFC, especially to an untrained eye, and some appear as “mimics” of medically significant FFC. This important issue has been discussed and illustrated elsewhere (e.g., Campbell and Lamar [37], Weinstein et al. [1, 3, 27]; see Figs. 13 and 14).

The explosion of popularity of reptiles (especially snakes) and amphibians in the pet industry and among amateur enthusiasts increases the importance of these considerations [1]. It is important that medical professionals are better informed about the potential clinical importance of NFFC termed “mildly venomous” or of those with unknown toxicity [1, 3, 18]. The medically relevant toxicity of oral secretions/venoms in the vast majority of NFFC remains unknown, but



Fig. 13 The false coral snake (*Erythrolamprus aesculapii*, Dipsadidae), an example of a NFFC, “mimic” of a medically important *Micrurus* spp. (Elapidae). Compare with the next figure. False coral snakes occasionally are handled carelessly (especially because they can be easily confused with *Micrurus* spp.), and a few reports describe mild local effects after bites by several species. It should be noted that the oft repeated aphorism, “red to black venom lack, red to yellow, kill a fellow,” and its variants only is *somewhat* applicable in the continental USA, and occasional *Micrurus* spp. specimens in the USA may have wholly different color phases (e.g. melanistic, aberrant patterns). Latin American *Micrurus* spp. do not exhibit any such defined pattern association with the “venomous state” (Photo copyright to Fabio Bucarechi)

there are likely taxa of several subfamilies that secrete venoms of clinical importance. Some large adult NFFC with modal or low lethal potency may also pose a risk to pediatric or geriatric patients and to those with chronic illness and/or multiple comorbidities [1, 3, 18]. Therefore, a medically qualified, patient-centered, evidence-based approach is crucial when conducting a medical risk assessment of NFFC based on published information, as well as personal clinical experience [3].

An Overview of Medically Important NFFC and Management of Their Bites

A patient-centered critical analysis of bites inflicted by NFFC found that only a small number of species (around 120 taxa) have been documented with clinical content acceptable for qualified medical assessment (Table 3) [1, 3]. Most cases were of insignificant or mild local effects (e.g., puncture wounds, abrasions, lacerations, limited bleeding, and mild edema; see Fig. 9). Only



Fig. 14 A Brazilian specimen of the southern coral snake, *Micrurus frontalis* (Elapidae), a medically important FFC that is responsible for a significant number of postsynaptic neurotoxic envenoming particularly in Brazil. These snakes can be (and have been) mistaken for several species of medically unimportant NFFC, which possess very similar pattern colors, and are thus “mimics” (see Fig. 13). Conversely, the NFFC mimics can be likewise mistaken

for several *Micrurus* spp. Accurate identification of a snake deemed responsible for a presenting patient’s bite is essential because the absence of correct identification can prevent the delay of life-saving intervention or, in contrast, may cause the administration of unnecessary treatments thereby exposing the patient to avoidable risk (Photo copyright to Fabio Bucarechi)

approximately 24 species-inflicted bites produced medically significant effects, and bites from an additional 31 taxa have produced nonprogressive mild local pathology insufficient to be tabulated as “medically significant,” but were ranked because of the near significance of their respective presentations. A small number of reports described bites producing moderate local effects that occasionally resulted in persistent symptoms.

The available information about the evidence-based medical risks posed by NFFC taxa are most conveniently considered by grouping those with a reliable database into broad categories defined by their degree of medical risk (Table 3). Thus, these groups are defined as “Hazard Index” 1–4.

Hazard Index 1

The life-threatening risks of venomous colubrine genera such as *Dispholidus typus* and *Thelotornis* spp. (African bird, twig, tree, or vine snakes) and

that of natricids such as two taxa of Asian keelbacks or flower snakes, *Rhabdophis* (*R. tigrinus*, tiger keelback or Yamakagashi, and *R. subminiatus*, red-necked keelback; see Figs. 3, 4, 5, and 6), are well established by unequivocal clinical evidence (Table 3). Bites from these species cause consumptive coagulopathy/disseminated intravascular coagulopathy (DIC) and hemorrhagic diathesis, complicated in some cases by acute kidney injury (most likely from prerenal effects, although direct nephrotoxicity is possible), and are thus designated “Hazard Index or Level 1” (Table 3) [1, 3].

Recently, a single report [38] carefully detailed a patient envenomed by the uncommon and poorly known monotypic natricid, *Balanophis ceylonensis* (Sri Lankan “flower” or “blossom krait”; see Fig. 10). The patient developed a serious consumptive coagulopathy with active bleeding [38], which is similar to that caused by envenoming by *Rhabdophis tigrinus* or *R. subminiatus*, close taxonomic relatives of this little-known taxon.

Fig. 15 The genus *Rhabdophis* (Natricidae) contains approximately 21 species, and two of these, *R. subminiatus* and *R. tigrinus*, are medically significant with the latter responsible for human fatalities. However, the medical relevance of the remaining members of the genus currently is unknown. Pictured is *R. conspicillata* (red-bellied keelback; Photo copyright to Indraneil Das)



Fig. 16 Another little-known *Rhabdophis* spp., *R. murudensis* (Gunung murud keelback). The medical significance of this taxon remains unknown (Photo copyright to Indraneil Das)



The common name used for *B. ceylonensis*, “flower krait,” should not lead to confusion of this NFFC of the family Natricidae with the elapids, *Bungarus* spp. (kraits). Shared or similar common names are often used for vastly different snakes, and identification of any snake involved in snakebite accident must be determined, whenever possible, by an individual qualified to identify the specimen when available or from a reasonable quality photo. In some cases when there are no available data about the snake, a combination of clinical manifestations and the most likely snake species found in the region of the incident may provide some guidance for presumptively assigning the taxon responsible for the bite.

It should also be noted that there are some 21 taxa of *Rhabdophis* (see Figs. 15 and 16 for

additional examples of *Rhabdophis* spp.) and another closely allied monotype, *Pararhabdophis chapaensis* (Vietnam water snake). Any possible medical significance of these species currently remains uncharacterized and unknown, but all of these snakes must be considered potentially medically important (e.g., capable of inflicting a life-threatening envenoming) until proven otherwise.

Toxins of Hazard Index 1 NFFC and the Pathophysiology of Envenoming

As noted, the clinical effects that result from a significant envenoming by snakes in this group consist of consumptive coagulopathy, generation of thrombi, active bleeding, visceral hemorrhage, thrombocytopenia, intravascular hemolysis,

elevated liver enzymes, notable ecchymoses (particularly severe in dependent anatomical sites; see Fig. 18), and, in some cases, acute renal injury (Table 3, Fig. 17). Although kidney injury most commonly complicates the severely envenomed patient, it may occur in patients who have what appears clinically to be a moderate envenoming and may be related to premorbid occult renal disease and/or individual venom variability or other factors. To date, catastrophic hemorrhage and bleeding has been reported in serious envenoming from *Dispholidus*, *Thelotornis*, and *Rhabdophis tigrinus*, while *R. subminiatus* and the single-documented serious envenoming by *Balanophis* have produced what most

parsimoniously appear to be self-limited consumptive coagulopathy with less severe bleeding [1, 3, 38]. However, the latter two taxa certainly must be considered as potentially lethal species, and there is the possibility that replacement therapy may have lessened the severity of the venom disease, although there is currently no firm evidence to support this.

To date, the toxinology of these medically important species has only been marginally explored. Snake venom metalloproteases (SVMP) and prothrombin activators have been characterized from the venoms of *Dispholidus*, *Thelotornis*, and the two taxa of *Rhabdophis* (Table 2, Fig. 17). It is important to note that

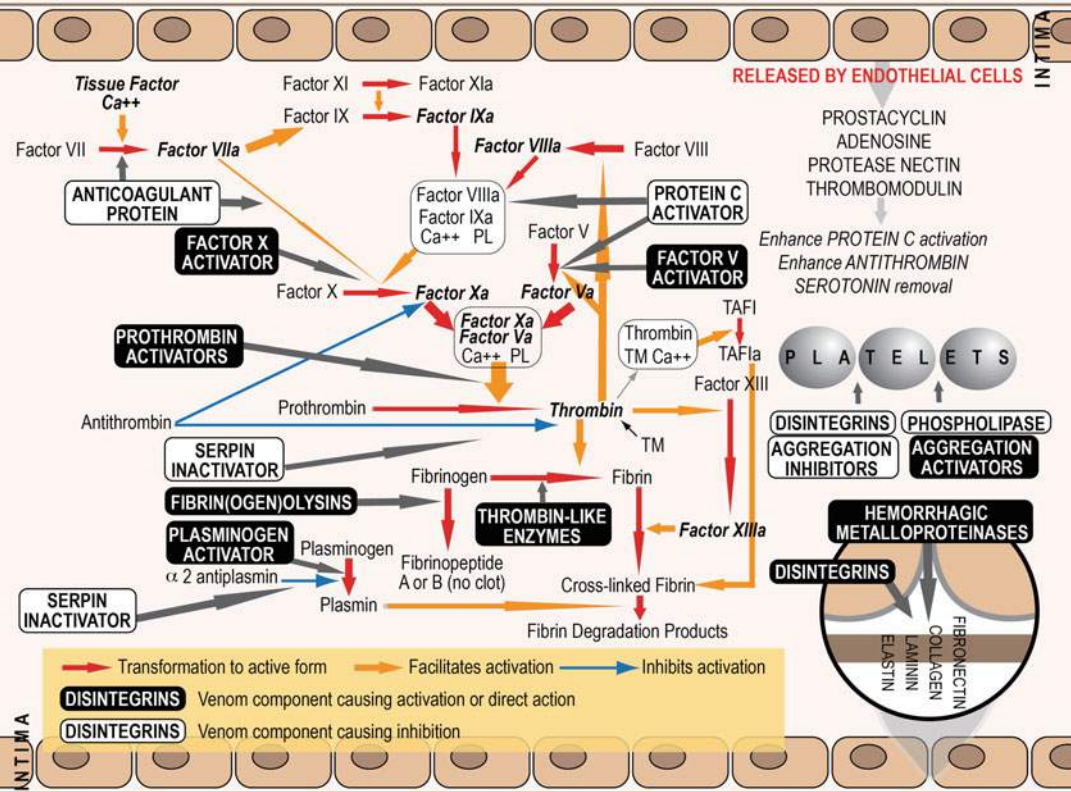


Fig. 17 Simplified outline of the coagulation cascade. Studied venoms and/or toxins of the natricids, *R. tigrinus* and *R. subminiatus*, and the dispholidine colubrids, *D. typus* and *T. kirtlandii*, act as prothrombin activators that function in concert with rhexic hemorrhagins (snake venom metalloproteases, SVMPs, see Table 2). This combined action causes a consumptive coagulopathy and proteolytic disruption of the microvasculature endothelial

basement membrane resulting in leakage from the vascular bed, active, clinically significant bleeding and hemorrhage. Patients seriously envenomed by these Hazard Index 1 species often exhibit extensive ecchymoses especially in recumbent or dependent anatomical sites, bleeding, AKI, thrombocytopenia, and intravascular hemolysis (Figure copyright to Julian White)

Fig. 18 A historical example of extensive dependent ecchymoses in a patient with a life-threatening envenoming by *D. typus* (From EU Schmid Geneeskunde 1962;4)



without the SVMP, the procoagulant, fibrinogen-consuming actions of the venom prothrombin activators would not likely induce the hemorrhagic diathesis commonly featured in serious envenoming by these species, as the SVMP probably cause rhexic disruption of the endovascular matrix, thus allowing uncontrolled vascular leakage per defibrinated blood. It is also likely that other yet uncharacterized venom components play a role in the complex pathophysiological effects of these venoms [3]. Although the toxinology of *B. ceylonensis* venom has not yet been reported, it is likely that it also contains some components similar to those of the medically important and allied *Rhabdophis* spp. This close taxonomic relationship had previously prompted caution about the potential medical significance of *B. ceylonensis* [3].

Important Features of Management of Medically Significant Hazard Index 1 Envenoming*

The essentials of evaluating a patient envenomed by any of these snakes share common features to that of any bite by a venomous snake and are summarized ahead in section “[Medical Risks Posed by Most NFFC Species Have a Notably Limited Evidence Base](#)” (Table 3). *It must be noted that all recommendations included here for management of Hazard Index 1–4 NFFC bites are based on Evidence Level 3.* [*Evidence

Level 3 (see Table 3) is assigned as the evidence for diagnosis and management of NFFC envenoming and is wholly based on case reports; low-powered, small series; respected opinion; and personal experience].

- In the event of a serious envenoming by either *Dispholidus*, *R. tigrinus* or *R. subminiatus*, or *B. ceylonensis*, a prime and early consideration is the need to locate at least 1–2 ampoules of monovalent antivenom (AV) for either *D. typus* (*D. typus* monovalent, South African Vaccine Producers [SAVP, 1 Modderfontein Road, Sandringham, Johannesburg, South Africa, Telephone +27 11 882 9940, Fax +27 11 882 0812, E-mail: savpunit@global.co.za/savpqual@global.co.za], formerly South African Institute for Medical Research [SAIMR]) or *R. tigrinus* (*R. tigrinus* antivenom, Japan Snake Institute, Yabuzuka-honmachi, Nittagun, Gunma Prefecture 379–2301, Japan, Telephone +81 277 78 5193, Fax +81 277 78 5520, e-mail snake-a@sunfield.or.jp). Presently, these are the only commercially prepared and effective AV for any NFFC envenoming and are notoriously difficult to rapidly procure from the manufacturer, although some American and European commercial venom suppliers occasionally have a small on-hand supply.

These AV must only be used for the following species (also see Table 3):

SAVP monovalent anti-*D. typus* AV (Equine, F(ab)₂, liquid preparation, 10 mL, “pepsin refined,” contains 0.35% cresol) – *may only be used to treat envenoming by D. typus. It is ineffective against all other species tested to date including Thelotornis spp.* There have been multiple well-documented fatalities from *D. typus* envenoming that have been recorded since the early twentieth century, and any patient with coagulopathy and active bleeding should receive this AV whenever possible and as promptly as is feasible, a major reason to immediately seek a supply when presented with a patient envenomed by this taxon. This AV has been effective up to 5 days post envenoming.

Japan Snake Institute anti-*R. tigrinus* AV (Caprine or lepid, F(ab)₂, lyophilized, constitute to 10 mL, pepsin digested/salt precipitated) – may be used to treat envenoming by *R. tigrinus*, *R. subminiatus*, and *B. ceylonensis*. This AV has effectively reversed envenoming by the homologous species, while all envenoming by *R. subminiatus* have been successfully managed by replacement therapy or without specific intervention. There is strong likelihood that this AV affords some paraspecific protection against *R. subminiatus* venom. Likewise, because of the close taxonomic alliance among *Rhabdophis* and *Balanophis* (which previously was placed in the genus *Rhabdophis* until it was reassigned as a monotype), there is a reasonable likelihood that *R. tigrinus* AV might have paraspecificity for *B. ceylonensis* venom. Therefore, in the event of a life-threatening envenoming by *B. ceylonensis*, provision of this AV should be considered and provided if it can be procured with the understanding that there is no evidence for or against its use for envenoming by either *R. subminiatus* or *B. ceylonensis*. Patients or their legal family proxy must be fully informed of the essential facts, as well as potential risks and benefits posed by the use of these AV.

- Complete patient medical and social history must include any recent dental work (including dental hygienic procedures such as uncomplicated scaling), recent hospitalization, and/or recent outpatient venipuncture or other procedures; tattoos, piercings, and complete medication (especially anticoagulants, nonsteroidal anti-inflammatories {NSAIDs}); and recreational drug/alcohol use.
- It is important to determine whether the patient maintains a captive reptile collection (this obviously includes lizards), works with snake venoms, or has in the past. Likewise, any previous medically significant snakebites and any previous treatment with AV are essential information. Some of this information (especially the history of involvement in captive reptile husbandry) is occasionally neglected or omitted. Previous exposure to squamate reptile oral secretions (not solely venoms), shed skins, body fluids, and defecate (including solid urates) may predispose to variable sensitization to ophidian antigens, some of which are shared between venoms and body fluids and even occur in excreta (especially in FFC who shed fangs and swallow them, thus later appearing in their excreta). This is not only a laboratory phenomenon, as there is a gathering body of information derived from clinical reports that suggest a role of ophidian antigen atopy in the severity/clinical manifestations of envenoming or even in the degree of individual reactivity to otherwise clinically unimportant NFFC bites [3, 26]. In a small series of eight patients envenomed by either the FFC, *Vipera berus*, or *V. aspis* (respectively, the European viper and the European asp, Viperidae, Viperinae), the development of systemic envenoming was correlated in seven with a sensitized state supported by elevated IgE levels and venom skin testing [39]. The clinical manifestations of a local envenoming by a Hazard Index 3 NFFC, *Heterodon nasicus* (Western hognose snake, Dipsadidae, Fig. 19; also see Fig. 20), included some effects strongly suggestive of localized type 1 hypersensitivity (Figs. 21 and 22) [26]. Cutaneous type 1 hypersensitivity can cause local effects



Fig. 19 The Western hognose snake, *Heterodon nasicus* (Dipsadidae), is a popular species among private collectors in the USA and Europe. This benign species puts on an impressive display of huffing, mock striking and, if all else fails, shamming death. Bites are rare, and almost always result from exposure of the handling person to food items or occur while offering food to the snake. There are only a handful of well-documented bites and most consist of mild local edema and transient pain/bleeding. A few cases have included progressive edema, significant pain, and blistering that resembles mild-moderate local envenoming from a

crotaline viperid (see Figs. 21 and 22). Some of the effects closely resemble localized, cutaneous Type I hypersensitivity, and it is likely that some private collectors become to some extent sensitized to products of captive husbandry (venoms and other oral products, snake defecate, body fluids incorporated on shed skins, etc.), as many contain shared antigens. There is no reason for any considered legal regulation of these or other NFFC that very rarely inflict medically significant bites (Photo copyright to Barney Oldfield)



Fig. 20 The Eastern hognose snake, *Heterodon platirhinos* (Dipsadidae), another of the four species in the genus, is also popular in captive collections but is less frequently maintained because of its more commonly restricted diet (anuran amphibians, particularly toads [e.g., *Anaxyrus* spp.], while *H. nasicus* readily accepts rodents). There are only a couple of well-documented accidental “bites” from this species, which occurred from penetration of an enlarged posterior maxillary tooth (which are nongrooved) into a digit or hand (Photo copyright to Pedro H. Bernardo)

that may resemble the local effects of some snakebites (e.g., erythema with some progression, edema, blistering). This factor that contributes to the clinical manifestations of some snakebites has unfortunately received little qualified attention and/or has been incorrectly dismissed in the literature or on the Internet by medically unqualified opinion. Thus, the related possible previous exposure to squamate reptiles and their antigens is an important part of the collected history.

- Patients with any significant cardiovascular comorbidities (including poorly managed hypertension) should, whenever possible, have cardiac telemetry and regular examination. Patients with preexisting renal disease should have careful, serial renal output and urine protein and creatinine measured. Even simple serial dipstick measurement can detect early, increasing proteinuria.
- Any patients with relevant history, as noted above, should have careful serial examination



Fig. 21 Effects of local envenoming 72 hours after a protracted bite by a Western hognose snake, *H. nasicus*. The patient was bitten while offering food to the snake, and the pictured effects progressively developed over several hours postbite. Note the extensive erythema, edema, and blistering, which could be misinterpreted as resulting from a mild-moderate crotaline viperid envenoming. Some of the effects likely were a result of cutaneous Type I hypersensitivity (also see Fig. 22; Photo copyright to Daniel E. Keyler)



Fig. 22 Effects of local envenoming five days after a protracted bite by a Western hognose snake, *H. nasicus*. Note the focal blistering distant from the bite site (also see Fig. 21). The patient's recovery was not complete for several months (Photo copyright to Daniel E. Keyler)

of the involved anatomical site (careful serial examination of the gingival sulci, recent procedure sites, recent tattoos, etc.) for bleeding. Avoid extended recumbence on a given anatomical region because this may result in extensive ecchymoses; shift the patient periodically and support with wedge pillows as needed.

- Hazard Index 1 NFFC-envenomed patients require serial laboratory testing including activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, complete blood count including platelets, and creatinine and urine protein (as noted above). Initial laboratory tests should also include liver function tests, electrolytes,

blood urea nitrogen, creatinine, and creatinine phosphokinase. Cardiac enzymes (e.g., troponin I) should be included for any envenomed patient with a significant cardiovascular history or any with signs/symptoms suggestive of cardiac involvement. Measured 24 h urine creatinine/albumin should be carefully monitored in any patient with previous (e.g., diabetic nephropathy) or evolving evidence of renal insult.

- A substantial subgroup of patients with life-threatening Hazard Index 1 envenoming may exhibit severe thrombocytopenia, intravascular hemolysis, and/or DIC with active bleeding and/or massive hemorrhage. Some of these patients may require replacement therapy, depending on the specific clinical circumstances (risk of cerebral hemorrhage, massive

ongoing bleeding, etc.) and the likely risk vs. benefit of replacement. There are insufficient clinical data supporting the provision of replacement therapy to patients with sustained consumptive coagulopathy caused by life-threatening envenoming from Hazard Index 1 dispholidines (*Dispholidus* and *Thelotornis*) or natricids (*R. tigrinus*, *R. subminiatus*, nor also in the rare event of a serious envenoming by *B. ceylonensis*) [1, 3]. However, considering the probable prolonged action/persistence of some of the venom prothrombin activators and rhexic hemorrhagins, this may present a therapeutic conflict between the need to treat severe thrombocytopenia/bleeding with replacement therapy in order to lessen the risk of a catastrophic hemorrhage and/or life-threatening anemia and to add additional substrate for toxin action (“throwing fuel on the fire”). Therefore, it is advisable to cross and match and have at the ready several units of packed erythrocytes (PRBC), platelets, cryoprecipitate, and/or fresh frozen plasma (FFP), but the need for provision of these should be carefully evaluated on an individual patient basis (see Table 3).

- Seriously envenomed patients with premorbid history of cardiovascular or renal disease should have early cardiology and/or nephrology consults. Patients who might require emergent dialysis or percutaneous coronary artery intervention present special concerns because of the obvious issue of the need for placement of the catheter in the probable setting of consumptive coagulopathy and the concomitant risk of uncontrollable bleeding (see Figs. 23 and 24). When absolutely necessary, vessels that may facilitate control of bleeding (e.g., sufficient surface for application of significant compression) should be chosen for dialysis access, e.g., a peripherally inserted central catheter placed in the superior vena cava or, in some cases, a femoral line.
- It is important to note that there are several *Rhabdophis* spp. that are also poisonous, as they synthesize secretions from nuchal-dorsal glands that contain steroid toxins (bufodienolides) derived from their anuran



Fig. 23 Brisk bleeding from an angiocatheter site on the extremity of a patient with a life-threatening defibrinating coagulopathic envenoming from an Eastern brown snake, *Pseudonaja textilis* (Elapidae), the most medically important FFC in Australia. Medical professionals managing patients envenomed by Hazard Index 1 NFFC or FFC that cause coagulopathic envenoming must very cautiously perform venipuncture and catheter placement and be prepared to aggressively staunch potentially uncontrollable bleeding. Only clinically essential procedures should be performed in these patients and always at sites that allow some direct pressure, as needed to help control bleeding (also see Fig. 24; Photo copyright to Judy Ou)

prey (toads). A handful of cases of toxin ophthalmia have been reported after ocular contamination with their nuchal gland secretions [40]. There are also other NFFC with unknown medical significance (e.g., *Macropisthodon* spp., also Asian natricids that are commonly called “keelbacks”), which possess nuchal glands with so far uncharacterized products. Management of ophthalmia from exposure to these nuchal gland secretions should consist of aggressive decontamination with large volumes of sterile saline, water, or, ideally, ophthalmic buffered eyewash and additional treatments with cycloplegics, antibiotics, and possibly steroids, as clinically indicated (see Chu et al. [41]). Continuous ophthalmic irrigation can be facilitated with employment of an intravenous saline bag or a Morgan lens.



Fig. 24 Expanding hematoma at the site of a venous catheter placed in a patient with life-threatening coagulopathic envenoming from a coastal taipan, *Oxyuranus scutellatus* (Elapidae). If placement of any catheter, especially a central line, is deemed absolutely necessary in a patient envenomed by any Hazard Index I NFFC or FFC capable of inflicting a coagulopathic envenoming, a site must be selected (e.g., a peripherally inserted central catheter [PICC] placed in the superior vena cava or, in some cases, a femoral line) that might facilitate control of active bleeding. Although associated with a lower infection rate than that of PICC/femoral lines, the subclavian or internal jugular routes should be avoided, as these do not allow effective control of the brisk bleeding that is likely to occur under the circumstances of defibrinating coagulopathic envenoming (Photo copyright to Julian White)

Hazard Index 2–3 NFFC: Features of Well-Documented Bites

There are few well-documented data about bites by several NFFC species that have been suspected of inflicting significant local envenoming that in uncommon cases have included systemic effects. However, one of these, the brown tree snake, *Boiga irregularis* (Fig. 25), has been involved in a larger series of extensively documented medically significant bites. This is a consequence of the larger-sized individuals that comprise populations of *B. irregularis*, which were accidentally introduced to Guam and several other Micronesian islands during the Second World War (see Table 3). These snakes constitute a significant medical risk to neonates and infants (especially on Guam) and may rarely inflict bites that cause systemic effects including respiratory

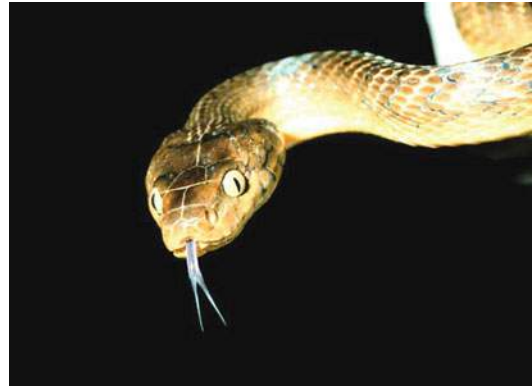


Fig. 25 The brown tree snake, *Boiga irregularis* (Colubridae, Colubrinae). Accidentally introduced to Guam and other Micronesian islands during the Second World War, this invasive species has been subject of largely ineffective control measure by several Acts of Congress. It poses distinct problems wherever it occurs because large individuals attempt predation on infants, and >400 bitten victims have been presented to hospitals on Guam including several infants with systemic effects either from venom and/or constriction by these snakes (Photo copyright to Gordon Rodda)

insufficiency or failure that may be a result of venom or asphyxiation by constriction (*B. irregularis* are powerful constrictors) or a combination of both. Of some 400+ well-documented cases, there are currently known approximately five pediatric patients who exhibited systemic effects after a *B. irregularis* bite [3]. Neurotoxicity in humans is unlikely given that the known neurotoxins of this species are highly specific for lizards and birds, the natural prey of these snakes (see Tables 2 and 3). To date, the etiology of the clinical syndrome involving *B. irregularis* bites inflicted on a small subset of neonates or infants remains incompletely characterized. However, as these snakes can, on very rare occasion, inflict systemic effects in pediatric victims, they must be classed as Hazard Index 2–3.

The two remaining taxa included in this index also have inflicted bites that may cause well-documented, but rare systemic effects. Medically significant bites by the South American green racer, *Philodryas olfersii* (Dipsadidae, Fig. 8), most commonly cause mild to moderate local effects (progressive edema, erythema,



Fig. 26 An example of local effects that commonly occur after a protracted bite from Lichenstein's racer, *Philodryas olfersii* (Dipsadidae). This patient presented with a clear bite site and developed mild local erythema and slight edema (Photo copyright to Fabio Bucaretti)

ecchymoses, and uncommon blistering, Figs. 26 and 27), but at least two well-documented cases showed that widespread ecchymoses distant from the bite site could occur (e.g., Figs. 27 and 28), thus providing evidence of systemic envenoming. However, although there have been anecdotal reports of "coagulopathy" purportedly resulting after medically significant *P. olfersii* bites, so far there has been no documented evidence of coagulopathy in qualified, documented clinical reports [1, 3]. There are approximately 22 species of *Philodryas*, and there is well-documented information regarding the medical effects of bites for only four species with medically significant envenoming reported for only *P. olfersii* and *P. patagoniensis* (Fig. 29) [3]. As previously noted in regard to the unknown medical risks of other species of *Rhabdophis*, the remaining *Philodryas* spp. (e.g., see Figs. 30, 31, and 32) should be viewed cautiously until there is well-documented information about their potential to inflict medically significant envenoming.



Fig. 27 Marked ecchymoses after *Philodryas olfersii* envenoming. The patient was bitten on the right hand and developed extensive, widespread ecchymoses distant from the wound. There was no reported coagulopathy (also see Fig. 28; Photo copyright to Fabio Bucaretti)



Fig. 28 Evidence of systemic envenoming by *Philodryas olfersii*, view of the right axilla of the patient shown in Fig. 27. The patient was bitten on the right hand and developed extensive, widespread ecchymoses distant from the wound. There was no reported coagulopathy (Photo copyright to Fabio Bucaretti)

There is also a single well-documented case [42] of transient cranial nerve (CN) palsies (probably CN III, IV, and VI) that was caused by an envenoming from *M. monspessulanus* (Montpellier snake, Lamprophiidae, Psammophiinae, Fig. 33) in France and established the potential danger associated with bites from this species (also Hazard Index 2–3, Table 3). To date, this is the only NFFC species that has inflicted a



Fig. 29 The Patagonian racer, *Philodryas patagoniensis* (Dipsadidae), another *Philodryas* spp. with some limited medical importance. To date, unlike its congener, *P. olfersii*, there are no well-documented cases of systemic effects after bites by this taxon (Photo copyright to Fabio Bucaretschi)



Fig. 30 Baron's racer, *Philodryas baroni* (Dipsadidae), a *Philodryas* spp. popular in private collections, particularly because of the attractive color variants (e.g., green, blue, etc.). There are only a few documented bites by this species, and so far these have only included mild local effects (Photo copyright to Pedro H. Bernardo)

clinically convincing, thoroughly documented neurotoxic envenoming [1, 3].

Provision of neostigmine and atropine should be considered for any Hazard Level 2/3 envenoming that presents with symptoms/signs consistent with neurotoxicity (neostigmine 0.03–0.07 mg/kg, i.v. x 1, total dose not to exceed 5 mg; atropine 0.6–1.2 mg i.v. per each 0.5–2.5 mg neostigmine; pediatric dose of neostigmine is the same as the adult dose; pediatric dose of atropine is 0.02 mg/kg for



Fig. 31 The striped sharpnose snake, *Philodryas argentea*. There are no documented bites by this *Philodryas* spp. (Photo copyright to Pedro H. Bernardo)



Fig. 32 The Paraguayan green racer, *Philodryas nattereri*. There are no well-documented bites by this *Philodryas* spp. (Photo copyright to Pedro Bernardo)

each 0.04 mg/kg neostigmine). Atropine administration in patients with bradycardia should immediately precede or be simultaneous with the neostigmine [or other cholinesterase inhibitor].

Hazard Index 3 NFFC: Features of Well-Documented Bites

Available quality evidence and personal experience so far suggest that many NFFC genera occasionally inflict bites that cause mild to moderate local effects, but most of these species have no medical importance. Rarely, protracted bites from the Western hognose snake (*H. nasicus*,



Fig. 33 The Montpellier snake, or hooded malpolon, *Malpolon monspessulanus*, Lamprophiidae, Psammophiinae. This psammophiine is the only NFFC so far to inflict a well-documented envenoming that caused cranial nerve palsy. The victim had placed his fingers into the mouth of the snake and received a protracted bite (Photo copyright to Julian White)

Dipsadidae; see previous sections) [26], the Puerto Rican racer (*Borikenophis* [*Alsophis*] *portoricensis*, Dipsadidae), some larger specimens of *Boiga* spp. (Colubridae, Colubrinae; see Figs. 34, 35, and 36), and *Leptodeira* spp. (cat-eyed snakes, Dipsadidae, Fig. 37) [43] may result in medically significant local effects of moderate severity (e.g., more evidence of higher modified objective pain scores, locally progressive edema, blistering, etc.; see Fig. 38). However, even juvenile specimens of some NFFC species (e.g., false water cobras, *H. gigas*, Dipsadidae; see Fig. 11) can inflict local envenoming with progressive edema and significant local pain [44]. Likewise, *Philodryas patagoniensis* inflicted a handful of well-documented bites that caused mild to moderate local effects, but so far there has been no documented evidence of coagulopathy or any other systemic effect, unlike the widespread ecchymoses that occasionally occur after envenoming by its congener, *P. olfersii* (see Figs. 27 and 28) [1, 3].

It is noteworthy that of the approximately 32 species of *Boiga* spp., only a few well-documented bites have been recorded involving seven taxa. As noted earlier, only *B. irregularis* has been identified as a medically important



Fig. 34 Mangrove or ringed cat eye snake, *Boiga dendrophila* (Colubridae, Colubrinae). The most common *Boiga* spp. in private collections; this species is popular among USA, European, and Asian collectors. Although there are undoubtedly quite a few collectors who have been bitten by this species (including the author), only a few well-documented bites have been reported, and these have consisted of mild-moderate local effects and, rarely, progressive local edema (Photo copyright to Taksa Vasaruchapong)



Fig. 35 The green cat eye snake, *Boiga cyanea* (Colubridae, Colubrinae). Another frequently collected *Boiga* spp.; the very few reported bites have been so far limited to mild local puncture wounds, brief bleeding, and mild local pain. The pictured specimen has notable damage to the rostral scale, a problem that may occur in captive specimens maintained in cages with screens or irregular surfaces (Photo copyright to Taksa Vasaruchapong)

member of the genus. During the last decade, an increased number of *Boiga* spp. has entered the commercial snake trade. Previously, mostly *B. dendrophila* ssp. (mangrove or gold-ringed cat snakes, Fig. 34) and *B. cyanea* (green cat snake, Fig. 35) were imported into the USA,

Western Europe, and some Asian countries, and these species remain the most popular in private collections. To date, there are only a few well-documented reports describing the effects of their bites, which included only mild to moderate local pain, edema (which may be progressive), and erythema [1, 3, 43]. Although there is limited information about the possible effects of bites inflicted by other members of the genus, for reasons discussed earlier, it is important not to prematurely base unproven medical significance of these on murine lethal potency data, nonclinically derived information such as chromatographic profiles, or by using purely in vitro observations obtained from studying their venoms/oral secretions [1, 3, 18].



Fig. 36 The white-spotted cat eye snake, *Boiga drapiezii* (Colubridae, Colubrinae). There are thus far no well-documented bites by this species (Photo copyright to Taksa Vasaruchapong)

Fig. 37 The rain forest cat eye snake, *Leptodeira frenata* (Dipsadidae). There is a documented case of local envenoming by this species. The victim was bitten on the third digit of the right hand and experienced significant local pain, progressive edema that involved the hand and lower forearm, and blistering (see next figure, Photo copyright to Rowland Griffin)



Hazard Index 4 NFFC: Features of Well-Documented Bites

This category contains the majority of NFFC species that have inflicted bites and for which there is some reasonable quality documented evidence. These taxa so far inflict bites that cause mild pain limited to the bite site, some minor bleeding, and mild erythema. Some cause mild local edema, but this may also include the effects in some individuals of local type 1 hypersensitivity. In addition, some medically unqualified anecdotal accounts of “persistent bleeding” after bites by some Hazard Index 4 species are most likely a result of the dentition morphology of many of these snakes, which produce wounds that have irregularly opposed disrupted epidermal planes [3]. These wounds may be disposed to the slowed formation of a fibrin clot, especially if complicated by a protracted grip that often may inflict “raking” wounds that occur during the common withdrawal reaction of a bitten victim. Of course, there is always the possibility that some of these snakes may have venom or other oral products that could contain anticoagulant components that inhibit local clotting, but, to date, there is no evidence of this in any medically qualified report documenting bites, or in bitten patients personally examined, by those species classed here as Hazard Index 4 [1, 3]. Representative Hazard Index 4 genera include the common North American natricids, *Thamnophis* (garter snakes and ribbon

snakes; see Fig. 39; this genus is not to be confused with any of the ten species of African garter snakes (*Elapsoidea* spp., Elapidae), which are all FFC) and *Nerodia* (water snakes). Some clinicians, especially in the Northeastern USA, are occasionally presented with a patient who claims incorrectly to have been bitten by a “cotton-mouth” or “water moccasin,” *Agkistrodon piscivorus*, Viperidae, Crotalinae, because the

snakebite occurred in location nowhere near even extralimital extensions of the *A. piscivorus* range. Although on rare occasions, this is a result of a bite inflicted by an illegal specimen in a private collection or even one released in a location out of the natural range of the species; most of the time, it is a result of misidentification of a *Nerodia* spp. for *A. piscivorus*. Some *Nerodia* spp. readily bite when disturbed and can inflict multiple, painful, bleeding wounds. The colubrine colubrids, *Coluber* (American and Neotropical racers and whip snakes; this now purely New World genus previously contained numerous taxa that have been correctly reassigned to numerous other genera, which especially occur in the Old World), are similarly comprised of approximately 12 species and some of these readily bite when handled or restrained. Resulting wounds typically feature mild pain, local bleeding, erythema.

Many diverse species of snakes are called “racers” or “whip snakes,” and identification must be ascertained as specifically as possible because common names are often shared by numerous taxa. Therefore, it is important to seek the biological/taxonomic history of NFFC snakes involved in any medically significant bite because this can provide information that may aid the management of the afflicted patient.



Fig. 38 Right hand of victim 4.5 days following local envenoming on third digit by the rain forest cat eye snake, *Leptodeira frenata*. The victim experienced rapidly progressive edema, pain, and blistering. Local arthralgia persisted for almost five weeks (Photo copyright to Rowland Griffin)

Fig. 39 The common garter snake, *Thamnophis sirtalis sirtalis* (Natricidae), a species very commonly kept in North American and European collections. Most bites from these snakes produce uncomplicated puncture wounds, variable mild bleeding, and mild pain. There are occasional, rare bites that cause some local edema and erythema (Photo copyright to Christopher E. Smith)



The NFFC Bitten Patient: A Summary of Assessment and Special Considerations*

(*All of the included current information is Evidence Level 3 (see Table 3). Assessment of evidence for diagnosis and management of NFFC envenoming is thus wholly based on case reports; low-powered, small series; respected opinion; and personal experience.)

First Responder/First Aid

Although there are no evidence-based first aid recommendations applicable for NFFC bites, in general, most recommendations for snakebites are still advisable (see Warrell [29], Weinstein et al. [45], Kanaan et al. [46]). However, specific recommendations for NFFC bites/envenoming were evaluated and summarized by Weinstein et al. [1, 3].

The patient should be kept as calm as possible – death from NFFC bites are rare – and the victim should refrain from ambulation to whatever extent possible. Provide fluids (not orally if possible), but withhold food. To whatever extent possible, protect the wound(s) from environmental contamination. Apply a splint to the affected limb, position below heart level. Arrange urgent transport to the nearest medical facility and call ahead. This is especially important in Hazard Level 1 NFFC envenoming because of the aforementioned scarcity of AV for the few species covered, or potentially covered by these products, which are very difficult to procure.

As in any snakebite, all jewelry (hands, wrists, feet, and ankles) should be removed in order to decrease the risk of digital ischemia in the event of progressive edema, and any recent site of dental work, piercing, or tattoos must be carefully scrutinized with any bleeding temporarily managed with carefully applied pressure. Alcohol and any recreational drugs are obviously contraindicated, and, if the patient has any comorbidity, these must be carefully considered along with the continued intake of essential medications (e.g., anticoagulants such as warfarin, or

platelet inhibitors including low-dose aspirin, as well as medications carrying a risk of prerenal effects or bleeding [e.g., NSAIDs], will have to be discontinued until the envenoming has been successfully managed).

If a victim bitten by a Hazard Level 1 NFFC is >2 h transport from a medical facility, application of a pressure pad or use of pressure bandage immobilization (PBI) could be beneficial, although the victim must be informed that this first aid measure is unproven in management of NFFC envenoming and that there is no evidence about the risk vs. benefit of this intervention. It should also be noted that some NFFC bites, including those from Hazard Level 1 species, could cause significant local effects that could be exacerbated by pressure immobilization methods. This is why the important features of the envenoming and associated circumstances must be carefully considered prior to the use of this intervention. Consideration must be given to the likelihood of systemic vs. predominantly local effects, the travel time to hospital, and the availability/ability to rapidly procure AV.

If PBI/pressure pad is performed, it is most important to reasonably occlude local lymphatic drainage, but beware of excessive pressure, as vascular return must not be compromised, and too much local pressure might induce massive ecchymoses/vascular leakage. Although there is no current firm evidence of specific benefit, in an emergent situation, the use of a portable sphygmomanometer (if available) could facilitate this needed balance by maintaining the pressure on the wound site to between 50 and 60 mmHg. Otherwise, this could be roughly approximated by careful application of an elastic bandage or pad with the edge of the application barely allowing a fingertip to slightly lift the edge. The management team should remain cognizant of the possibility on release of the pressure pad or PBI of a sudden release of sequestered venom (“proximal venom surge”). Therefore, serious envenoming managed initially with PBI or pressure pads should be viewed as requiring the prompt availability of AV, whenever possible as clinically indicated, in order to begin AV administration prior to removal of the immobilizing method.

Cryotherapy/ice application, NSAIDs, illicit drugs/alcohol of any kind, constricting ligatures, incision/suction, or any other kind of interference with the wound are contraindicated.

For bites from Hazard Level 2/3 species, the aforementioned pressure pad/PBI should be considered for significant bites by either of the two *Malpolon* spp., or the related *Rhagerhis* (*Scutophis*, Barata et al. [47]; *Malpolon*, Largen and Spawls [48]) *moilensis*, although, as noted previously, only *M. monspessulanus* has inflicted a single well-documented neurotoxic envenoming.

For bites from Hazard Level 4 species for which there is significant documented evidence, most commonly all that is required is thorough irrigation of the wound (mild soap and water are all that is needed) and basic wound dressing. In the event of more medically significant bites from Level 4 species, the victim should receive comprehensive review, as noted for the more medically important, higher-risk index taxa.

Important Considerations

See previous section entitled, “[Important Features of Management of Medically Significant Hazard Index 1 Envenoming](#),” as well as the section “Important Features of Envenoming” for Hazard Levels 2/3 and 4.

Any significant Hazard Index 1 envenoming, or progressive Index 2/3 envenoming, should prompt consultation with an experienced clinical toxinologist or medical toxicologist familiar with snakebite envenoming.

Indications for Antivenom

As described above, the only AVs available for any NFFC envenoming are against D. typus and R. tigrinus. AV against R. tigrinus probably has paraspecific neutralizing activity for R. subminiatus and, possibly, B. ceylonensis venom and should be used whenever possible in any case of life-threatening envenoming by these

two species. To date, there is only animal experimental data-based evidence of the paraspecificity for *R. subminiatus* venom, and all well-documented envenoming by this taxon have been successfully managed with either replacement therapy (see ahead) or have simply been observed with subsequent spontaneous resolution. As mentioned earlier, possible paraspecificity of this AV against *B. ceylonensis* venom is hypothetically based on the close relationship between these genera and the similarity of the single well-documented serious envenoming inflicted by this species with that of *R. tigrinus* and *R. subminiatus*.

It is essential to note that there is no AV for any other NFFC species, including the Hazard Level 1, *Thelotornis* spp., and no evidence of any efficacy of any other AV for bites by any other NFFC taxa. This includes the known medically important two taxa of *Philodryas* (*P. olfersii* and *P. patagoniensis*) for which there are a few data suggesting some in vitro neutralization of venom hemorrhagic activity, but for which there is no evidence of clinical efficacy of any AV. Also, so far there is no well-documented envenoming by these species that would necessitate provision of AV even if an effective preparation were available.

Therefore, aside from the Hazard Level 1 species specifically described above, no AV should be given for any other NFFC.

Efforts to obtain AV must begin early, as the procurement of these scarce AV is notoriously difficult (and markedly expensive). The indications for AV in Hazard Level 1 envenoming include:

Evidence of coagulopathy including active bleeding (gingiva, persistent bleeding from wound site(s), recent surgical sites, recently shaved skin, persistent epistaxis, lacerations/injuries, tattoos, hemorrhoids, or piercings, hematemesis, hematuria, etc.).

Abnormal lab tests indicative of serious envenoming (abnormal PT/aPTT/INR), thrombocytopenia or trend of decreasing platelet counts; intravascular hemolysis, abnormal renal function tests, etc. Abnormal tests can include >20 min whole blood clotting assay (in the circumstance of unavailability of

instrumented laboratory testing), although this test may have poor sensitivity/specificity under certain circumstances and its accuracy for clinical diagnosis in NFFC Hazard Level 1 envenoming is so far undocumented.

Clinical evidence of serious systemic envenoming as noted in results of physical examination or vital observations such as an isolated systolic hypotension, diaphoresis and tachycardia (e.g., early signs of impending shock), the aforementioned signs of active bleeding, etc.

Any patient with cardiovascular comorbidities including history of stroke or myocardial infarct must be closely monitored (with telemetry whenever possible), a baseline electrocardiogram obtained, and, when indicated, cardiac enzymes serially monitored before and after receiving AV.

Provision of antivenom

- A. Large-gauge IV access for fluids; provide fluid bolus and repeat as clinically indicated.
- B. Anaphylaxis protocol with crash cart must be in place *before* the administration of AV.

Antivenom dosing and administration:

- For *D. typus* envenoming, dilute one vial (10 mL) of *D. typus* AV in 250 mL saline, and infuse intravenously initially 60–100 mL per hour. Carefully monitor patient for any signs of adverse reactions (e.g., hypotension, maculopapular rash [often first appears on trunk and centrifugally spreads], bronchospasm, fever, etc.). If there is no adverse reaction, administer the entire dose within 30 min.
- For *R. tigrinus*, *R. subminiatus*, or *B. ceylonensis* envenoming, reconstitute one vial of lyophilized *R. tigrinus* AV in 10 mL saline (*do not shake or agitate*; only very gently swirl to facilitate optimum dissolution), and dilute in 250 mL saline. Administer and monitor the patient as noted for provision of *D. typus* AV.
- If possible, obtain an additional vial in case a larger dose is required for particularly severe envenoming. Most well-documented cases

have required only a single vial of either AV, but there have been several patients severely envenomed by *D. typus* or *R. tigrinus* that have required two or (rarely) more vials. Both AVs have shown clinical efficacy for up to 5 days after the initial presentation.

- As previously described, so far there has been only a single well-documented neurotoxic envenoming from a NFFC bite (from *M. monspessulanus*), although the envenomed patient experienced only transient cranial nerve palsy without any evidence of descending paresis; the possibility of a more severe paralytic envenoming by this taxon (or other related or yet other medically uncharacterized species) must be considered. Therefore, even though intubation and ventilation have so far been unnecessary in management of a neurotoxic NFFC envenoming, the lack of any AV for NFFC species (so far only this single psammophine lampprophiid) likely to inflict such an envenoming suggests that in the event of descending paralysis after an envenoming by *M. monspessulanus*, intubation and ventilation may be necessary in some patients.
- Any patient seriously envenomed by a Hazard Level 1 species and those with less severe envenoming but with cardiovascular, hematological, and/or oncological comorbidities should be admitted to the intensive care unit.
- Wound care and supportive management (e.g., fluid resuscitation, nonsedating analgesia) should be promptly provided and the clinical response to treatment carefully monitored.

Special Populations (Seriously Envenomed Pediatric and Pregnant Patients)

- Pediatric patients should receive the same antivenom dose as an adult, and severely envenomed children may require larger amounts.
- Pregnant patients should also receive the same antivenom dose and should have closely

scrutinized cardiotocography (CTG, fetal heartbeat and uterine contraction monitoring) and serial review by an obstetrician, preferably with experience with high-risk patients. It is relevant to note that there has been little formal investigation of the pharmacokinetics of antivenom when provided to pregnant patients. Although studies of most pharmaceuticals provided to pregnant patients have shown that bioavailability remains essentially unaltered, it is unclear if this also applies to antivenom. It is possible that through changes in the volume of distribution and clearance, pregnancy might cause an increase or decrease in the terminal elimination half-life of pharmaceuticals that have not been thoroughly studied in pregnant women [49]. This could include antivenom, and thus some seriously envenomed pregnant patients may require larger doses of antivenom. It is noteworthy that in a pharmacokinetics study of three monospecific antivenoms against Malayan pit viper (*Calloselasma rhodostoma*), the total apparent volume of distribution for each antivenom was 1.5–3 times larger than that of the central compartment [50]. This suggests the occurrence of significant tissue distribution in addition to complex formation, and this could be a factor of increased significance for some envenomed pregnant patients especially in the second and third trimesters.

Indications for and Concerns Regarding Replacement Therapy

Some patients envenomed by Hazard Index 1 species have on occasion been provided with FFP, cryoprecipitate, PRBC, platelets, and/or fibrinogen.

Fresh Frozen Plasma and Cryoprecipitate

The use of these products in life-threatening envenoming by Hazard Level 1 species has been critically reviewed with the conclusion

that there is so far insufficient evidence to recommend inclusion of FFP, cryoprecipitate, or fibrinogen in the standard management of envenoming by these taxa because there is no clear benefit, and possibly increased risk, associated with their use [3]. Some patients with life-threatening envenoming by Hazard Index 1 NFFC species (particularly by *R. subminiatus* and *R. tigrinus*) have been given prodigious amounts of FFP and/or cryoprecipitate [3]. However, there may be patients who present with notably increased bleeding/massive hemorrhage risk, and judicious use of these (with AV whenever possible; see ahead) *may* be clinically justified. In most snake venom-induced coagulopathy (from envenoming by FFP and NFFC), fibrinogen levels are often undetectable for some 12–24 h post envenoming but usually become detectable 24–36 h post envenoming [51–53]. However, some hypofibrinogenemic patients may require cryoprecipitate if fibrinogen is <100 mg/dL (3 μ mol/L) and/or there is clinically significant hemorrhage [54].

The use of these products in the setting of life-threatening snake venom-induced coagulopathy raise concerns about adding substrate for the continued action of procoagulant toxins, e.g., “throwing fuel on the fire,” as well as increased risk of exposure to blood-borne pathogens and bacterial contamination [3, 54]. As noted above, most well-documented cases of Hazard Index 1 NFFC envenoming that have included provision of these products have demonstrated no clear therapeutic benefit from these interventions. However, some patients envenomed by *R. subminiatus* and *T. capensis* have recovered after being managed with replacement therapy including, in some cases, FFP and/or cryoprecipitate [3]. It remains unclear whether these patients clinically benefitted from this therapy or rather had simply received self-limiting, non-life-threatening envenoming.

As previously emphasized, management of life-threatening envenoming by *D. typus*, *R. tigrinus*, *R. subminiatus*, and *B. ceylonensis* should whenever possible include the central use of appropriate AV for these species.

Although there is little quality evidence supporting the provision of FFP or cryoprecipitate in consumptive coagulopathic envenoming, one group of investigators have suggested that the provision of FFP may provide some benefit in the management of defibrinating coagulopathic envenoming from an Australian elapid (*Pseudonaja textilis*, Eastern or common brown snake) provided it is given with AV and within 4 h of the envenoming [55]. Further careful study of this question is desirable.

Packed Red Blood Cells

Packed red blood cells should be provided if the patient develops significant anemia, and the threshold for transfusion should not strictly conform to standard protocol, but should be determined by the individual patient's cardiovascular, perfusion, respiratory, and oxygenation status. Some patients with serious Hazard Index 1 envenoming have required >10 units of PRBC.

Platelets

Likewise, platelet infusions should be provided as indicated by clinical need and individual bleeding risk of a given patient. There is no uniform consensus on platelet transfusion thresholds, but patients who develop thrombocytopenia often show a rapid reduction in platelet levels that may remain below 50,000/mm (normal adult range: 150,000–400,000) [3] for as long as a week or even more [53]. Platelet infusions rarely shorten or notably improve the duration of snake venom-induced thrombocytopenia [3], but the provision of infused platelets is necessary if the patient spontaneously bleeds or has an increased risk of clinically significant bleeding. The threshold for prophylactic provision of platelets varies on circumstances and patient morbidities and can range between 5,000 and 100,000/mm [3] [56, 57]. Patients with marked and persistent thrombocytopenia require frequent neurological monitoring because these patients are at increased risk for a fatal outcome. Non-contrast

computerized tomographic study of the head should be performed in any patient with altered sensorium in the setting of a severe coagulopathic envenoming because of the increased risk of central nervous system bleeding. A well-known and tragic example of this is the hemorrhagic infarct that caused the death of the esteemed, historically important herpetologist, Robert F.W. Mertens, after severe envenoming from a *T. kirtlandii* [58].

General Treatment Considerations

Serial assessment of INR, renal function, and platelets is essential (e.g., reversal of prolonged INR is sufficient to withhold any additional AV that might be available, but INR must be monitored for at least 3–4 days after severe envenoming, and sometimes longer) (Table 3). Serious envenoming by any of the Hazard 1 Index taxa requires ICU admission, close monitoring, and extended serial laboratory assessments.

Compartment syndrome requiring surgical intervention is a rare complication of some (mainly viperid) snakebite envenoming that may be confused with direct venom-induced muscle necrosis or myositis. One patient with local envenoming from a Hazard Level 3 NFFC species (*Philodryas viridissima* Wallach et al. 2014] *viridissimus*; green palm snake; common green racer, Dipsadidae) was probably subjected to an unnecessary fasciotomy because of the aforementioned confusion [3]. In addition to serial clinical evaluation, a Stryker[®], wick catheter, or other intracompartmental pressure measurement >30 mmHg is required for diagnosis of any suspected compartment syndrome. If this equipment is unavailable, even a bedside Doppler measurement may help resolve clinical suspicion. In the rare event that envenoming-induced compartment syndrome is present, urgent surgical consultation is required. It must be noted that the pressure threshold for defining compartment syndrome varies among different surgical specialties. For instance, several vascular and orthopedic surgeons informally indicated that they, respectively, used intracompartmental

pressures ranging between 30 and 35 mmHg, or 35 – >40 mmHg, as thresholds for diagnosing compartment syndrome [53].

Additional treatments may include non-sedating analgesia, dialysis for established renal failure (hemodialysis is superior to peritoneal dialysis), aggressive fluid resuscitation, and respiratory support, as indicated.

After administration of antivenom, a short, nontapered course of prednisone (40–60 mg daily for 5 days) should be given to decrease the incidence of type III immune complex disease (grade III recommendation).

Meticulous wound care and tetanus prophylaxis should be provided as indicated. Aggressive wound care is especially important in the event of non-sterile interference with the wound (e.g., inappropriate first aid, exposure to saprophytic or marine organisms, etc.). Antibiotics are indicated only if evidence of infection is present.

All patients with serious envenomation must be counseled about the risk of antivenom anaphylaxis, immune complex disease, and possible loss of function, regardless of treatment effectiveness.

Discharge and Follow-Up

Patients who have had life-threatening Hazard Index 1 envenoming must have had several serial sets of normal laboratory investigations and be clinically stable. Patients with comorbid renal and/or cardiovascular disease (including resistant essential hypertension) who are recovering from a life-threatening envenoming should be very carefully assessed before being discharged. A longer inpatient management period should be expected for these patients. Those with less serious local envenoming by Hazard Index 2–4 species should have an arranged follow-up appointment with their primary care physician, as well as arrangements for meticulous wound care when clinically indicated.

Any patient with evidence of an acute kidney injury (AKI) or cardiovascular insult must have timely respective follow up with a nephrologist or cardiologist.

Long-Term Considerations/Prognosis

Most patients envenomed by NFFC have a complete, uncomplicated recovery. However, patients seriously envenomed by Hazard Index 1 species who had AKI may experience some association of this injury with long-term mortality and morbidity, as has been shown for AKI with varied etiologies [59, 60]. Likewise, any patient with cardiovascular complications including cerebrovascular infarct may have a guarded prognosis depending on the extent of injury, age, and comorbidities. Careful follow-up of these patients is mandatory.

Legal Pitfalls

All patients, including those with significant local envenoming, should be carefully counseled about possible loss of function, delayed and incomplete healing, and possible loss of local sensation (especially after significant and prolonged digital edema) even after correct treatment. Any patient or their legal proxy must be informed of the risks and benefits of AV, as well as the likely significant delay in procuring AV as needed for Hazard Index 1 envenoming. They should also be counseled about the possibility of failed therapy even with the provision of timely and effective treatment and should be informed if these products have not been specifically approved by the relevant regulatory agency. The lack of high-quality evidence supporting replacement therapy should be clarified especially when it is deemed necessary for serious envenoming by *Thelotornis* spp. because it is the sole management strategy for envenoming by these snakes, as there is no AV.

Similarly, in the event of treatment of life-threatening envenoming by *R. subminiatus* or *B. ceylonensis* with anti-*R. tigrinus* AV, the patient or legal proxy should be carefully informed about the lack of any evidence for clinically effective paraspecific neutralization of the venoms of these species by this AV.

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The American Association of Poison Control Centers reported 90 coral snake bites in 2014 [1]; 51 (57%) of these were reported from Florida [2]. Of these, three patients required ventilator support or airway protection either due to a late presentation or shortage of antivenom. In 2006, a death occurred in Florida in a 29-year-old male who did not seek medical attention. Coral snakes belong to the family *Elapidae* (Fig. 1). Among the elapids are cobras, mambas, sea snakes, and corals. Coral snakes comprise three genera: *Leptomicrurus*, *Micrurus*, and *Micruroides*. *Micrurus* and *Micruroides* are the only endemic North American elapids [3]. *Micrurus fulvius* has five subspecies; *M. fulvius fulvius* (Eastern coral snake) and, to a lesser extent, *M. fulvius tenere* (Texas coral snake) are the most medically important. No reports exist of significant human toxicity due to *Micruroides euryxanthus* (Sonoran coral snake).

The Eastern coral snake, small in comparison to the pit vipers, grows to 129.5 cm (51 in.) [4] and has a black, rounded head with a flat snout and rounded eyes (Fig. 2). The concentric banding pattern with black, yellow, red, yellow gives rise to the mnemonic: “red on yellow, kill a fellow; red on black, venom lack.” Several nonvenomous snakes in North America mimic the coral snake, most notably the king snake. Coral snakes should be distinguished easily from these if a specimen is available for examination; however, misidentification, even by professionals at a pet store, has led to envenomation [5]. Occasionally, albino

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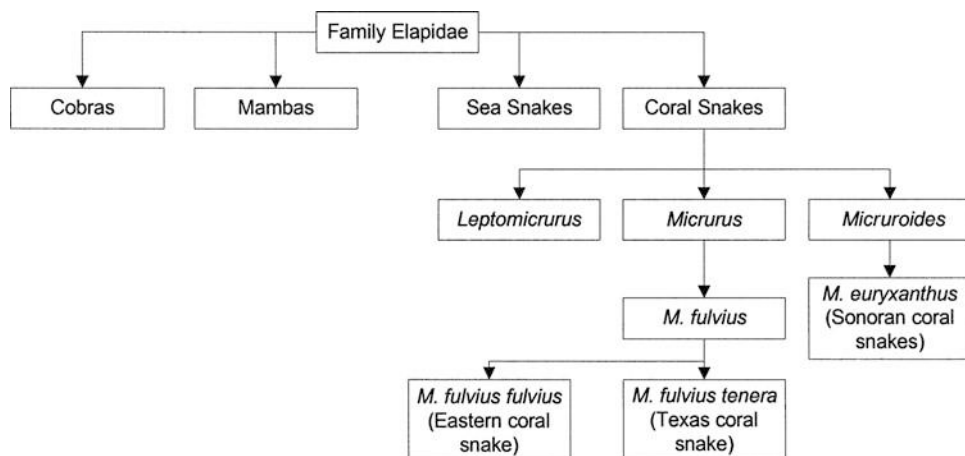


Fig. 1 Family Elapidae



Fig. 2 *Micrurus fulvius* (Courtesy of J.D Wilson under a Creative Commons license)

snakes and phenotypic variations that break the rule are found in the wild.

M. fulvius is solitary, except when breeding. It can be aggressive toward its own species, but it is otherwise mild-mannered and does not attack humans. The defensive posture of the coral snake often includes a popping sound made with the tail. This behavior is thought to be an evolutionary tactic, used to confuse predators. The first description of a coral snake bite by True [6] in 1883 expressed surprise that the snake did not sting with its tail. As with pit viper envenomation, most coral snake bites are the result of the animal defending itself.

Venom Biochemistry and Pathophysiology

The chemical components of *Micrurus* toxin still are not well understood in comparison to Old World elapids. The dry venom consists of 75% protein [7], representing a complex mixture of enzymes and nonenzymatic toxins. Recently, high-throughput transcriptomic sequencing of the venom gland transcriptome of *Micrurus fulvius* has been performed [8]. Approximately 86% of the venom gland genome identified as toxin were identified as unique sequences for phospholipase A_2 and three-finger toxins. Together the two toxins account for the majority of coral snake venom's clinical neurotoxicity. Phospholipase A_2 , in particular, is responsible for neurotoxicity both presynaptically and postsynaptically, as well as myotoxicity, cardiotoxicity, hemolytic activity, and anticoagulant activity [9]. Zinc-dependent anticholinesterase may be partially responsible for effects on neuromuscular transmission at the nicotinic endplate resulting in curare-like effects [10, 11]. The long-term effects of coral snake envenomation, occasionally lasting up to 6 weeks, are most consistent with a presynaptic toxin and destruction of the neuronal cell. This is further supported by the clinical observation that toxicity, once established, cannot be reversed even by tripling the standard dose of antivenom.

Three-Finger Toxins, named for the appearance of their chemical structure postsynaptically inhibit acetylcholine at the nicotinic receptor or the neuromuscular endplate [12]. Long-chain neurotoxins are similar to three-finger toxins with the addition of side chains. Metalloproteinases, a hemorrhagic toxin found in *Crotalinae*, have less clear significance in the corals. Kunitz proteins, the fifth most abundant toxin found in the *Micrurus* genome, are an inhibitor of serine proteases and calcium and potassium ion channels. Hyaluronidase, L-amino acid oxidase, phosphatases, phosphodiesterases, adenosine triphosphatase, and deoxynucleoside phosphatase (DNPase) have been described [13–17]. Other venom components include lipids, carbohydrates, riboflavin, zinc, calcium, magnesium, and potassium.

Coral snakes are proteroglyphodonts, having two anteriorly located fixed maxillary teeth, or fangs, attached to venom apparatus. The amount of venom injected into a victim is difficult to determine; however, this seems to be controllable by the coral snake [18]. The average amount of venom available varies from species to species and is proportionate to the size of the snake. The average yield of venom obtained from milking snakes is 12–20 mg for *M. fulvius* and only 6 mg from *M. euryxanthus* [15, 18, 19].

The average median lethal dose for 18-g mice is reported to be 9 μ g [20]. Given the average yield per snake, it is apparent that a bite from *M. fulvius* easily could be fatal to a human if the weight-adjusted median lethal dose is similar. However, there is a considerable difference in the LD₅₀ even among different species of mice and extrapolation to humans may not be possible.

Clinical Presentation

Fang marks are the most frequent initial clinical finding. Fang marks may be multiple, may appear as an abrasion, or may be absent. The ability to express a small drop of blood may be present in 85% of patients [21]. However, envenomations have occurred with minimal local signs

[22]. The practice of injecting lidocaine or saline into the bite site to observe expression of fluid from the fang marks has little, if any, clinical value. It has been stated that these snakes need to chew venom into the wound to inject sufficient venom [21]. Patients occasionally report a “Velcro-like” sensation when removing a coral snake, and this is believed to correlate with the subsequent development of toxicity. However, this chewing action may not be necessary for envenomation. Only a few patients in the Florida Poison Information Center database have given a history of the snake “holding on” during a bite.

Local swelling occurs in approximately one-third of patients [21] and is typically mild compared with pit viper envenomation. The lack of local tissue injury often leads medical personnel to underestimate the severity of the injury, particularly if the patient is intoxicated. Localized pain at the bite site is common, as are paresthesias.

The mean time to onset of symptoms is 140 min; however, toxicity may be delayed 13 h [18]. Most patients who present to the hospital are asymptomatic. Asymptomatic patients, if adequately treated with antivenom before the onset of symptoms, do not go on to develop toxicity. Nausea and vomiting occur in approximately 25% of patients [21]. One patient described the following symptom to the author, “It was like thousands of bees buzzing in my ears.”

Cranial nerves are affected early, with the patient experiencing diplopia, ptosis, dysarthria, difficulty swallowing, and depressed gag reflex. Aspiration pneumonia is a frequent complication, particularly when early, aggressive airway protection is not maintained. Paralysis of the muscles of respiration and respiratory failure may follow, with subsequent paralysis of skeletal muscles, which is preceded by muscle fasciculations in only about 5% of cases [21]. Whether paralysis proceeds in an ascending or descending fashion has not yet been described. Although paralysis in an untreated patient may last as long as 2 months, long-term sequelae have not been observed. Mental status most often remains normal. Some patients with incomplete paralysis have been able to communicate through writing.

Cardiovascular toxicity has been shown in dog models with lethal doses of venom from *M. fulvius fulvius* [23]. No such toxicity has been reported in humans. Hemolytic effects on in vitro human red blood cells have been shown, but this does not seem to be clinically relevant for patients [16].

Diagnosis

The diagnosis usually is evident from the history given by the patient. In the series by Kitchens and Van Mierop [21], nine patients who intentionally handled the snake believed they were handling a king snake. In one report of envenomation, the patient was told by a local pet shop that a snake was a king snake [5]. Occasionally a patient, often intoxicated, gives a history of having been bitten by an unknown brightly colored snake. It is often difficult to determine if envenomation has occurred. If no snake is available for identification, the risks of antivenom administration must be weighed against the risks of untreated envenomation. Experimentally, and in rare clinical circumstances, enzyme-linked immunosorbent assay has been performed on the blood of unconscious patients to diagnose coral snake envenomation. This test is not routinely commercially available, however, and can be expensive. Enzyme-linked immunosorbent assay is not indicated in cases in which the diagnosis already is known. Treatment of suspected envenomation should not be delayed for laboratory work of any kind. Routine laboratory studies may be required before intensive care unit admission per protocol and custom in many hospitals. The laboratory is not helpful, however, in making a specific diagnosis because neither coagulopathy nor rhabdomyolysis occurs in routine coral snake envenomation. A chest x-ray should be obtained, particularly if aspiration is suspected. Because paralysis lasts several days to months; arterial access is preferable for multiple arterial blood gas measurements.

Treatment

Indications for ICU Admission in Poisoning by North American Coral Snakes and Related Elapids

1. All patients with strong suspicion of coral snake bite should be treated or monitored in the intensive care unit for the first 24 h.
2. Symptomatic patients should remain intubated in a critical care unit until a patent airway can be maintained by the patient.
3. Patients who have had anaphylactic/anaphylactoid symptoms from antivenom should be admitted to the intensive care unit.
4. Prior history of administration of antivenom or history or allergy to antivenom does not contraindicate administration of antivenom. The risk-benefits should be weighed preferably with the input of a clinical toxicology consultant.

Early and aggressive airway management and ventilatory support are mandatory because aspiration pneumonia is a frequent early complication. The supportive treatment of symptomatic patients mirrors the treatment of Guillain-Barré syndrome or botulism. The patient may have complete or partial paralysis of skeletal musculature but typically has normal mental status. It is important that the patient's psychological needs are met in addition to ventilatory and nutritional support.

Antivenom

The mainstay of treatment of *M. fulvius* is North American Coral Snake Antivenin (Wyeth Laboratories, Marietta, PA) (Grade II-3 evidence). This antivenom is produced by progressive immunization of horses and subsequent harvest of immune serum, presumptively rich in IgG. The immune horse serum is lyophilized for longer storage life. Because neurotoxic effects from *M. fulvius fulvius*, when manifest, are largely irreversible

by antivenom, it is important to administer antivenom even when the diagnosis is suspected but not confirmed (Grade II-3 evidence). The Florida Poison Centers performed a retrospective observational study to determine if a “wait and see” approach to the administration of antivenom could be used in asymptomatic patients. However, due to the retrospective nature of the study, this cannot be recommended [24].

North American Coral Snake Antivenin was licensed in 1967. Until that time, it was estimated that the mortality from untreated Coral Snake bite was 10% [4]. The effectiveness of North American Coral Snake Antivenin is virtually 100% effective if given prior to the onset of effects as the development of toxicity after administration of antivenom is unheard of. At the time of discontinuation of antivenom production in 2003, Wyeth Laboratories produced a 5-year supply of antivenom to allow the transition to a newer product. The existing lots were to expire in 2008. In 2009, Pfizer purchased Wyeth as a wholly owned subsidiary. But, to date, no new antivenom has been produced. The US Food and Drug Administration has allowed for the extension of two lots of Wyeth antivenom, both of which had the original expiration date of October 2008. Lot 4030026 was renewed annually from October 2009 until October 2014. Lot 4030024 was first renewed in April 2014 but has been extended twice since that time.

For asymptomatic patients with clear evidence of significant coral snake bite, a minimum of 3–5 vials of North American Coral Snake Antivenin is considered to be appropriate (Grade III evidence). The Wyeth *Micrurus* antivenom package insert recommends consideration of a repeat course of 3 to 5 vials; however, the indications for repeat treatment are left to the discretion of the practitioner. Asymptomatic patients who have received five vials of coral snake antivenom have not been described to display subsequent signs of envenomation, and the administration of five vials seems to be adequate for this population.

For patients develop clinical effects before or during the administration of antivenom, the author recommends administering 3–5 additional vials of antivenom. Although additional higher doses of

antivenom have not been shown to reverse the effects of coral snake envenomation, application of the higher end of the recommended therapeutic dosing range seems prudent.

The package of Wyeth *Micrurus* antivenom contains two vials: lyophilized antivenom with 0.25% phenol and 0.005% thimerosal and 10 mL of bacteriostatic water with phenylmercuric nitrate (1:100,000) as a diluent. The powdered protein contained in the lyophilized antivenom vial can be reconstituted either by using the diluent that comes in the package or by filling the vials with 10 mL of 5% dextrose in water (D₅W) or normal saline from an intravenous bag. The latter process makes antivenom reconstitution and placement of the contents of the vials back into the intravenous bag easier and more efficient. The vials are warmed gradually and rolled gently (not shaken, as this may cause foaming and also denature the proteins) between the hands until all powder has gone into solution. Care should be taken to ensure that all particles of the lyophilized powder are dissolved completely (suspension in foam causes powder to catch in filters). This process typically takes 15–30 min.

I place 3–5 vials of antivenom in a weight-appropriate volume of diluent (250–500 mL of either D₅W or normal saline is appropriate for adults). An infusion is begun through a micropore filter at a rate of about 3 mL/h. The rate may be doubled every 2 min as tolerated. The initial goal of therapy should be the administration of six vials over 1–1.5 h.

Pretreatment with antihistamines, steroids, or antibiotics is unnecessary for most patients. Caution should be taken with patients with a prior history of allergic reaction to horse serum or prior administration of horse serum-based antivenom. Although antivenom administration is not contraindicated in these patients, the risk-to-benefit ratio must be assessed. If therapy is deemed necessary in these patients, pretreatment with H₁ and H₂ antagonists and corticosteroids is indicated (Grade III recommendation). Tetanus immunization should be updated if necessary. Because animal sera contain foreign protein, immediate hypersensitivity reactions are common. Experience with

Wyeth Laboratories (Crotalidae) Antivenin Polyvalent, another equine-derived antivenom revealed the incidence of anaphylactic, anaphylactoid, and serum sickness to be 83% [25]. Serum sickness (type III hypersensitivity) is a delayed (days to weeks) manifestation of immune complex formation. Adverse reactions to antivenoms are described in ► Chaps. 116, “Overview of Scorpion Envenoming,” and ► 151, “Immunotherapy.”

During the administration of antivenom, I recommend observing the patient vigilantly for type I, or immediate, hypersensitivity reactions. Hypersensitivity reactions range from a mild rash to acute bronchospasm or anaphylactic shock or both. This may be true anaphylaxis or, more commonly, a nonspecific anaphylactoid reaction (i.e., not IgE mediated). If there is concern about the possibility of a reaction, it is prudent to prepare an intravenous epinephrine infusion (1 mg in 250 mL of D₅W), which could be started immediately if necessary. The infusion rate, if needed, is typically 0.1–1.0 µg/kg/min for adults or 0.05–1.0 µg/kg/min for children. The first step in the treatment of acute allergic phenomena is to stop the antivenom infusion. Fluid administration and Trendelenburg positioning may be helpful in blood pressure support. The patient should be given weight-appropriate doses of diphenhydramine and an H₂-blocker, such as cimetidine or ranitidine. Intravenous methylprednisolone may not be immediately helpful but may have a role if restarting the antivenom infusion is considered. β₂-Adrenergic agonists should be administered if necessary for the treatment of bronchospasm. Epinephrine should be given for hypotension or bronchospasm. Serum sickness, a type III (or immune complex) hypersensitivity reaction, occurs in many patients 3–21 days after antivenom administration (most commonly between days 7 and 14) [25]. The risk of serum sickness is related to the number of vials of antivenom given (i.e., total foreign protein load). Serum sickness typically presents as a flulike illness, arthralgias, and rash. More severe cases with glomerulonephritis and pericarditis have been reported. Most cases however respond well to antihistamines and a course of prednisone. Fear of serum sickness should not be used as an argument to avoid the use of antivenom.

A Costa Rican polyvalent anti-coral antivenom (Instituto Clodomiro Picado, Universidad de Costa Rica) exists for treatment of coral snake envenomation in Central and South America. There is no literature on its effectiveness in North American coral snake bites although activity against venom from *Micrurus nigrocinctus*, *Micrurus carinicaudus*, *Micrurus fulvius fulvius*, and *M. fulvius tenere* is reported. It is derived from horse serum and precipitated using caprylic acid.

An F(ab')₂ Coralmyn (Instituto Bioclon, Mexico) exists for treatment of coral snake envenomation in Central and South America. There is no literature on its effectiveness in North American coral snake bites, although both report activity against venom from *Micrurus fulvius fulvius* and *M. fulvius tenere*. It was developed with venom from *Micrurus nigrocinctus*. It is prepared by immunizing sheep and digesting the IgG molecule with pepsin. The result of splitting the molecule is a 100,000 molecular weight F(ab')₂ and a 50,000 molecular weight Fc fraction. The Fc fragment, which is responsible for binding to and triggering degranulation of mast cells and activating the complement cascade, is removed. F(ab')₂ has theoretical, but untested, advantages over Fab and whole IgG. The product is believed to be less allergenic to humans than crude IgG preparations due to the absence of albumin, other foreign proteins, and Fc fragment. The allosteric configuration of F(ab')₂ is closer to that of IgG and may bind to antigen more tightly than Fab. There is concern that Fab may be filtered by the glomerulus and has a short biologic half-life; this is less likely to occur with F(ab')₂ given the latter's greater molecular weight. This F(ab')₂ antivenom has been used successfully for the treatment of coral snake bite in Mexico and Central and South America. Though no US clinical trials have been performed, it has been shown to be equally effective at neutralizing venom from *M. fulvius tenere* and *M. fulvius fulvius* in mice. Neither the Instituto Bioclon antivenom nor the Costa Rican polyvalent anti-coral antivenom is commercially available in North America. They occasionally may be found in local zoos and theme parks that handle poisonous animals or through the Miami-

Dade Fire Rescue Antivenom Unit [26]. An ovine Fab antivenom has been developed from *M. fulvius fulvius* but has not been tested in humans [27].

Criteria for ICU Discharge in Poisoning by North American Coral Snakes and Related Elapids

1. Asymptomatic patients may be discharged after 24 h of observation from the time of the bite.
2. Symptomatic patients may be discharged when adequate airway and ventilation can be maintained.
3. Symptomatic patients should have an absence of progression of symptoms for 24 h before discharge.

It may be possible to use antivenoms from Central and South America should a shortage of North American Coral Snake Antivenom exist. Cross-neutralization of *M. fulvius fulvius* venom by anti-*Micrurus carinicauda dumerilii* serum has been shown [28]. General considerations regarding immunotherapy are discussed in detail in ► Chap. 151, “Immunotherapy.”

Currently, patients are being enrolled in a clinical trial for an F(ab')₂ in Florida (INA2013).

Neostigmine was used to improve symptoms in a single case report of a 35-year-old patient with suspected envenomation from *Micrurus* [29]. No experience with neostigmine exists for treatment of North American coral snakes, although it has been used for other elapids whose venoms exert postsynaptic neurotoxic effects on the neuromuscular junction [30]. The irreversibility of symptoms through the destruction of neurons by a presynaptic toxin would suggest that neostigmine might be, at best, a temporizing measure.

Special Populations

Pediatric Patients

The antivenom dosage for children should not be altered. Antivenom contains immunoglobulins, which have an affinity for venom. The amount of

venom to be bound by antivenom, not the weight of the patient, is the determining factor for the effective dose of antivenom. However, reducing the total fluid volume may be reasonable to avoid fluid overload. The rate of administration of antivenom may need to be slowed if the volume is reduced resulting in a more concentrated solution.

Pregnant Patients

There is a paucity of literature on coral snake bite in pregnancy, probably because pregnant women are less likely to be exposed to the risk of envenomation. In one Brazilian study, three of eight pregnant snakebite victims developed premature contractions, threatened abortion, fetal arrhythmia, and intrauterine fetal demise [31]. The use of antivenom in pregnancy has been inferred from the literature on other envenomations. Wyeth Laboratories *Micrurus* antivenin carries a US Food and Drug Administration pregnancy C category. Although no relevant human studies exist, the risk-to-benefit ratio must be weighed [32]. Because of the possible adverse fetal effects of maternal envenomation, the indications to use antivenom in pregnant patients should be the same as for nonpregnant patients (Grade III recommendation).

Patients with Late Presentation

A dilemma often exists with asymptomatic patients who have presented to the hospital many hours after a presumed coral snake bite. Although the likelihood of a significant envenomation decreases for a patient 12 h from the time of the bite, the consequence of the delay in treatment may be a missed opportunity to prevent a prolonged hospital course, one that often is fraught with complications. In these instances, it is usually best to err on the side of caution by giving antivenom. Expectant observation also is an acceptable option. The risks and benefits must be discussed in detail with the patient. Consultation with a clinical toxicologist is highly recommended in this situation.

Common Errors in Treatment of Poisoning by North American Coral Snakes and Related Elapids

Delay in protecting the patient's airway
 Undertreatment of pediatric patients with antivenom

Approaching the coral snake victim similar to the victim of crotaline snakebite (i.e., using soft tissue swelling or laboratory findings as an indicator for therapy)

Using *Crotalinae* or other antivenom for treatment of coral snake

Key Points in Poisoning by North American Coral Snakes and Related Elapids

1. Victims of a coral snake bite present with little, if any, local symptoms.
2. Patients with known or suspected coral snake bite should be treated before the onset of symptoms.
3. Aggressive, early airway protection in patients with evolving symptoms avoids the common complication of aspiration pneumonia.
4. There is no role for steroids (except in the treatment of reactions to antivenom).
5. There is no role for prophylactic antibiotics.
6. Tetanus immunization should be updated, if needed.
7. Untreated patients with full-blown toxicity have paralysis, not coma, and appropriate psychological considerations for a conscious but paralyzed patient should be maintained.

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North America is home to more than 30 species and subspecies of venomous snakes (Table 1). These fall within two snake families: the Viperidae and Elapidae. The majority of human envenomations occurring in the United States (US) result from bites by members of the subfamily of Viperids known as Crotalinae. The Crotalinae, alternately referred to as crotaline snakes, crotalids, New World vipers, or pit vipers, are comprised of snakes from the genera *Crotalus* and *Sistrurus* (rattlesnakes) and *Agkistrodon* (cottonmouths and copperheads). A minority of native venomous snakebites are due to coral snakes, which are discussed in ► [Chap. 125, “North American Coral Snakes and Related Elapids.”](#)

Pit vipers possess heat-sensing organs, or “pits,” located posterior to each nostril which function in locating prey. Other characteristics that distinguish pit vipers include a triangular-shaped head and elliptical pupil. Pit vipers, like all Viperidae, possess mobile fangs located in the front of the mouth that can be rotated forward during a strike and retracted quickly back into the mouth. The paired fangs deliver venom via venom ducts, from paired specific venom glands located towards the posterior part of the head, laterally. In addition to these characteristics, rattlesnakes also possess a modified scale structure, the “rattle,” which is an appendage at the base of the tail that, when shaken, signals a warning to predators. However, the rattle may be absent in very young rattlesnakes or it may be lost. Even

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Table 1 US Crotalinae – medically important species and selected subspecies

Genus/Species	Common name	General range in U.S.
<i>Crotalus</i>	Rattlesnakes	
<i>C. adamanteus</i>	Eastern diamondback rattlesnake	Southeastern
<i>C. atrox</i>	Western diamondback rattlesnake	Southwestern
<i>C. cerastes^a</i>	Sidewinder	Southwestern
<i>C. cerberus</i>	Arizona Black rattlesnake	Arizona
<i>C. helleri</i>	Southern Pacific rattlesnake	Southern California
<i>C. horridus</i>	Timber rattlesnake	Southern, Eastern
<i>C. lepidus klauberi</i>	Banded rock rattlesnake	Southwestern
<i>C. lepidus lepidus</i>	Mottled rock rattlesnake	Southern
<i>C. mitchelli pyrrhus</i>	Speckled rattlesnake	Southwestern
<i>C. molossus molossus</i>	Black-tailed rattlesnake	Southwestern
<i>C. oreganus</i>	Western rattlesnake	
<i>C. o. abyssus</i>	Grand Canyon rattlesnake	Northern Arizona
<i>C. o. concolor</i>	Midget Faded rattlesnake	Western
<i>C. o. lutosus</i>	Great Basin rattlesnake	Western
<i>C. o. oreganus</i>	Northern Pacific rattlesnake	Northwestern
<i>C. ornatus</i>	Chihuahuan Black Tailed rattlesnake	Texas
<i>C. pricei</i>	Twin-spotted rattlesnake	Arizona
<i>C. ruber</i>	Red diamond rattlesnake	Southern California
<i>C. scutulatus scutulatus</i>	Mojave rattlesnake	Southwestern
<i>C. stephensi</i>	Panamint rattlesnake	Western
<i>C. tigris</i>	Tiger rattlesnake	Arizona
<i>C. viridis nuntius</i>	Hopi rattlesnake	Western
<i>C. viridis viridis</i>	Prairie rattlesnake	Western
<i>C. willardii^a</i>	Ridgenose rattlesnake	Southwestern
<i>Sistrurus</i>	Pigmy rattlesnakes and massasauga	
<i>S. catenatus catenatus</i>	Eastern massasauga	Great Lakes region
<i>S. catenatus edwardsi</i>	Desert massasauga	Southwestern
<i>S. catenatus tergeminus</i>	Western massasauga	Central, Southern
<i>S. milarius^a</i>	Pigmy rattlesnake	Southeastern
<i>Agkistrodon</i>	Copperheads and cottonmouths	
<i>A. contortix^a</i>	Copperheads	Southern, Eastern
<i>A. piscivorus^a</i>	Cottonmouths	Southern, Southeastern

^aSubspecies not listed

when present, a rattle is not always heard before a strike. Cottonmouths and Copperheads do not possess a rattle (Fig. 1).

Crotalids are found in nearly all US states. Although not endemic to Alaska, Hawaii, and Maine, venomous snakebites have been reported in all states except Hawaii [1]. Snake bites are most common in the south, with Florida and Texas reporting the greatest number of bites nationally, and Arizona reporting the greatest number of bites per capita [1]. The average number of native venomous snakebites reported to US

poison centers each year is approximately 5000; however, not all bites are reported and the true incidence is likely higher [1]. Most bites occur in the warm months, between April and September [1, 2].

Crotalinae species do not “attack” humans and will avoid encounters if possible. As a result, many snakebites occur following intentional interaction with the snake by the patient. At-risk populations include herpetologists, religious snake handlers, and those who work outdoors in snake-endemic areas [3]. Others at risk are those who decapitate



Fig. 1 The characteristic rattle, elliptical pupil, and heat-sensing pit (posterior to nostril) can be seen on this speckled rattlesnake (*C mitchelli*)

a rattlesnake and subsequently pick up the head. Persistent reflexes in the venom apparatus allow the snake's head to "bite" the handler and deliver venom [4]. Perhaps due to increased propensity toward risk-taking behavior, bites are much more common in men than in women, with males typically comprising 70–80% of subjects in reported case series. Children are also frequent bite victims, however, representing 10–20% of subjects in various studies [1, 2]. Bites most often involve the upper or lower extremity, though bites to the head, neck, and torso are also reported. Many series report a preponderance of upper extremity bites, consistent with intentional interaction with the snake [2].

In the USA, rattlesnakes are responsible for the greatest morbidity and mortality due to crotaline envenomation. While an uncommon cause of death, a handful of fatalities are reported annually [1]. Despite the low mortality rate, rattlesnake envenomation can produce serious morbidity. Permanent tissue loss, especially following envenomations to a digit, is not uncommon. Good data on outcomes following North American snake envenomation are not available, but in a small prospective study of patients with copperhead envenomation, functional disability lasted 1–3 weeks in most patients [5]. Patients with more severe rattlesnake envenomations may have a longer recovery time.

Biochemistry and Clinical Pharmacology

Snake venom is a complex mixture of enzymatic and nonenzymatic proteins, polypeptides, lipids, biogenic amines, metal ions, and amino acids. Crotalinae venom contains a large variety of toxins, many of which produce physiologic effects in humans, and only some of which are characterized and fully understood. While some toxins are expected to be present to a certain extent in all North American crotaline venoms, the specific composition of venom in an individual snake may vary with the age, diet, and geographic location of the snake. Even snakes of the same species and general geographic location may differ in the toxicity of their venom [6].

Medically important components in crotaline venom include snake venom metalloproteinases (SVMPs), snake venom serine proteases (SVSPs), and phospholipases A₂ (PLA₂s). Other significant toxins include disintegrins, bradykinin potentiating peptides (BPPs), and C-type lectin-like proteins. Other toxins found in snake venoms may be less relevant to crotalid envenomation, such as vascular endothelial growth factors, which induce hypotension and increase vascular permeability, and cysteine-rich secretory proteins, which may block ion channels [7]. Snake venom toxins may act independently or synergistically on different cellular targets and organ systems to produce the observed clinical effects.

Snake venom metalloproteinases are enzymes with catalytic activity which is dependent on metal (usually zinc) ions. Dozens of SVMPs have been characterized in snake venom. They may produce many effects, including inflammation, proteolysis, and hemorrhage, contributing to local tissue toxicity; pro-coagulant or anticoagulant effects, contributing to coagulopathy; and antiplatelet actions. Hemorrhagic SVMPs act to damage the vascular endothelium and increase vascular permeability [8]. This may lead to extravasation of plasma and blood at the site of local injury manifesting as tissue edema and ecchymosis. In combination with coagulopathy and/or thrombocytopenia, hemorrhagic SVMPs may increase risk of bleeding [9–11]. Many

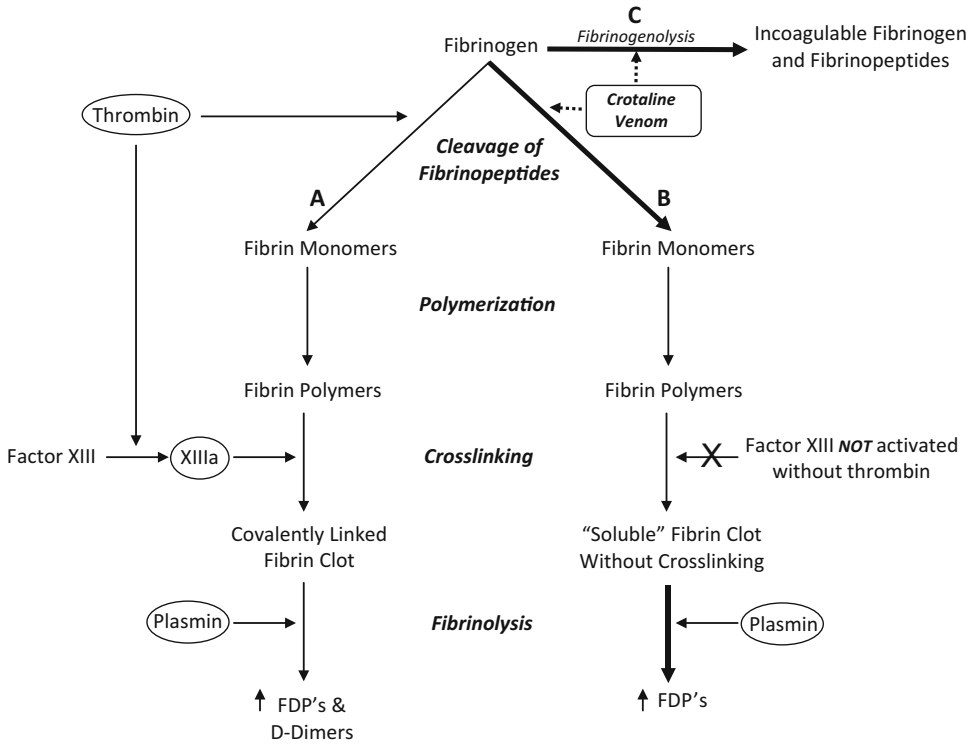


Fig. 2 Comparison of a normal clotting pathway (A) and fibrinogenolysis and fibrinolysis by crotaline venom (B and C). The normal pathway (A) requires thrombin to cleave fibrinopeptides a and b to form fibrin and to activate factor XIII to form XIIIa to catalyze covalent cross-linking and thereby produce an insoluble clot. Crotaline snake venom contains enzymes that degrade fibrinogen directly

to incoagulable fibrinogen and fibrinopeptides (C). Thrombin-like crotaline enzymes form “soluble” clots that are rapidly lysed by plasmin (B). Endogenous components of the coagulation system appear in ovals. **Boldface arrows** represent the pathway steps most affected by crotaline venom. *FDPs*, fibrin degradation products

SVMPs possess fibrinogenolytic and/or fibrinolytic activity. Fibrinogenolytic SVMPs preferentially cleave either the alpha or beta chain of fibrinogen. This results in degradation of fibrinogen without production of fibrin.

While most fibrino(geno)lytic enzymes in venom are metalloproteinases, some are serine proteases. SVMPs more often cleave the alpha chain of fibrinogen preferentially, while serine proteases tend to cleave the beta chain. Like the SVMPs, many serine proteases have both fibrinogenolytic and fibrinolytic activity, but some act only on fibrinogen [10]. Other serine proteases deplete fibrinogen through a thrombin-like effect. These thrombin-like enzymes (TLEs) release either fibrinopeptide A or B from

fibrinogen, rather than both fibrinopeptide A and B. Unlike thrombin, TLEs do not activate Factor XIII, and as a result, cross-linking of fibrin does not occur and a stable fibrin clot does not form. Rather, a friable, translucent, and easily degraded fibrin clot results, with an overall anticoagulant effect produced clinically [10, 12, 13] (Fig. 2). Some TLEs, such as crotalase, present in *Crotalus adamanteus* venom, also possess kinin releasing activity [14]. Some SVSPs have a direct anticoagulant effect through activation of Protein C. Snake venom metalloproteinases may also possess hemorrhagic activity, whereby they disrupt the basement membrane leading to loss of capillary integrity and local hemorrhage at the wound site [10, 11]. Other actions of SVSPs include

effects on platelets, such as inhibition or promotion of platelet activity, or reduction of platelet availability.

Hundreds of PLA₂ enzymes have been identified in snake venoms. They have diverse actions and may contribute to many effects of envenomation, including local tissue toxicity, neurotoxicity, myotoxicity, and hemotoxicity [13, 15]. Neurotoxic PLA₂s are found in the venom of some North American Crotalinae species. *Crotalus scutulatus* (the Mojave rattlesnake) is most well known for possessing a specific neurotoxin, called Mojave toxin. This toxin is a heterodimer composed of an alpha subunit without PLA₂ activity and a beta subunit with PLA₂ activity. The neurotoxin acts presynaptically to prevent acetylcholine release [16, 17]. Related neurotoxins in other crotaline species include canebrake toxin, isolated from some populations of *C. horridus* (the Timber rattlesnake), and a neurotoxin identified in some populations of *C. helleri* (the Southern Pacific rattlesnake) [15, 17].

Disintegrins are small nonenzymatic proteins which affect platelets. Disintegrins bind to the GPIIb/IIIa receptor on platelets to prevent fibrinogen binding and inhibit platelet aggregation. They may also inhibit platelet aggregation by binding fibronectin receptors and other integrins on the surface of endothelial cells and fibroblasts [7]. Disintegrins in *C. scutulatus* and *C. adamanteus* venom have been shown to produce antiplatelet activity through multiple mechanisms [9, 18].

Bradykinin-potentiating peptides have been isolated from venom of various Crotalinae snakes. The first BPPs were identified in *Bothrops jararaca* venom, and this discovery led to the development of captopril, the first angiotensin-converting enzyme (ACE) inhibitor. BPPs may induce formation of bradykinin or may inhibit the breakdown of bradykinin by ACE. Increased bradykinin may produce vasodilatory and hypotensive effects [19, 20]. Bradykinin-potentiating peptides may also stimulate nitric oxide generation by endothelial cells and leukocytes and cause eicosanoid release, contributing to local inflammatory effects. A bradykinin inhibitory peptide has also been identified in Crotalinae venoms [20].

C-type lectin-like proteins are nonenzymatic proteins that may affect plasma components and

blood cells, leading to hemorrhage. They may possess pro-coagulant, anticoagulant, and platelet modulating activities. CLPs found in venom of some Crotalinae species have been shown to inhibit thrombin. Other crotaline CLPs affect platelets through interactions with various platelet receptors and von Willebrand factor (VWF). Botrocetin, for example, a CLP found in *Bothrops* venom, forms complexes with VWF and the platelet receptor GPIb resulting in platelet activation [21, 22].

The venom of individual rattlesnakes, even within the same species, may possess a predominance of certain toxins. Venom is sometimes classified by SVMP activity versus lethal toxicity in mice, for which there appears to be an inverse relationship. Venoms with high SVMP activity and lower toxicity have been described as type 1 venoms, whereas venoms with low SVMP activity but high lethal toxicity have been described as type 2 venoms. While lacking in SVMP activity, type 2 venoms tend to be rich in other specific toxins, such as PLA₂ neurotoxin [23]. Such variation in venom within species has been described for *C. oreganus*, *C. horridus*, and *C. scutulatus* [16, 23, 24].

Pathophysiology of Toxic Effects

When a snake bites, venom is usually deposited in the subcutaneous tissues. Only rarely do fangs penetrate fascia, depositing venom intramuscularly. Absorption of venom by the lymphatic system begins immediately [25]. A depot of venom may remain at the bite site for several hours, leading to ongoing absorption of venom [26]. Venom antigens have been shown to be present in the circulation for 2 weeks following envenomation [27, 28].

Local Tissue Effects

Local tissue inflammation and edema are characteristic of crotaline envenomation. The most important contributors to this inflammatory process appear to be PLA₂s and SVMPs. Snake venom

serine proteinases may also contribute to inflammation and have been shown to activate endogenous matrix metalloproteinases [29]. Experimental models have shown that injection of crotaline venom leads to an increase in serum nitric oxide levels and release of pro-inflammatory cytokines and eicosanoids, with recruitment of leukocytes to the bite site, and ultimately development of a profound inflammatory response [29, 30]. Snake venom metalloproteinases, PLA₂s, SVSPs, and endogenous inflammatory mediators may all act together to produce capillary basement membrane damage, resulting in extravasation of plasma from the microcirculation, edema, and ecchymosis. Microvascular damage produced by hemorrhagic SVMPs may dispose to significant subcutaneous bleeding even in the absence of thrombocytopenia and coagulopathy. Snake venom metalloproteinases have also been associated with blister formation [15, 29, 30].

Hematologic Effects

Coagulopathy following crotaline envenomation is primarily due to the action of TLEs on fibrinogen. Both TLEs and fibrino(geno)lytic enzymes produce an overall anticoagulant effect resulting from degradation of fibrinogen with failure to produce a stable fibrin clot. Hemotoxins in North American crotaline venom do not activate the clotting cascade or affect clotting factors. The pathophysiological mechanisms for thrombocytopenia in the setting of crotaline envenomation are less well understood than for coagulopathy, and there are likely multiple contributing toxins and mechanisms. Venom may contain both disintegrins and CLPs, which may act in different ways to aggregate or inhibit platelets. Hemorrhagins in venom may also damage the blood vessel endothelial wall, leading to extravasation of blood and fluids.

Although bleeding is uncommon following envenomation by North American Crotalinae, the combined actions of coagulants, anticoagulants, platelet modulators, and hemorrhagins in venom present risk for severe bleeding, especially in the setting of injury.

Neurotoxic Effects

Snake venom neurotoxins are categorized as alpha and beta neurotoxins. Alpha-neurotoxins antagonize the postsynaptic nicotinic acetylcholine receptor and are found in venom of many Elapidae snakes [31]. Beta neurotoxins have been found in venom of many snake families, including Crotalinae. Beta neurotoxins in rattlesnake venom, such as Mojave toxin found in some populations of *C. scutulatus*, act presynaptically to inhibit neuronal release of acetylcholine [32]. This may lead to severe weakness, and in some cases paralysis, which may last many weeks.

The pathophysiologic mechanism behind venom-induced myokymia or fasciculations is less clear. The terms myokymia and fasciculations are often used interchangeably in the snakebite literature and are difficult to distinguish clinically. Myokymia represents bursts of multiple motor unit action potentials, which on electromyography are recorded as doublets, triplets, or multiplets. Myokymia has been documented following *C. horridus* (Timber rattlesnake) envenomation [33]. Fasciculations are single motor unit potentials. Although often described as fasciculations, the undulating involuntary contractions of muscles noted following envenomation by several Western US species, including *C. scutulatus*, *C. atrox*, *C. helleri*, and *C. cerastes*, may represent myokymia [34–36]. It is theorized that venom-induced myokymia may occur as a result of interaction of venom components with calcium or calcium-binding sites at the peripheral nerve membrane. However, effect on potassium channels, as occurs with other acquired myokymic syndromes, has also been suggested [32, 33].

Cardiovascular Effects

Crotalid snake venom toxins do not appear to have direct cardiac toxicity; however, rare cases of stroke and myocardial infarction associated with envenomation have been reported [37–39].

Venom-induced hypotension and/or shock may develop as a result of different mechanisms. Unabated fluid extravasation from damaged

microvasculature over hours to days can lead to significant hypovolemia and subsequent hypotension. Patients with previous exposure to snake venom may develop IgE antibodies to venom antigens, resulting in anaphylactic reaction following subsequent envenomation. Hypotension, at times accompanied by angioedema, may also occur in response to increased bradykinin resulting from the effect of BPPs in venom.

**Clinical Presentation
and Life-Threatening Complications**

It is estimated that approximately 80% of crotaline snakebites result in delivery of venom [40]. Thus, the remaining 20% of bites are “dry,” without venom deposition. Patients with dry bites will not experience any symptoms following a snakebite and will exhibit only puncture marks, scratches, or lacerations on physical examination.

For those patients with envenomation, the clinical presentation can be highly variable and exist along a wide spectrum. Specific clinical effects that develop, as well as the severity of the effects, may depend upon the composition of the venom to which the patient is exposed, the amount of venom delivered and absorbed, and other patient-related factors, such as co-morbidities and medication use. The location of the bite (i.e., head and neck vs. distal extremity) may also influence the presentation. An envenomation can range from very mild, with only minimal localized swelling on presentation that improves over hours without intervention, to life-threatening, with rapid development of airway compromise and cardiovascular collapse occurring within minutes of the bite. Most typically, patients exhibit findings somewhere between the ends of this spectrum. Additionally, findings at presentation to health care rarely represent peak severity of effects. In rare cases, swelling may not be immediately apparent and may take up to 8–12 h to develop, yet can become significant. Envenomation is a dynamic process, which may continue to evolve for days following the bite if not treated (and sometimes despite treatment).

Table 2 Clinical effects of crotaline envenomation

<i>Common</i>
Local Tissue Damage:
Edema
Ecchymosis
Erythema
Hemorrhagic bullae
Dermonecrosis
Hemotoxicity:
Coagulopathy
Thrombocytopenia
Neurotoxicity:
Myokymia
<i>Less Frequent</i>
Compartment Syndrome
Paralysis
Myonecrosis
Rhabdomyolysis
Shock
Angioedema
Bleeding
Vomiting and Diarrhea

Of the US crotalids, rattlesnake envenomations are associated with the most severe clinical presentations, followed by cottonmouth, and then copperhead envenomations. However, even copperhead envenomations may be serious, and although not reported in the peer-reviewed medical literature, a death has been attributed to anaphylaxis following a copperhead bite in the lay press [41].

The most common effects of native pit viper envenomation are swelling and pain, which occur in the majority of envenomations. Hematologic findings are common in rattlesnake envenomations but less so in cottonmouth and copperhead envenomations [2, 42]. Neurotoxicity and cardiovascular toxicity are less common, but may be life-threatening when they occur. Nonspecific systemic effects include metallic taste, anxiety, tachycardia, and nausea. Vomiting and diarrhea may also occur. Repeated episodes of vomiting or diarrhea may signal impending severe systemic toxicity, with hypotension or angioedema. (Table 2)

Local Tissue Effects

One or more puncture wounds, small lacerations, or scratches are nearly always present in the setting of pit viper envenomation, although there is one documented report of rattlesnake envenomation where only a small area of ecchymosis was noted at the bite site [34]. Most often, one or two puncture wounds are seen. Early after envenomation, pain and swelling develop locally at the bite site, and there may be oozing of blood or sero-sanguinous fluid from wounds. Ecchymosis and erythema are common findings but are not universally present. Ecchymosis is often a prominent finding in foot bites, where the entire dorsal aspect of the foot may exhibit a bluish tinge (Fig. 3). Toes remain pink and well perfused however, with preserved sensation and motor function, which helps to distinguish the blue appearance of the foot from cyanosis.

As venom is absorbed, swelling and pain increase. With distal extremity bites, patients may develop pain and tenderness along lymphatic pathways even prior to proximal extension of swelling. Axillary nodes are commonly tender following upper extremity envenomations and inguinal nodes are tender after lower extremity envenomations. Erythema, lymphangitic streaks, and ecchymosis may also extend along these pathways, dissociated from swelling (Fig. 4).



Fig. 3 Following a rattlesnake bite to the ankle, subcutaneous bleeding produced a bluish discoloration to the dorsal aspect of the foot

It is impossible to predict the ultimate extent of swelling in the first hours after an envenomation. If left untreated, one distal extremity envenomation might progress to involve only the lower leg or forearm prior to cessation of swelling, while another might continue to swell for days, until the entire extremity and the trunk are involved. Unabated extravasation of fluid and blood from “leaky” capillaries can lead to anemia, hypovolemia, and hypotension. Most bites are to a distal extremity, but occasionally patients are bitten in the head or neck. In these cases, progressive edema and swelling present a high risk of airway obstruction.

Superficial necrosis of the dermis, with development of hemorrhagic bullae, is a common finding after direct envenomation of a digit. In the first hours after a bite, faint cyanosis may be noted at the bite site. This may evolve into hemorrhagic bullae over the first 12–36 h after envenomation. If dermonecrosis does not develop within 1–2 days of the bite, it is not likely to occur. However, if blisters develop, they may continue to expand over several days. Deeper tissue necrosis may progress over a week or more. Extensive or circumferential hemorrhagic bullae involving large portions of the digit are more likely to be associated with necrosis of deeper tissue structures than are small bullae. Superficial dermonecrosis most often occurs on digits, but may rarely occur in other sites (Fig. 5).



Fig. 4 Following a rattlesnake bite to the foot, this patient exhibited proximal bruising along lymphatics



Fig. 5 Hemorrhagic bullae involving large areas of the digit are more likely to be associated with necrosis of deeper tissue structures

Compartment Syndrome

Swelling due to snake envenomation is often very severe, causing extreme expansion and deformity of the digits, hand, foot, arm, or leg. The swelling can feel tense on examination and the patient may have exquisite tenderness and great pain. Pulses may be difficult to palpate due to swelling. Clinically, it can be impossible to determine whether a patient has a compartment syndrome. Since venom is most often deposited subcutaneously, superficial to the muscle fascia, compartment syndrome is rare. However, it may occur and anecdotally seems to be more common in patients bitten in the anterior compartment of the leg. Since clinical examination is so unreliable in diagnosing compartment syndrome in snake envenomation, objective measurements of compartment pressures must always be performed and documented to be elevated prior to performing a fasciotomy. In the author's practice, clinical findings that may prompt measurement of compartment pressures include very tense tissue overlying a muscle compartment, decreased motor or sensory function distally that is inconsistent with the degree of soft tissue swelling, or severe pain out of proportion to physical examination findings that is not easily treated with analgesics.

Digits do not have true compartments, but due to the limited ability of the skin to expand to accommodate swelling, increased pressure may develop

risking neurovascular structures. Patients may present with pale, cool, or even blue and insensate digits, necessitating emergent neurovascular decompression, or digit dermatomy [43, 44].

Hematologic Effects

After local tissue effects, coagulopathy and thrombocytopenia are the most common findings associated with rattlesnake envenomation. In the Southwest USA, nearly two thirds of patients with rattlesnake envenomation develop coagulopathy and approximately one third develop thrombocytopenia [2]. Thrombocytopenia is a common feature of Timber rattlesnake (*C. horridus*) envenomation [45]. Coagulopathy and thrombocytopenia are uncommon following native *Agkistrodon* envenomations, although they may occur [42].

Coagulopathy results primarily from degradation of fibrinogen, which may occur within minutes of envenomation or may develop and progress more slowly over many hours. Native crotaline venom does not deplete other clotting factors. The isolated fibrinogen deficiency results in elevation of the prothrombin time (PT). Fibrin degradation products may also be elevated. Bleeding usually does not occur, although risk is increased when there is no measureable fibrinogen. Disseminated intravascular coagulation (DIC) is not a feature of venom-induced coagulopathy [46, 47].

Thrombocytopenia may also develop rapidly and be severe, or, alternatively, platelet count may begin to drop hours after a bite and continue to slowly decrease for days. As with coagulopathy, venom-induced thrombocytopenia is not typically associated with bleeding. However, when platelet counts are very low, patients are more likely to exhibit minor bleeding, such as oozing of blood from puncture sites and gums. Bleeding risk also appears to be increased when severe venom-induced coagulopathy and thrombocytopenia coexist or when patients are chronically using antiplatelet or anticoagulant medications at the time of envenomation [48].

Although serious systemic bleeding is very rare, subcutaneous bleeding near the envenomation site may occur in the days following the bite due to combined effects of venom hemorrhagins and other toxins that produce microvascular injury, especially when coagulopathy or thrombocytopenia are present. This can lead to a significant drop in hemoglobin, with continued swelling, pain, ecchymosis, and tenderness in the extremity.

Late Hematologic Toxicity

After the acute envenomation and treatment phase, during which venom-induced hemotoxicity is either identified and treated or prevented with administration of antivenom, the patient enters a subacute phase of the envenomation which may last several weeks. During this time the patient may continue to have absorption and circulation of venom antigens, placing the patient at risk for late hemotoxicity as any antivenom they received is eliminated from the body. Late (either delayed onset or recurrent) hematologic toxicity is thought to result from differences in pharmacokinetic properties between venom and antivenom. As it is of smaller molecular size, Fab antivenom undergoes more rapid clearance than venom. It is also theorized that venom and antivenom complexes may dissociate, and that there may be delayed absorption of venom from tissue depots [49–51].

It is not clear exactly why late hematologic toxicity develops in some patients and not in others. Predictors for recurrence or delayed onset of hematologic toxicity have not been identified, and all patients treated with Fab antivenom following rattlesnake envenomation are considered at risk. While patients with severe coagulopathy or thrombocytopenia during the initial treatment phase appear to be at increased risk for developing recurrence, even patients with completely normal fibrinogen levels and platelet counts during their acute treatment phase may develop hematologic toxicity days after treatment [52, 53]. Although bleeding complications are uncommon with late hematologic toxicity, life-threatening and fatal bleeding events have been reported [48, 54–56]. One retrospective study compared bleeding

events in patients on anticoagulant or antiplatelet medications to patients not taking these medications. An increased risk of both early and late bleeding was found in patients using anticoagulants or antiplatelet agents (relative risk = 6.8; 95% CI = 2.82–16.4) [48].

Neuromuscular Effects

The most common neurological finding associated with North American crotalid envenomation is myokymia (often described as fasciculations). Myokymia appears as wavy, rolling, involuntary contractions of muscles, sometimes referred to as a bag of worms under the skin. Timber rattlesnakes (*C. horridus*) are best known for producing myokymia, although the finding of myokymia or fasciculations has now also been reported in several Western *Crotalus* species [33–36, 45]. Myokymia or fasciculations may be associated with muscle weakness leading to respiratory failure. Case reports and a retrospective poison center study suggest that patients with fasciculations in the shoulder, chest, or diaphragmatic areas are at risk for progression to respiratory failure, possibly due to incoordination of respiratory muscles [36, 46].

The Mojave rattlesnake (*C. scutulatus*) is famous for its neurotoxic venom and potential to produce paralysis. However, there are few reports in the literature of respiratory failure or paralysis due to Mojave envenomation, which may be attributable to the presence of Mojave toxin in only some populations of *C. scutulatus*. In these reports of paralysis, myokymia or fasciculations are not described. In one such report, a young child developed progressive weakness and respiratory failure 30 h after envenomation despite treatment with Antivenin Crotalidae Polyvalent (ACP) antivenom [47]. Similar neurotoxic effects have been reported following Timber rattlesnake (*C. horridus*) envenomation, for which some populations possess crototoxin, a neurotoxin analogous to Mojave toxin. In one report, a child developed weakness and paralysis, without documentation of myokymia, after a Timber rattlesnake bite. In this case, the weakness did not respond to Fab antivenom, required prolonged

mechanical ventilation, and was associated with severe rhabdomyolysis [48].

Rhabdomyolysis is another feature of envenomation by some crotaline snakes. A subpopulation of the Timber rattlesnake (*C. horridus*), formerly classified as a subspecies known as the Canebrake rattlesnake (*C. h. atricaudatus*), is particularly known for producing systemic rhabdomyolysis. Patients envenomated by the Timber rattlesnake in southern Georgia and northern Florida have been reported to have creatinine phosphokinases (CPKs) measured over one million IU/L, without localized myonecrosis [49]. In general, significant rhabdomyolysis following snake envenomation is often associated with neurotoxic findings. Most North American snake envenomations do not produce rhabdomyolysis.

Systemic Effects

Some patients develop severe systemic toxicity, with hypotension and shock, following rattlesnake envenomation. Hypotension may occur for different reasons. Patients who have previously been sensitized to snake venom proteins may develop IgE antibodies to venom and experience acute anaphylaxis when bitten. In such cases, the anaphylactic reaction occurs in parallel to envenomation, and when severe can be difficult to distinguish from systemic effects due to venom toxicity. Clinical findings of venom-induced anaphylaxis are the same as those occurring with anaphylaxis due to any cause, and may include urticaria, rash, bronchospasm, hypotension, and when severe, shock and acidosis [62].

Hypotension may also result from the action of bradykinin potentiating peptides in venom, possibly with contribution from other vasoactive venom components [19, 63]. Patients typically develop symptoms within the first hour after envenomation. Some patients will have a depressed level of consciousness, hypotension, and shock within minutes of the bite. Others may develop vomiting and diarrhea prior to onset of hypotension. Angioedema resulting in airway obstruction may also occur.

Rattlesnake envenomation causes fluid to extravasate from microvasculature near the bite site and can lead to extensive third-spacing with significant intravascular hypovolemia and anemia if left untreated. In such cases, patients may have delayed onset of hypotension. Since most rattlesnake envenomations produce some degree of hypovolemia, often evidenced by hemocentration on initial laboratory analyses, dehydration or ethanol intoxication at the time of envenomation may also predispose to development of hypotension.

Hypotension and shock may also result from bleeding. On occasion, patients develop serious bleeding after envenomation, usually in the setting of both severe thrombocytopenia and afibrinogenemia. Venom-induced thrombocytopenia and coagulopathy do not represent disseminated intravascular coagulation (DIC). However, in rare cases, activation of the clotting cascade with DIC has been reported following rattlesnake bite, such as with a case of direct vascular envenomation [64].

Diagnosis

The diagnosis of snake envenomation is usually straightforward, based on history of a snakebite and presence of physical findings consistent with envenomation. Unfortunately not all patients see the snake, and the diagnosis should always be considered in areas where pit vipers are endemic and a patient presents with a bite, sting, or puncture wound of unknown origin. Children in particular are at risk when playing outdoors and may be unable to report what happened. Children with a puncture wound and unexplained progressive swelling should be monitored closely for a possible pit viper envenomation.

The diagnosis of snake envenomation is dependent on physical examination findings and sometimes laboratory studies. One or more punctures, small cuts or other disruption to the dermis should be present, with swelling and pain developing at the site. If swelling is not present, laboratory studies may aid in diagnosis. While most rattlesnake envenomations produce swelling, occasionally patients may exhibit significant

thrombocytopenia or coagulopathy without appreciable swelling.

All patients with potential pit viper envenomation should have a platelet count, fibrinogen level, and PT obtained. Prothrombin times rise as a result of fibrinogen consumption and return to normal faster than fibrinogen levels, as clotting function is restored [50]. Some clinicians also assess fibrin degradation products (FDPs). Since baseline fibrinogen levels range widely and fibrinogen is an acute phase protein which may rise in response to inflammatory effects of venom, elevated FDPs in the setting of “normal” fibrinogen may reveal fibrinolytic activity that would otherwise be undetected. Other laboratory studies which may aid in management include a baseline hemoglobin and hematocrit, and in patients who present with evidence of shock, electrolytes, liver and renal function tests, and arterial blood gases. Patients with neurologic findings or concern for compartment syndrome should also have a CPK measured.

If there are no clinical signs of envenomation and laboratory studies (platelet count, fibrinogen, prothrombin time) are completely normal, the patient may have a dry bite. However, evidence of envenomation can be delayed in onset for more than 8 h. Therefore, patients with potential dry bites should be observed for 8–12 h prior to discharge with diagnosis of a dry bite. During this time, serial physical examinations as well as reassessment of platelets and fibrinogen at least 4 h from the time of the initial laboratory assessment and eight hours from the time of the bite should be performed [40].

Treatment

Snakebite management begins with immediate airway support when necessary, intravenous fluid resuscitation, and close monitoring for hypotension or other evidence of systemic toxicity. While the specific supportive therapies indicated vary depending on the presentation and progression of the envenomation, the definitive treatment for a serious or progressing North American rattlesnake envenomation is antivenom (LOE III).

After a snakebite, patients should be placed on a cardiac monitor and have intravenous access established in an unaffected extremity. An initial 20 mL/kg fluid bolus is appropriate even in the absence of symptoms, since envenomation will lead to third spacing of fluids and many patients present with early laboratory evidence of hemoconcentration. Initial laboratory studies to be obtained include a complete blood count, fibrinogen level, and prothrombin time. If unable to measure fibrinogen, then a D-dimer, fibrin monomer, or fibrin degradation products can be helpful. Ill-appearing or unstable patients, as well as those with evidence of neurotoxicity, should also have renal function studies, electrolytes, and a CPK measured. An electrocardiogram and chest radiograph should be obtained in patients with chest pain or respiratory distress.

All constrictive clothing, bandages and rings should be removed. Pressure immobilization bandages (PIBs) are sometimes placed in the field, although not recommended for the treatment of North American Crotalinae envenomation [51]. Although PIBs have been shown to delay systemic absorption of snake venom and are used in the prehospital management of elapid envenomations in Australia, the bandages have been shown to increase tissue necrosis and compartment pressures in an animal model of crotaline envenomation when compared to controls [52]. There are rare case reports of clinical deterioration following removal of constrictive bandages [53], however, the risk of such an event appears to be very low. In most cases, pressure bandages are applied incorrectly and are either too loose or too tight [54, 55]. Decreased perfusion to the extremity resulting from tight bandages and tourniquets may produce greater risk to the extremity than the bite itself. It is thus recommended that pressure bandages and tourniquets be removed, without waiting for antivenom availability. (Level of evidence (LOE III))

The affected extremity should be extended and immobilized with a posterior splint, and the splint loosely secured to the extremity with a nonconstrictive dressing. Immobilization may improve comfort and prevents the patient from

holding the extremity in a flexed position at the elbow or knee, which can trap edema, increase pain, and delay functional recovery. Children in particular tend to keep the knee bent at 90° and later have difficulty extending the knee and walking during the sub-acute phase of envenomation. After splinting, the immobilized extremity is then elevated above the level of the heart. For upper extremities, placing a stocking net around the splinted extremity and attaching the distal end to a raised IV pole provide maximal elevation. Lower extremities can be elevated on several pillows. Although evidence does not exist to support an association between a particular limb position and outcome, expert opinion is that elevation limits dependent edema and related pain in the distal extremity [40] (LOE III).

Some patients will present shortly after the bite with no symptoms or with only minimal swelling at the bite site. In such cases, the patient should be observed closely for development of symptoms, coagulation abnormalities, or progression of swelling, to determine if treatment with antivenom is indicated. There are several ways to assess swelling. One common way is to draw a line on the skin at the “leading edge” of the swelling, repeating the measurement and drawing a new line every 15–30 min. Since not all patients have an obvious “leading edge” noted on physical exam, another common method is to draw an outline of a tape measure in three locations, such as the hand, forearm and arm, or the foot, leg, and thigh, and measure the circumference at these same locations every 15–30 min until stable, after which measurements can be done progressively less frequently. Asking the patient if pain and swelling are worsening and performing repeated physical assessments for tenderness along lymphatic pathways are also helpful in determining whether the envenomation is progressing. If it is determined that antivenom is indicated, the frequency of swelling assessments can be decreased to every 1–2 h until the envenomation is under control.

Most patients with a pit viper bite will develop swelling or other symptoms within 8 h of the bite, although sometimes onset of appreciable swelling

may take up to 12 h. Similarly, onset of thrombocytopenia and hypofibrinogenemia are expected to occur within that time frame. The author’s practice is to obtain laboratory studies to assess for hemotoxicity upon presentation and again 6–8 h after the bite. If a patient has not developed any signs or symptoms of envenomation in the first 8–12 h after the bite, the patient likely has a dry bite, without venom deposition, and can be safely discharged from the hospital [40] (LOE II-3).

More often than not, patients present with clear signs of envenomation after a pit viper bite. Usually this amounts to pain and obvious swelling at the bite site, but occasionally patients present with shock or pending airway obstruction. Patients with bites to the head or neck area, and those with angioedema, are at risk for airway obstruction and should be intubated early if evidence of airway compromise is noted. Others who may be at risk for respiratory failure are those with neurotoxicity (weakness or fasciculations/myokymia) or decreased level of consciousness due to shock. Myokymia has been reported to respond to calcium chloride infusion [33, 45]. Hypotension can be initially treated with normal saline or lactated Ringers boluses, but if blood pressure does not quickly respond to fluids, then epinephrine should be administered. Epinephrine acts directly on peripheral alpha-1 receptors to produce vasoconstriction, which counteracts the vasodilatory effects of venom. Patients can be placed on an epinephrine infusion, titrating as needed. Anaphylactic reactions to venom are treated the same as anaphylaxis due to other causes, with epinephrine, antihistamines, and steroids.

There is general agreement that antivenom is indicated for patients who exhibit progressive swelling, hematologic toxicity, neurotoxicity, or systemic toxicity. Blood products are not indicated in the routine management of venom-induced thrombocytopenia and coagulopathy. Patients with serious bleeding despite administration of antivenom may require transfusion of packed red blood cells to replace losses. Platelets and fresh frozen plasma may be indicated as part of a massive transfusion protocol when bleeding is severe. Some clinicians also administer

cryoprecipitate to replace fibrinogen when patients are bleeding in the setting of venom-induced coagulopathy. In the absence of bleeding, there is no evidence to support transfusion of platelets, even when platelet counts are very low. However, some clinicians will administer platelets when platelet counts fall below 10 K/mm^3 despite antivenom treatment. Unfortunately, thrombocytopenia that is resistant to antivenom treatment may not improve with platelet transfusions either, and platelet count may rise only transiently, if at all, due to continued venom effect. Crotaline venom does not directly affect coagulation factors; however, management of severe, life-threatening bleeding may result in a dilutional coagulopathy for which factor replacement may be necessary.

Local wound care includes cleansing and superficial debridement or decompression of tense bullae. Tetanus prophylaxis should be updated. Erythema is a common characteristic of rattlesnake envenomation, which appears to occur as a result of venom-induced inflammation. Retrospective reviews of North American crotaline envenomation reveal a very low incidence of infection. Prophylactic antibiotics are not recommended [56, 57] (LOE II-3). Rarely, some patients may develop late infection following envenomation and should be assessed for such if fever, new erythema, swelling, or tenderness localized to the bitten limb develop in the days to weeks following the snakebite.

Compartment Syndrome

Envenomation of an extremity often results in tense swelling and severe pain. Pulses may be difficult to palpate due to massive edema, and the patient may have difficulty moving the fingers or toes due to edema and pain. Severe swelling can also alter sensation. In such cases, it can be impossible to determine clinically whether or not a compartment syndrome is present. Compartment syndrome is uncommon following crotaline snake envenomation because the fangs typically

do not penetrate the fascia. Animal studies demonstrate that injection of Crotalinae venom superficial to the muscle does not lead to myonecrosis [58]. However, cases of compartment syndrome do occur and the clinician must consider the diagnosis. When suspected, direct measurement of compartment pressures should be performed. (LOE II-3)

An extensive review of the role of fasciotomy in the treatment of Crotalinae envenomation found little evidence to support the practice, even in the setting of elevated compartmental pressures [58]. When venom is injected subfascially, myonecrosis occurs due to the direct toxic effect of venom, and this myonecrosis is not prevented or improved with fasciotomy [58]. A porcine model of intramuscular envenomation demonstrated that fasciotomy does not decrease myonecrosis and may actually worsen it [59]. However, there are very few case reports and no studies demonstrating use of antivenom alone to treat elevated compartment pressure. One case report involved a 17-month-old girl with a copperhead bite who received 12 vials of Crotalidae Polyvalent Immune Fab antivenom. Subsequent measurement of intracompartmental pressure (ICP) in the anterior compartment of the leg revealed ICP of 85 mmHg (normal: 0–20 mmHg). The patient did not have evidence of neurovascular compromise. Another 6 vials of antivenom were administered and 2 h later both swelling and ICP were declining. An additional 8 vials were administered and the patient had recovery with full function of the leg without fasciotomy [60]. Other case reports of elevated ICP treated without fasciotomy document pressures less than 60 mmHg [61–63]. If compartment pressure is elevated and the patient has evidence of continued perfusion to the distal extremity, it is reasonable, based on current evidence, to give additional antivenom in an effort to lower compartment pressure and avoid fasciotomy. The patient requires close clinical monitoring however, and if the pressure is not declining in response to antivenom, or there is clinical deterioration, fasciotomy should be performed. (LOE III)

Digit Dermotomy

Fingers are a common site for envenomation and have limited ability to expand in size to accommodate inflammatory responses to venom. The digit itself can function as a small compartment, and on occasion patients will lose perfusion in the finger necessitating a dermatomy, or neurovascular decompression procedure. Most permanent tissue loss in the digits is related to direct venom toxicity and will not be prevented with prophylactic digital dermatomy. However, in patients who present with or develop a cold and pale or cyanotic digit, without evidence of perfusion, a dermatomy is recommended as soon as possible. This procedure involves a longitudinal incision through the skin along the radial or ulnar aspect of the digit to decompress the neurovascular bundles. The incision extends from the web space to the mid-portion of the distal phalanx, avoiding the neurovascular structures. Digit dermatomy is performed based on clinical diagnosis of “compartment syndrome” of the digit, since intracompartmental pressures cannot be measured [43, 44] (LOE III).

Antivenom

Antivenom is the definitive treatment for snake envenomation. Antivenoms are produced by immunizing animals against venom and then collecting the serum from the animals, purifying it, and precipitating desired antibodies. First-generation antivenoms, initially developed during the late 1800s, consist of minimally purified sera and are associated with high risk of acute and delayed hypersensitivity reactions. Second-generation antivenoms represent an improvement upon these crude antisera, in that they undergo purification techniques to remove unwanted protein components and concentrate whole immunoglobulins [64]. Whole IgG antivenoms are in common use throughout the world for the treatment of snake envenomation. Despite improved potency and purity compared to first generation antivenoms, high rates of acute and delayed

hypersensitivity reactions are reported with some whole IgG antivenoms. Antivenin Crotalidae Polyvalent, the only antivenom used to treat North American crotalid envenomation from the 1950s through the turn of the century, was a whole IgG product. Acute and delayed hypersensitivity reactions were frequent occurrences with use of this product [2, 65].

Antivenoms that are currently FDA-approved for use in the treatment of North American Crotalinae envenomation represent “third generation” antivenoms. The antibodies in these products are cleaved and purified to isolate the Fab or F(ab')₂ fragments. Antibody fragments generally have an improved safety profile over second-generation whole IgG antivenoms due to elimination of the immunogenic Fc portion of the antibody [64]. Despite this improvement in safety, caution must always be used when administering antivenom, since anaphylaxis or rate-related anaphylactoid reactions can occur with exposure to any animal-derived protein and may be life-threatening. All patients should receive antivenom in a monitored unit, such as an emergency department or intensive care unit.

The advent of whole IgG antivenoms purified using caprylic acid has the potential to change perceptions of safety for whole IgG antivenoms, as this technique appears to be associated with comparatively safe antivenoms, similar in overall safety profile to fractionated IgG antivenoms and with arguably similar or greater neutralizing potency, but significantly lower production costs [66].

Antivenoms work by binding and neutralizing venom antigens and enhancing their elimination. While antivenom can stop the progression of swelling and reverse some venom effects, such as coagulopathy, antivenom is not effective in reversing tissue injury that has already occurred. Antivenom has also not been demonstrated to prevent tissue necrosis. However, animal studies have demonstrated that antivenom can increase perfusion pressure and decrease compartment pressure in an extremity following intramuscular venom injection [67, 68].

The effectiveness of a particular antivenom at reversing a specific venom effect depends on the specificity of the antivenom for the venom antigens to which a patient was exposed. Polyvalent antivenoms offer protection against the venom of more than one snake species. Often, these antivenoms are also effective against snake venoms that are closely related to that of the species used to make the antivenom. However, efficacy against different venom effects may vary. Thus, an antivenom may not consistently reverse all effects of envenomation, even when indicated for treatment of envenomation by a particular species. For example, antivenom may or may not reverse neurotoxicity due to North American crotaline envenomation [35, 46]. Thrombocytopenia may also be refractory to treatment with antivenom [69]. In particular, thrombocytopenia following Timber rattlesnake (*C. horridus*) envenomation is known for resistance to antivenom [70].

Crotalidae Polyvalent Immune Fab (Ovine)

Crotalidae Polyvalent Immune Fab (Ovine) (CroFab[®]) is approved by the United States Food and Drug Administration (FDA) for use in the management of envenomation by all North American crotalid species. Although not FDA-approved for use in envenomations by nonnative crotaline snakes, CroFab has also been used with apparent success in a *Crotalus durissus* (South American rattlesnake) envenomation [71]. When administered with venom, CroFab has decreased lethality in mice from two South American crotaline venoms (*C. durissus* and *Bothrops atrox*) [72].

CroFab is made by immunizing sheep with venom from one of the following four North American snakes: *Crotalus atrox* (Western Diamondback rattlesnake), *C. adamanteus* (Eastern Diamondback rattlesnake), *C. scutulatus* (Mojave rattlesnake), and *Agkistrodon piscivorus* (cottonmouth). The ovine venom-specific immunoglobulins are collected and cleaved with papain to isolate the Fab fragments. Since small amounts of papain may be present in the final product, allergy to papain or papaya is considered a contraindication to CroFab [73]. After cleavage, the

four monovalent antivenoms are then mixed and prepared as a lyophilized powder in vials requiring reconstitution prior to use. The protein content of each vial is approximately 1 g [73]. The antivenom can be reconstituted in sterile water or normal saline. When done correctly, reconstitution of the lyophilized antivenom should take approximately 1 min [74]. A rapid and effective approach to preparation of antivenom is to take a 250 ml bag of saline, withdraw 20–25 mL and inject into a vial of CroFab until the vial is filled. As the vial fills, air must be withdrawn from the top of the vial. The bottles should be manually rolled and inverted to facilitate dissolution of the powder [74]. When solid particles have dissolved, the contents can then be drawn up and injected back into the original 250 mL bag. The reconstituted dose of antivenom (4–6 vials for a typical control dose), now dissolved in 250 mL of saline, can be administered over 1 h [73]. The infusion may be initiated at a slow rate, 25 mL per hour, for the first 5 min to ensure the patient does not develop an acute hypersensitivity reaction to the antivenom. After 5 min, the infusion rate should then be increased to the full 250 ml per hour [73]. Some authors have advocated administering CroFab as a continuous infusion, but this method has not been studied and is not recommended at this time [75].

CroFab should be initiated as soon as possible after diagnosis of envenomation is made and indications for antivenom are met. (LOE II-3) Early administration will ideally prevent further progression of local tissue effects which contribute to morbidity. For example, the more swelling that has occurred, the longer it will take for resolution and functional recovery. No time limit has been identified after which antivenom is no longer effective. There are cases reported in which antivenom was used successfully more than 24 h after envenomation [63, 76]. An evidence-informed treatment guideline is available to assist in clinical decision-making regarding administration of CroFab antivenom [40].

The initial dose of CroFab is 4–6 vials, unless the patient presents in shock or with serious active bleeding, in which case an initial dose of 8–12 vials has been recommended by

an evidence-based consensus [40]. This can be followed by additional 4–6 vial doses as needed to achieve initial control of the envenomation. The manufacturer describes “initial control” as complete arrest of local injury and return of coagulation abnormalities and systemic signs to normal [73]. This may be an overly optimistic target for establishment of initial control, and strict adherence to these guidelines may lead to unnecessary dosing of antivenom. While complete arrest of swelling and systemic toxicity (such as hypotension) should be criteria for initial control, resolution of hypofibrinogenemia may require several hours despite adequate antivenom administration. Additionally, local findings such as hemorrhagic bullae and ecchymosis may continue to progress for days and are not expected to arrest with antivenom treatment. Neurotoxic effects may respond to antivenom, but experience is mixed.

Once initial control is obtained, administration of maintenance doses is then recommended per the manufacturer’s prescribing information [73]. Maintenance antivenom consists of two vial doses which are given every 6 h \times 3 doses, for a total of six vials over 18 h. In clinical trials of this antivenom, maintenance doses were shown to decrease recurrence of local swelling in the first 24 h after control of the envenomation and to decrease the risk of late hematologic toxicity [73] (LOE I). All patients, particularly those with copperhead envenomations, which are generally less severe than rattlesnake envenomations, may not benefit from maintenance doses. Clinicians should speak with local medical toxicology specialists to determine the need for maintenance antivenom based on regional experience.

Acute hypersensitivity reactions to CroFab have been reported in 6% of patients. Although most reactions appear to be mild, are easily treated, and do not preclude completion of antivenom, severe life-threatening reactions with airway swelling and hypotension do occur [73, 77]. Delayed hypersensitivity reactions appear to be less common. These Type III hypersensitivity reactions, known as serum sickness,

develop between 3 days and 3 weeks after treatment and are characterized by urticaria, rash, arthralgias, fever, and myalgias [65]. They may be treated with antihistamines and corticosteroids.

Late Venom Toxicity Following Treatment with CroFab

After CroFab is administered, venom antigens are bound to antivenom and are no longer detected in the serum. As CroFab is eliminated, unbound venom antigens may return to the circulation. The elimination half-life of CroFab is estimated to be approximately 15 h [73]. The rate of clearance of unbound antivenom exceeds the rate of clearance of unbound venom antigens, which may be present in the circulation for weeks following an envenomation. This recurrent venomemia has been associated with recurrence of clinical venom effects [27, 28].

Local recurrence is the renewed progression of swelling after initial cessation following treatment with antivenom. In the initial clinical trial of CroFab, 27% of patients developed recurrent swelling in the first 24 h after antivenom treatment. In the second clinical trial, after initial control was established, patients were randomized to receive either scheduled maintenance doses of antivenom or “as needed” doses for recurrent venom effects. Local recurrence did not occur in patients who received maintenance doses [73, 78]. Patients who do not receive maintenance doses of antivenom should be observed in the hospital for 18 h following control of the envenomation with CroFab [40]. Local recurrence or worsening trends in platelets or fibrinogen during that time may be treated with additional antivenom. (LOE III)

Late hematologic toxicity is an important and potentially dangerous consequence of rattlesnake envenomation that has been treated with CroFab. In a clinical trial of CroFab where maintenance antivenom was not used, 53% of patients developed hematologic recurrence [78, 79]. With maintenance dosing following initial control, the incidence of late hemotoxicity was decreased [73]. In two subsequent cohorts of rattlesnake envenomation in Arizona, hematologic

recurrence was reported in 28.5% and 32% of patients receiving routine maintenance doses of antivenom [80, 81]. The risk of recurrence appears to be highest in patients who exhibit hematologic toxicity during their initial treatment phase. However, patients who had normal laboratory studies throughout their initial presentation and hospitalization have also been reported to develop late onset hematologic toxicity [80]. This is thought to be due to early prevention or “masking” of these effects by administration of antivenom. Predictors of late hematologic toxicity have not been identified. Data from one retrospective case series suggest that lack of fibrin degradation products or other evidence of coagulopathy, as well as normal platelets that do not rise >20% following CroFab treatment, may identify those patients who are not at risk for late toxicity [82]. However, larger studies must be done before recommendations can be made against diligent laboratory monitoring of all rattlesnake envenomation patients treated with CroFab. For patients with copperhead envenomations who do not exhibit hematologic toxicity during initial treatment, routine laboratory reassessment in the days to weeks following CroFab administration may not be necessary [42] (LOE III).

Delayed or recurrent coagulopathy and/or thrombocytopenia are relatively common following treatment of rattlesnake envenomation with CroFab, but are rarely associated with serious bleeding. Nonetheless, life-threatening and even fatal bleeding complications have occurred in this setting [83–86]. Clinicians must be diligent in monitoring patients for delayed or recurrent hematologic toxicity in the days to weeks following treatment. Patients should be warned to watch for evidence of hemotoxicity, such as excessive bruising, gingival bleeding, or hematochezia, and to avoid activities that place them at risk for injury, such as contact sports. Even minor surgeries should be avoided during the 2 weeks after CroFab treatment. It is strongly recommended that all patients have platelets, fibrinogen, and prothrombin time rechecked 2–3 days following

the last dose of antivenom and again 5–7 days following the last dose of antivenom. Some patients manifest late toxicity soon after treatment, but for others the initial laboratory evaluation may be normal yet they will still go on to develop severe hematologic toxicity, with undetectable fibrinogen and dangerously low platelet counts [81] (LOE III).

Not all patients with late hematologic toxicity require retreatment with antivenom. Mild to moderate coagulopathy, thrombocytopenia, or even a combination of the two can be managed with observation on an out-patient basis. When platelets or fibrinogen are first noted to drop, they should be repeated within a day or two depending on how severe the drop and how rapidly it developed. Retreatment with antivenom should be considered if platelets drop below 25 K/mm^3 regardless of fibrinogen level, if platelets drop below 50 K/mm^3 with fibrinogen less than 80 mg/dL , or if there is any evidence of bleeding or other risk of bleeding. Spontaneous bleeding is unlikely to occur above these cut-offs [78]. Isolated hypofibrinogenemia or afibrinogenemia does not require retreatment with antivenom if platelet count is normal. The risk of bleeding in the setting of isolated afibrinogenemia is low [78], and in the author’s practice such coagulopathy without thrombocytopenia is not routinely retreated with antivenom. However, if the patient has additional risk factors for bleeding or has been using aspirin or another antiplatelet agent that would render platelets dysfunctional, then the author’s practice is to retreat with antivenom. Other potential risk factors for bleeding that would favor retreatment for late hemotoxicity include high risk of injury (i.e., a toddler prone to falls), hypotension or shock following the initial snakebite event, pregnancy, or use of anticoagulant medications [83] (LOE III). The ideal treatment strategy for late hemotoxicity has not been identified. Initial antivenom doses ranging from 2–6 vials have been used with varying success in patients with delayed or recurrent hematoxicity. Late hemotoxicity can be refractory to retreatment with CroFab.

Crotalidae Equine Immune F(ab')₂

Crotalidae equine immune F(ab')₂ (Anavip[®]) received FDA approval for the treatment of North American rattlesnake envenomation in May 2015, although it is not expected to be available for commercial use in the USA until 2018. Anavip is made by immunizing horses with venoms from *Bothrops asper* and *Crotalus simus*. The immunoglobulins are isolated and cleaved with pepsin to yield F(ab')₂ fragments. These fragments have a longer elimination half-life than Fab fragments [27, 87]. The protein content is approximately 120 mg per vial. Anavip is provided in lyophilized form in vials that can be reconstituted with 10 ml of normal saline. Reconstitution can be achieved in less than 1 min with gentle swirling of the vials.

The initial dose of Anavip is 10 vials. After reconstitution of each vial, this total dose can be administered in a volume of 250 mL normal saline. The initial rate should be set at 25–50 mL per hour to observe for evidence of acute hypersensitivity. If the patient tolerates this rate for 5 min, the infusion rate should be increased to 250 mL per hour so that the entire dose is administered in 1 h. The patient should then be reassessed for signs of ongoing venom toxicity, such as continued progressive swelling, worsening thrombocytopenia or coagulopathy, or systemic effects such as hypotension. If control of the envenomation is not gained with the initial dose of Anavip, an additional 10 vial dose may be given. Reassessment and redosing should continue until the patient is stable and clinical signs of envenomation are not worsening. Once control of the envenomation has been established, the patient should continue to be observed for any reemergence of venom effects for 18 h after the last dose of antivenom. If swelling, hemotoxicity, or other symptoms do reemerge, then additional 4 vial doses of Anavip are indicated [87].

The advantage of Anavip over CroFab is a decreased risk of developing late coagulopathy or thrombocytopenia. (LOE 1) In a small phase 2 clinical trial where subjects were followed for 2 weeks, venom levels measured

via immunoassay remained undetectable throughout follow-up in those treated with Anavip, while venom levels rose during the follow-up period in four out of six subjects treated with CroFab. All subjects treated with CroFab developed late hemotoxicity in this study, while only one in the Anavip group developed late thrombocytopenia, with a platelet nadir of 127 K/mm³, and no Anavip subject developed hypofibrinogenemia [27]. In a subsequent phase 3 randomized, blinded, controlled trial, rates of late coagulopathy and thrombocytopenia were compared between three groups: Anavip with maintenance doses, Anavip without maintenance doses, and CroFab with maintenance doses. Late coagulopathy occurred in 10% of subjects receiving Anavip with maintenance and 5% of subjects receiving Anavip without maintenance. In the CroFab group, 30% of subjects developed late hematologic toxicity, consistent with previous studies. Interestingly, all (6) subjects in the Anavip groups who developed late hemotoxicity were enrolled at a single site in California, while the 11 subjects in the CroFab group with late hemotoxicity were distributed among seven sites in five states [88]. Future studies will need to determine if late hematologic toxicity following treatment with Anavip is truly limited to a single geographical area. There was no difference in incidence of immune reactions between groups [88]. Until Anavip becomes available for use and further clinical experience is gained, specific recommendations regarding use of Anavip vs. CroFab for the treatment of rattlesnake envenomation cannot be made.

Special Populations

Children

Children experience the same clinical manifestations as adults following snake envenomation [89]. Dosing of antivenom follows the same guidelines as that for adults, and total doses administered to children and adults are similar

[2, 73]. Fluid overload as a result of antivenom dosing has not been reported in children, but in very small children requiring large doses of antivenom, the drug may be diluted in lower total volumes of fluid if necessary and administered over 1 h.

Pregnancy

There is limited information available regarding outcomes in pregnant patients envenomated by North American rattlesnakes. Snake venom poses a risk to both the mother and fetus, and poor fetal outcome may result despite a good outcome in the mother. Venom has been shown to induce uterine contractions in animal models, and placental abruption has been reported. Most published reviews and case series of snakebite in pregnancy include nonnative envenomations, limiting the applicability of findings to patients envenomated by native species. In one review of 30 envenomations during pregnancy, maternal death occurred in 10% of cases while 43% of fetuses died [90]. A more recent review of the worldwide English literature regarding pregnancy and snakebite identified 213 cases. Maternal death rate was found to be 4.2%, with a fetal death rate of 19.2%. Deaths occurred in all three trimesters. Of those with bites by North American species, there was one fetal death and one neonatal death [91]. The fetal death was reported in a small case series in 1966, in which the mother was described to be hypotensive and tachycardic on presentation following the bite by an unknown species of snake. A dead fetus was delivered at 9 weeks gestational age 24 h after the bite [92]. The neonatal death, reported in 1984, occurred 6 weeks after the bite in a 28-week pregnant patient who presented with hypotension after a copperhead envenomation and was treated with epinephrine. The baby had evidence of intracranial hemorrhage at birth and died at 4 days of age [93]. A more recent poison center database review of native snake envenomations included 65 pregnant

patients, most of whom were reported to have copperhead bites. Eleven patients were treated with antivenom and there were no deaths. Long-term outcomes were not reported [1].

Pregnant patients who present with a snake envenomation should receive supportive care and fetal monitoring. Neither CroFab nor Anavip have been studied in pregnant women and both are classified as Category C drugs [73, 87]. CroFab has been given to pregnant women without evidence of harm. Due to the potential morbidity to both mother and fetus resulting from snake envenomation, pregnant women should receive antivenom if they meet usual indications for treatment. Signs of fetal distress or uterine contractions considered to result from the envenomation should also prompt treatment with antivenom (LOE II-3).

Following treatment with antivenom, pregnant women should be monitored very closely for late hemotoxicity. This recommendation is based on a recent, as-of-yet unpublished case of massive vaginal hemorrhage and first-trimester fetal loss that occurred in the setting of late coagulopathy with afibrinogenemia and normal platelet count. The author recommends monitoring fibrinogen levels and platelet counts every 1–2 days during the first 7–10 days after antivenom treatment, until clearly stable without a trend toward abnormal values. Due to the risk for spontaneous abortion in the setting of hypofibrinogenemia or afibrinogenemia, the author recommends treatment of late coagulopathy with antivenom, even if platelets are within the range of normal.

Indications for ICU Admission

Evidence of envenomation with local progression
Significant coagulopathy, thrombocytopenia, or bleeding
Systemic symptoms, such as hypotension or shock
Neurotoxic findings
Need for antivenom treatment

Key Points

1. Presenting clinical findings following rattlesnake envenomation rarely represent peak severity of illness
2. Frequent clinical reassessment is important, as envenomation is a dynamic process, which may appear to stabilize and then subsequently worsen and require additional therapy
3. Antivenom therapy should be administered as early as possible to prevent worsening local findings and reduce morbidity
4. Thrombocytopenia and coagulopathy should be treated with antivenom, not with blood products, unless these findings are resistant to antivenom therapy and patient is bleeding
5. Fasciotomy should not be performed unless compartment pressure is measured and elevated
6. Following treatment with antivenom and prior to hospital discharge, it is important to give patients clear information regarding risk of late hematologic toxicity, potential for bleeding, and importance of continued laboratory monitoring up to 2 weeks post antivenom

Criteria for ICU Discharge

Envenomation no longer progressing
Further need for antivenom not anticipated

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Snakebites can cause life-threatening injuries, sometimes requiring intensive care. The most important snakebites occurring in Latin America are provoked by species of the family Viperidae (*Bothrops*, *Crotalus*, and *Lachesis*) and Elapidae (genus *Micrurus*). Viperid venoms induce prominent local tissue pathology, which may lead to permanent sequelae and systemic disturbances associated with coagulopathies, bleeding, hemodynamic alterations, and acute kidney injury. Elapid snake venoms, and South American rattlesnake venoms, induce neurotoxic manifestations associated with paralysis of various muscles, including respiratory muscles. Treatment of envenomation is based on parenteral administration of antivenoms. Severely envenomed patients need an adequate life support therapy such as treatment of shock, assisted ventilation, and renal therapy replacement.

Epidemiological Aspects

Snakebite envenomation constitutes a relevant public health problem in Central and South America, where an estimated number of 70,000 cases occur every year [1]. However, owing to underreporting of this neglected tropical disease in the region, it is likely that the actual magnitude of snakebite envenomation is higher.

As in other parts of the world, this disease affects mainly people living in impoverished agricultural settings, including native communities. It affects predominantly young males, but accidents are reported in people of all ages. A large proportion of snakebites occur while people are performing agricultural work, being therefore a rural occupational health problem. The majority of snakebites occur in the feet (about 50% of the cases), followed by hands (about 30%), implying that basic preventive measures should include the use of shoes and exercising care when touching the ground with the hands. The number of bites varies depending on the time of year, with higher incidence during the rainy season, probably in association with the onset of agricultural duties; natural disasters, particularly flooding, increase the risk of snakebites. Weather fluctuations,

including El Niño Southern Oscillation (ENSO), are known to affect the incidence of snakebites [2]. Indigenous communities are particularly vulnerable to this disease due to a high incidence, and to the difficulties in accessing health centers.

It is estimated that the total number of snakebites occurring every year in Central and South America are approximately 4,000 and 50,000 cases, respectively [1, 3]. In Central America, the highest number of cases and incidence is in Panama, with around 2,000 bites per year [1]. In South America, Brazil reports 26,000–29,000 cases per year [4], Venezuela 7,000, Colombia 4,000, and Peru, Ecuador and Bolivia around 1,500 cases per year each (see [1] and references therein), although the actual numbers are likely to be higher. Regarding fatalities, the mortality rate per 100,000 population described for some countries are: Costa Rica: 0.02–0.15 [5]; Panama, 0.5 [1]; Venezuela, 0.1–0.2 [6]; Brazil, 0.05 [4]; Ecuador, 0.05 [7]. The case fatality rate in Brazil is around 0.42%, and in Costa Rica is about 0.5%. Snakebite envenomation results in permanent physical and psychological sequelae in an unknown number of affected people, thus generating significant personal and social suffering, an aspect of this disease which has not been appropriately documented.

Snake Species of Highest Medical Relevance

The vast majority of snakebites occurring in Latin America are caused by species of the family Viperidae, particularly of the genus *Bothrops* spp. [8, 9]. In Brazil, for instance, about 70% of snakebite cases are inflicted by species of *Bothrops*. The most important species are *Bothrops asper* (Fig. 1a) in Central America and northern parts of South America and *B. atrox* (Fig. 1b) in the Amazonian regions of South America. Other species of *Bothrops* spp. which cause a high number of cases in South America are *B. jararaca* (Fig. 1c), *B. alternatus*, *B. moojeni* (Fig. 1d), and *B. neuwiedi*. On the other hand, envenomation by various subspecies of the South American rattlesnake *Crotalus durissus* (Fig. 2) can be of high severity [9, 10], with a



Fig. 1 *Bothrops* snakes. (a) *B. asper* from Costa Rica; (b) *B. atrox* from Brazilian Amazonia; (c) *B. jararaca* from Brazil; (d) *B. moojeni* from Brazil (Photograph of *B. asper*

by Mahmood Sasa, published in [90]. Photographs B, C, and D by Giuseppe Puorto)



Fig. 2 *Crotalus durissus terrificus* from Brazil (Photograph by Giuseppe Puorto)



Fig. 3 *Lachesis muta* from Brazil (Photograph by Giuseppe Puorto)

reported case fatality rate in Brazil of 0.98% (as compared to 0.39% in the case of *Bothrops*) [11]. Envenomation by *Lachesis* spp. (Fig. 3) in Central and South America are scarce, although they usually are highly severe [12].

Coral snakes (genera *Micrurus*, *Leptomicrurus* and *Micruroides*) (Fig. 4) are the representatives of the family Elapidae in the Americas, together with

the pelagic sea snake, *Pelamis platura*. Coral snakes are responsible for 1–2% of snakebites in Central and South America, with the following species being responsible for the majority of these cases: *Micrurus nigrocinctus* in Central America and *M. mipartitus*, *M. corallinus*, *M. frontalis*, *M. lemniscatus*, and *M. spixii* in South America. Bites by *Pelamis platura* are extremely rare.

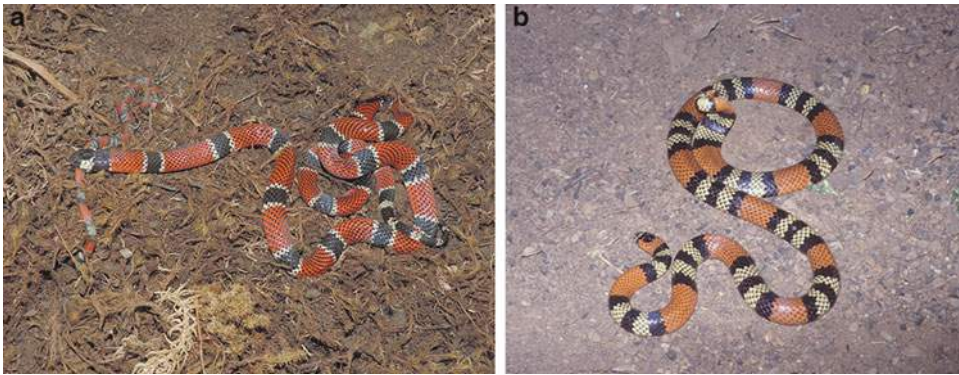


Fig. 4 *Micrurus* snakes from Brazil. (a) *M. corallinus*. (b) *M. frontalis* (Photographs by Giuseppe Puorto)

Pathophysiology: Mechanism of Action of Venoms

Venoms of the majority of species of the family Viperidae: These venoms are characterized by a high content of hydrolytic enzymes, mostly zinc-dependent metalloproteinases, phospholipases A_2 , and serine proteinases [13]. Metalloproteinases and phospholipases A_2 are largely responsible for the drastic local tissue pathology characteristic of envenomation by viperid species, i.e., hemorrhage, myonecrosis, dermonecrosis, blistering, lymphatic vessel damage, and extracellular matrix degradation [14]. These pathological alterations are associated with a prominent inflammatory reaction characterized by edema and pain.

Myonecrosis is due to a direct disruptive effect of myotoxic phospholipases A_2 on the integrity of the plasma membrane of skeletal muscle cells, in addition to the consequences of local ischemia generated by the vascular alterations induced by the venom [14]. Hemorrhage, in turn, is caused by the alterations induced by venom metalloproteinases on the basement membrane of capillary blood vessels, resulting in extravasation [15]. Alterations in the skin, i.e., dermonecrosis and blistering, are mostly caused by metalloproteinases, which also cause widespread degradation of the extracellular matrix.

Upon systemic distribution of venom components, metalloproteinases cause systemic hemorrhage, by damaging the structure of capillary vessels in various organs, including the brain. Systemic bleeding is potentiated by the alterations

induced by venom components in the hemostatic system. Procoagulant metalloproteinases (prothrombin activators and factor X activators) and serine proteinases (“thrombin-like enzymes”) induce the formation of microclots, with the consequent consumption of clotting factors, especially fibrinogen. This causes the alteration of clotting tests, such as the whole blood clotting time, prothrombin time, and partial thromboplastin time [16]. This defibrinogenating effect is associated with activation of the fibrinolytic system, with the generation of fibrin-degradation products. In addition, viperid venoms have components, such as disintegrins, that affect platelet aggregation. These alterations in coagulation and in platelet function contribute to the bleeding initiated by the disruption of microvessels by the action of metalloproteinases [17]. As a consequence of the systemic bleeding, hemodynamic alterations often ensue, which might end up in a cardiovascular shock.

Viperid snake venoms also affect the kidney, often causing acute kidney injury. This effect is of multifactorial origin, as it is due to (a) the action of nephrotoxic components; (b) the ischemia resulting in the kidney as a consequence of hemodynamic alterations; (c) the toxicity induced by the presence of hemoglobin and myoglobin in the kidney tubules; and (d) the action of metalloproteinases in the basement membrane of the glomeruli.

Venoms of South American rattlesnakes:

The venoms of South American rattlesnakes of the species *Crotalus durissus* have a mechanism of action which greatly differs from those of the

majority of viperid species. These venoms are characterized by a high concentration of the neurotoxic and myotoxic phospholipase A₂ heterodimeric complex “crotoxin.” This toxin provokes neuromuscular paralysis through a presynaptic mode of action, thus resulting in paralysis of various muscles, including respiratory muscles. In addition, crotoxin is a potent myotoxin, inducing generalized muscle damage, i.e., rhabdomyolysis. In turn, the massive release of muscle-derived proteins, such as myoglobin, exerts a deleterious effect in the kidneys, generating acute kidney injury [10]. In addition, the venoms of subspecies of *C. durissus* induce clotting disturbances, i.e., defibrinogenation [18], through the action of a thrombin-like serine proteinase.

Venoms of coral snakes: The venoms of coral snakes (*Micrurus* spp.) contain high amounts of postsynaptically acting neurotoxins of the three-finger family (α -neurotoxins), together with phospholipases A₂ [19]. The main effect induced by these toxins is a neuromuscular blockade owing to the high-affinity binding of α -neurotoxins to the nicotinic cholinergic receptor at the motor end plate of muscle fibers. This results in clinical manifestations of descending flaccid neuromuscular paralysis, which may eventually end in paralysis of respiratory muscles. Some of these venoms also possess neurotoxic phospholipases A₂ which affect neuromuscular transmission at the presynaptic level. *Micrurus* spp. venoms also contain myotoxic phospholipases A₂; however, owing to the relatively low amount of venom that these snakes are able to inject in a bite, systemic myotoxicity seldom develops in coral snakebites.

Clinical Presentation

In most cases of snakebite, the snake responsible is not captured for identification; even when it is captured, there is rarely an expert on hand to make the correct identification. Therefore, the diagnosis is typically based on the victim's history and especially on clinical manifestations and laboratory tests results. Consequently, careful history-taking and physical examination are essential, together with ordering the appropriate laboratory tests. In addition, some snakebites are so-called dry bites (i.e., those that result in no envenomation).

Antivenom should be administered only to patients who present with clinical and/or laboratory manifestations of envenomation.

The severity of envenomation depends on several factors, including the amount of venom injected, the time from the bite to the administration of antivenom, the anatomical area affected (bites on the head or neck are usually more severe), and the medical history, as well as the size of the victim (the consequences of a bite can be more severe in children). In addition, variations in venom composition observed within and between species, attributable to ontogenetic and geographic factors, can influence the severity of envenomation.

***Bothrops* and *Bothrops*-Like Snakes (Including *Agkistrodon*, *Atropoides*, *Bothriechis*, *Bothriopsis*, *Bothrocophias*, and *Porthidium*)**

The so-called *Bothrops* group includes the genera *Atropoides*, *Bothrops*, *Bothriechis*, *Bothriopsis*, *Bothrocophias*, and *Porthidium*, although snakes of the *Bothrops* genus itself are responsible for more bites than are those of the other genera. Although there is little information about snakebites caused by *Agkistrodon*, *Atropoides*, *Bothriechis*, *Bothriopsis*, *Bothrocophias*, and *Porthidium*, the available data indicate that envenomation by species belonging to any of these genera provokes manifestations similar to those observed in individuals with *Bothrops* envenomation. Therefore, the term “*Bothrops* syndrome” will be used in order to refer to such manifestations, collectively [20–23].

Clinical Presentation

Local Effects

After a *Bothrops* bite, there is a small extent of bleeding at the venom inoculation site, where there can also be edema, pain, redness, and bruising (Fig. 5). Less frequently, there is persistent bleeding at the bite site. The pain can initially be mild, becoming more severe as the edema increases. Bruising at the site can be minimal in the first hours after the bite and more pronounced

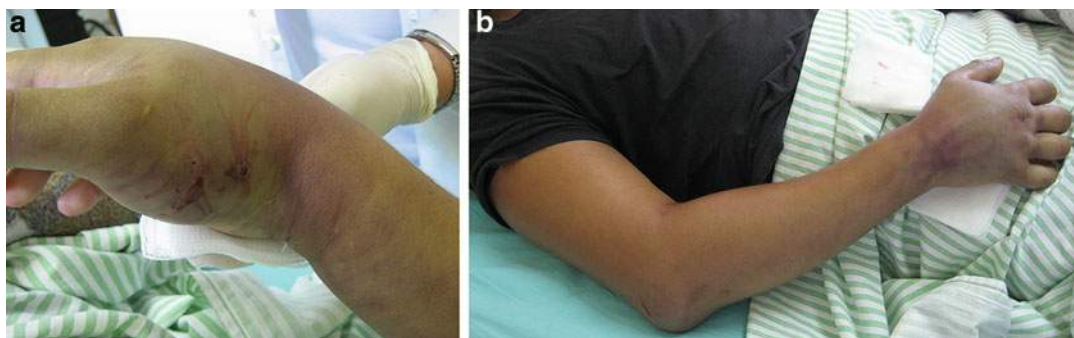


Fig. 5 Clinical features of *Bothrops* envenomation 3 h after bite. (a) Fang puncture marks are visible on hand. (b) Swelling and bruising in right arm

Fig. 6 *Bothrops* envenomation. (a) Serous-hemorrhagic blister at the bite site 1 day after snakebite. (b) Serous blisters at bitten limb 2 days after the snakebite



on the following day. The extent of edema increases during the first 24 h following the bite and can involve all of the affected extremity, reaching the trunk in some cases. Serous-hemorrhagic or hemorrhagic blisters (Fig. 6) can appear during the first 24 h after the bite [24–27].

Systemic Effects

The most common systemic manifestation in *Bothrops* syndrome is coagulopathy, i.e., blood

incoagulability [26]. However, in envenomations caused by *Bothriechis lateralis*, *Porthidium nasutum*, *P. ophryomegas*, or *P. lansbergii*, coagulopathy might not occur because the venoms of those snakes do not have procoagulant components and do not induce defibrin(ogen)ation in vivo [28, 29]. There can be ecchymosis (local and regional) (Fig. 7) and spontaneous bleeding (Fig. 8) (such as gingival bleeding, epistaxis, and hematuria). Although cases of



Fig. 7 *Bothrops* envenomation: patient was bitten in right hand; ecchymoses are observed in both arms



Fig. 8 Gingival bleeding 5 h after *Bothrops* snakebite

severe bleeding (hematemesis, hemoptysis, rectal bleeding, metrorrhagia, subcapsular hepatic hematoma, and central nervous system bleeding) have been reported, such cases are rare (Table 1). Even less common are reports of hypotension and shock, which can be due to bleeding and fluid loss into the third space, induced either directly by the action of venom in the microvasculature or by the release of inflammatory mediators [20, 24, 25, 30–33].

Snakebites caused by young snakes of some species can produce minimal local alterations (Fig. 9), although such bites often result in significant coagulopathy. That can be attributed to ontogenetic variations among venoms [34–37].

Complications

Local

Local complications of *Bothrops* syndrome include infection (Fig. 10) (cellulitis, abscesses, and fasciitis), necrosis (Fig. 11), and compartment syndrome (due to swelling, which can compress the neurovascular bundle). The frequency of amputation is low (Table 1).

Infection: The tissue damage resulting from envenomation predisposes to infection. Infection is caused by bacteria present in the mouth, fangs, or venom of the snake and is more common in moderate-to-severe envenomation. The organisms most often isolated from abscesses secondary to *Bothrops* envenomation are gram-negative bacteria, such as *Morganella morganii*, *Proteus mirabilis*, *Proteus rettgeri*, *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, *Escherichia coli*, and *Klebsiella pneumoniae*. Gram-positive bacteria (*Staphylococcus aureus*, group D streptococci, and *Streptococcus viridans*) and anaerobic bacteria have also been isolated [38–41].

Necrosis: Necrosis resulting from *Bothrops* envenomation is associated with bites from adult snakes, bites occurring in certain anatomical areas (necrosis is more common in the fingers), and with the use of tourniquet [35, 42, 43].

Compartment syndrome: Compartment syndrome is a less common complication [38, 42] that usually occurs early (in the first 24 h after the snakebite). It can evolve to severe outcomes, such as loss of muscle mass as well as neuropathy and amputation. The diagnosis of compartment syndrome in snakebite victims is difficult, because the usual manifestations of snake envenomation, i.e., pain and swelling, can mimic those of compartment syndrome. Careful clinical examination and serial reexamination is required. Tissue pressure should be measured when possible in order to avoid misdiagnosis and unnecessary surgery. The combination of clinical findings consistent with compartment syndrome and increased intracompartmental pressure is ideal for establishing the diagnosis and for more precisely determining whether fasciotomy is indicated [44, 45].

Table 1 Characteristics of envenomations induced by various *Bothrops* species

Variable	Otero et al. 1996 [51] (n = 39)	HVB, 2004–2005 (n = 50)	Pardal et al. 2004 [52] (n = 73)	Milani et al. 1997 [30] (n = 29)	Kouyoumdjian et al. 1990 [35] (n = 22)
<i>Bothrops</i> species	<i>B. asper</i>	<i>B. jararaca</i>	<i>B. atrox</i>	<i>B. jararacussu</i>	<i>B. moojeni</i>
Time from snakebite to admission	<5 h: 33%	<6 h: 92%	NA	<6 h: 63%	NA
Severity					
Mild	39%	80%	59%	NA	23%
Moderate	38%	16%	36%	NA	59%
Severe	23%	4%	5%	NA	14%
Dry bite	0%	0%	0%	3%	4%
Clinical presentation					
Local					
Edema	100%	100%	100%	93%	100%
Bleeding	49%	NA	38%	NA	NA
Blister	13%	7%	3%	24%	NA
Systemic					
Hemorrhage (all types)	NA	6%	16%	7%	5%
Gingival bleeding	31%	4%	14%	+	NA
Hemoptysis	NA	0%	7%	+	NA
Hematemesis	NA	2%	1%	+	NA
Macroscopic hematuria	23%	0%	7%	+	NA
Hypotension/shock	0%	0%	0%	7%	0%
Coagulopathy	85%	60%	41%	48%	64%
Complications					
Infection	10%	10%	10%	17%	18%
Necrosis	13%	12%	3%	21%	9%
AKI	20%	12%	40%	14%	0%
Evolution					
Amputation	3%	0%	0%	3%	NA
Death	0%	0%	0%	10%	5%

HVB Hospital Vital Brazil, NA not available, AKI acute kidney injury, +: the manifestation is observed, but the frequency is not available

Systemic

Systemic complications of *Bothrops* syndrome include acute kidney injury (AKI) and septicemia. Chronic renal failure is uncommon. Reversible posterior leukoencephalopathy was reported in a patient bitten by a *Bothrops asper* [46]

AKI: The frequency of AKI in *Bothrops* syndrome varies from 1.6% to 38.5%. The pathophysiology of *Bothrops* envenomation-induced AKI involves several factors, such as release of inflammatory mediators, hemodynamic

changes, disseminated intravascular coagulation, intravascular hemolysis, and a possible direct action of venom toxins in the kidneys. It is more common in older age groups and is associated with a longer time from snakebite to antivenom therapy. The most common change in renal structure is acute tubular necrosis. Cases involving bilateral cortical necrosis, acute glomerulonephritis, or interstitial nephritis with mesangial proliferation have also been reported [47, 48].

Septicemia: In *Bothrops* syndrome patients, septicemia is rare. It can occur secondary to infections in the subcutaneous tissue at the bite site [30, 38]. In patients subjected to invasive procedures, septicemia can be due to nosocomial infection, such as ventilator-associated pneumonia and central venous catheter-associated bloodstream infection.



Fig. 9 *Bothrops* envenomation. Patient bitten by a young *Bothrops* snake in toe presented with unclottable blood 3 h after the bite, and minimal alterations a bite site

Fig. 10 Soft tissue infection secondary to *Bothrops* envenomation, 4 days after snakebite



General

Deaths after bites from *Bothrops* group snakes are associated with AKI, central nervous system bleeding, shock, or sepsis [20, 30, 47, 49, 50]. There is little information in the literature about sequelae of infection, necrosis, and fibrosis. In general, victims are not monitored over the long term, and it is therefore not possible to evaluate late sequelae. Table 1 shows clinical data related to the occurrence and complications of snakebites from different *Bothrops* species.

Laboratory Tests

Ancillary exams can show alterations caused by or complications secondary to *Bothrops* envenomation.

Complete Blood Count

On admission, a complete blood count (CBC) for a patient with *Bothrops* syndrome can reveal elevated hemoglobin levels and hemoconcentration, secondary to increments in vascular permeability. However, some *Bothrops* syndrome patients present with bleeding or massive hemolysis, resulting in anemia. In such patients, the leukocyte count can be normal or elevated (indicating leukocytosis). There can also be neutrophilia (absolute or relative) and thrombocytopenia [53].

Biochemistry

In *Bothrops* syndrome patients with AKI, urea and creatinine are elevated. Levels of creatine kinase (CK) can also be elevated, which can be attributed to the myotoxic effects of the venom of some

Fig. 11 Necrosis after *Bothrops* envenomation. (a) Necrosis of finger tip 13 days after snakebite. (b) Necrosis of left foot 15 days after snakebite



Bothrops species, to infection or to compartment syndrome [44]. In addition, there can be intravascular hemolysis, which may result in high levels of lactate dehydrogenase (LDH) and indirect bilirubin in serum.

Blood Coagulation Tests

In patients with *Bothrops* syndrome, whole blood clotting time (WBCT), prothrombin time (PT), and activated partial thromboplastin time (APTT) can be normal or abnormal (prolonged), and some patients present with a complete loss of coagulability. In addition, *Bothrops* syndrome provokes fibrinogen consumption, together with elevated levels of fibrin degradation products (FDPs) and D-dimer [54, 55]. Coagulation tests are quite important, because they facilitate the diagnosis and inform decisions regarding treatment. Such tests should be ordered on admission, as well as at 12 and 24 h after antivenom administration. It should be kept in mind that venoms of several species of the genera *Porthidium* and *Bothriechis* do not affect clotting tests.

Urine Analysis

The results of the urinalysis of *Bothrops* syndrome patients can be normal. However, some patients present with hematuria, proteinuria, or both.

Arterial Blood Gas Analysis

Arterial blood gas analysis can reveal metabolic acidosis in patients with AKI or sepsis.

Others

In some cases, ultrasonography, computerized tomography, or nuclear magnetic resonance imaging is needed in order to diagnose complications and to determine the appropriate treatment strategy.

Lachesis

Clinical Presentation

Envenomations by snakes of the genus *Lachesis* present pathophysiological manifestations similar to those described for *Bothrops* envenomations,

and the clinical features can be indistinguishable. There have been few reports of *Lachesis* snakebites and most of the cases described have been severe. If the animal responsible is not captured for identification, the diagnosis can be made on the basis of vagomimetic signs and symptoms, together with epidemiological information. As in *Bothrops* envenomation, changes can occur at the bite site (local effects) and elsewhere (systemic effects) [12, 38, 56–59].

Local Effects

Victims of *Lachesis* snakebite present edema, which can be extensive, at the bite site. The site can also evolve to pain, bruising, and blisters.

Systemic Effects

The reported systemic effects of *Lachesis* snakebite include coagulopathy and spontaneous bleeding, such as epistaxis and macroscopic hematuria. Vagomimetic manifestations, such as nausea, vomiting, sweating, abdominal pain, diarrhea, hypotension, and shock, can also be observed. Although such manifestations strengthen the diagnosis, their absence does not rule out the possibility of *Lachesis* envenomation.

Complications

There have been few reports of *Lachesis* envenomation. Despite such limited information, there is indication that the complications are similar to those observed in *Bothrops* envenomations.

Local

Local complication of *Lachesis* snakebite includes skin infection and necrosis. Some victims develop compartment syndrome [38, 56].

Systemic

Victims of *Lachesis* snakebite can evolve to AKI [38] and sepsis. In patients who eventually died from *Lachesis* envenomation-induced sepsis, gram-positive and gram-negative bacteria (*Clostridium* spp. and *E. coli*, respectively) have been isolated [56].

Laboratory Tests

CBC

In cases of *Lachesis* envenomation, the CBC can be altered. Patients might develop leukocytosis, neutrophilia, and thrombocytopenia [12, 59].

Biochemistry

In *Lachesis* bite victims who develop AKI, urea and creatinine levels are elevated. CK levels are slightly elevated [12].

Blood Coagulation Tests

In *Lachesis* envenomation, as in *Bothrops* syndrome, the WBCT, PT, and APTT can be normal or abnormal (prolonged), and some patients present with a complete loss of coagulability. In addition, *Lachesis* envenomation reportedly causes fibrinogen consumption, as well as high levels of FDPs and D-dimer [12].

Crotalus

South America Versus Central America

The reported consequences of bites from rattlesnakes of the genus *Crotalus* in South America are mainly neuromuscular blockade and rhabdomyolysis, which may cause AKI. In contrast, envenomation by *Crotalus* snakes in Central America is characterized by effects similar to those of *Bothrops* envenomation.

Clinical Presentation in South America

Local Effects

In South America, the local signs and symptoms at a *Crotalus* bite site are less intense than those observed in cases of *Bothrops* and *Lachesis*. Victims of a *Crotalus* bite in South America present with edema, erythema, and pain – in most cases near the bite site (Fig. 12a).

Systemic Effects

Most of the alterations observed in *Crotalus* envenomation in South America are systemic. Initial symptoms are blurred vision and a “heavy



Fig. 12 Clinical features of South American *Crotalus* envenomation: (a) The bite site with fang puncture marks; (b) Bilateral palpebral ptosis; (c) Dark urine due to myoglobinuria

eyelids” feeling. Patients can evolve to palpebral ptosis (Fig. 12b), diplopia, mydriasis, anisocoria, mandibular ptosis, weakness, and tremors. Paralysis of the muscles of the soft palate causes dysphagia. In severe cases, patients progress to weakness and prostration, some developing respiratory failure secondary to paralysis of the respiratory muscles [10, 60–64]. In addition, there can be signs and symptoms of rhabdomyolysis, such as myalgia and dark urine (Fig. 12c) (due to myoglobinuria) [10, 65–67]. Bruising and bleeding (such as gingival bleeding) can occur, resulting from coagulopathy caused by the procoagulant enzymes of the venom, although those effects are less common.

General

In *Crotalus* envenomation in South America, the systemic effects are more pronounced than are the local effects. In one report of envenomation from the bite of a young *Crotalus* snake, the only alteration observed was coagulopathy, which was not accompanied by neuromuscular or myotoxic manifestations [68]. In mild cases, neuromuscular symptoms can appear late, approximately 12 h

after the bite. Therefore, in cases of *Crotalus* snakebite, it is necessary to monitor victims closely and for a prolonged period. In the days following the snakebite, victims report symptoms such as altered taste and smell. The neuromuscular effects can persist for days or weeks after antivenom therapy.

Complications

Local

In cases of *Crotalus* envenomation in South America, infection at the bite site can occur but does so infrequently [69]. In one reported case, a *Crotalus* bite victim developed compartment syndrome, which was managed without fasciotomy and evolved without sequelae [70].

Systemic

After *Crotalus* snakebite in South America, the most common complication is AKI due to rhabdomyolysis. In 10–29% of cases, the victim develops AKI [48]. Risk factors for developing AKI include delayed administration of

antivenom, plasma CK activity $>2,000$ U/L on admission, and being below 12 years of age [71]. Patients with severe neuromuscular manifestations can develop aspiration pneumonia and atelectasis. Death results from renal failure and respiratory failure. The case fatality rate is higher among patients with delayed treatment, receiving specific antivenom therapy more than 6 h after the bite [11].

Laboratory Tests

CBC

In victims of *Crotalus* snakebite in South America, the CBC can reveal a normal leukocyte count or leukocytosis, together with absolute or relative neutrophilia. Thrombocytopenia is not common [10, 60].

Biochemistry

After *Crotalus* snakebite in South America, musculoskeletal injury leads to increases in the serum levels of CK, aspartate aminotransferase, and LDH. The CK level can be extremely high, proportional to the severity of envenomation, and increases early (in the first 2 h after the bite), peaking after approximately 24 h. The dynamics of the increase in aspartate aminotransferase is similar to that of CK, whereas the LDH level rises more slowly, peaking between 48 and 72 h after the bite [72]. Serum concentration of urea, creatinine, potassium, phosphorus, and uric acid are elevated in the presence of AKI. Although calcium levels are decreased in the early stage of *Crotalus* envenomation-induced AKI, hypercalcemia can occur in the recovery phase of rhabdomyolysis, due to mobilization of calcium deposited in the injured muscle.

Blood Coagulation Tests

Coagulopathy is seen in 40–50% of patients with *Crotalus* envenomation in South America. The WBCT, PT, and APTT can be normal or abnormal (prolonged). In addition, the fibrinogen level can be low; elevated levels of FDPs and D-dimer can be observed [18].

Urine Analysis

Among victims of *Crotalus* snakebites in South America, those who do not develop AKI show normal urine analysis findings. Those who develop rhabdomyolysis can present with myoglobinuria.

Arterial Blood Gas Analysis

In patients with *Crotalus* envenomation-induced AKI, metabolic acidosis can be observed. Those with respiratory failure that is not properly managed, in terms of the ventilation strategy, can develop hypoxemia, hypercapnia, and respiratory acidosis.

Clinical Presentation of *Crotalus* Bites in Central America

Local Effects

Bites from *Crotalus simus* snakes (found in Mexico and Central America) provoke local changes such as swelling and pain. In severe cases, those changes can affect the entire limb. Bruising and blisters can also be observed. Local necrosis is reported in rare cases [73, 74].

Systemic Effects

In cases of *Crotalus* envenomation in Central America, bleeding – including epistaxis, gingival bleeding, hematemesis, and hematuria (macroscopic and microscopic) – has been reported [73, 74]. Victims of *Crotalus* snakebite in Central America can present with nausea and vomiting, although neuromuscular manifestations are rare. Coagulopathy with fibrinogen consumption are often observed [74]. The venom of young *C. simus* snakes exhibits a toxicological profile similar to that of the venom of young snakes of *Crotalus* species in South America, in terms of neurotoxicity, as well as in terms of the potential to induce rhabdomyolysis and coagulopathy [75]. Nevertheless, it is not known whether such effects occur in humans bitten by young *C. simus* individuals, as neurotoxic envenomings by *Crotalus simus* have not been described in Central America.

Elapidae Family

Clinical Presentation

Local Effects

In most cases of bites from snakes of the genus *Micrurus* (family: Elapidae), there is no significant alteration at the bite site, other than the bite marks and erythema. Most patients report mild local pain or paresthesia. However, there has been at least one report of severe pain in the bitten limb [76].

Systemic Effects

The main systemic alterations seen in *Micrurus* snakebite victims result from neuromuscular blockade. Manifestations of neurotoxicity include blurred vision, diplopia, palpebral ptosis (Fig. 13), mydriasis, anisocoria, mandibular ptosis, dysphagia, and weakness. In severe cases, the patient can develop dyspnea and respiratory failure due to paralysis of the respiratory muscles. Manifestations such as dizziness, nausea, vomiting, excessive salivation, and generalized paresthesia are also observed. Localized mild myalgia can occur, and, less frequently, there can be myalgia in areas distant from the bite [73, 76–79].

Bites from the so-called yellow-bellied sea snake (*Pelamis platura*) are rare, and there have been no reports describing the clinical manifestations. However, experimental studies of *P. platura* venom suggest that it causes neurotoxic manifestations similar to those observed in cases of bites from true coral snakes [80].



Fig. 13 Bilateral palpebral ptosis 4 h after bite by *Micrurus* snake

Complications

Elapidae snakebite victims with severe neuromuscular manifestations can develop aspiration pneumonia. Such individuals can also develop atelectasis.

Laboratory Tests

CBC

Patients with *Micrurus* envenomation present with leukocytosis. In one case report, an individual bitten by a *Micrurus lemniscatus helleri* in the Peruvian Amazon developed thrombocytopenia [76].

Biochemistry

In victims of *Micrurus* snakebite, CK levels can be slightly elevated.

Blood Coagulation Tests

Micrurus snakebite victims do not present with coagulopathy.

Arterial Blood Gas Analysis

Among patients with *Micrurus* envenomation, those who progress to respiratory failure and do not receive proper ventilatory support can develop hypoxemia and respiratory acidosis.

Non-Front-Fanged Colubroid Snakes (NFFC snakes)

The bites of some species of snakes previously classified in the family Colubridae (*sensu lato*) (such as *Boiruna*, *Philodryas*, and *Thamnodynastes*; all now in Family Dipsadidae, Subfamily Xenodontinae) can occasionally evolve to intense local effects such as swelling, pain, and bruising. However, such bites do not generally lead to systemic envenomation and therefore should not cause manifestations requiring intensive care [81–84]. These snakes, and their bites, are discussed in more detail in ► Chap. 124, “Non-Front-Fanged Colubroid Snakes.”

Treatment for Venomous Snakebites in Central and South America

Most of the knowledge about treatments for snakebites in Central and South America comes from accumulated clinical experience; there have been very few controlled studies of such treatments. Therefore, recommendations regarding the appropriate clinical approach are devised by consensus among regional authorities.

Antivenom Therapy

The only scientifically valid treatment for snake envenomation is parenteral antivenom administration. It is a heterologous product composed of either whole immunoglobulins (IgG) or immunoglobulin fragments (F(ab')₂ or Fab) obtained from the plasma of horses or sheep hyperimmunized with snake venoms. Antivenoms used in Latin America are either whole IgG or F(ab')₂ products. In Central and South America, the number of vials to be administered must be in accordance with the guidelines of the manufacturing laboratory and the guidelines generated in each country, because there is variation among countries

and producers in terms of the amount of venom neutralized per milliliter of antivenom. The number of vials of antivenom administered varies according to the severity of the symptoms, which is evaluated on the basis of the clinical manifestations on admission. However, the severity criteria can vary by country. Table 2 shows the severity criteria used for snakebite envenomation in Brazil.

In envenomations characterized by local manifestations at the bite site, such as those from snakes belonging to the genera *Agkistrodon*, *Atropoides*, *Bothrops*, *Bothriechis*, *Bothriopsis*, *Bothrocophias*, *Porthidium*, or *Crotalus* in Central America, or *Lachesis*, the edema can continue to progress, even after the administration of antivenom, for up to 24 h after envenomation. That is because the edema and pain are consequences of the release of endogenous inflammatory mediators after venom inoculation.

Regarding antivenom therapy, certain aspects must be born in mind:

- Antivenom should be administered only to patients with manifestations of envenomation; some bites (“dry bites”) do not lead to envenomation and antivenom should not be used in these cases.

Table 2 Specific treatment for snakebites in Brazil according to the severity of the clinical presentation on admission^a

Snake genus	Clinical presentation
<i>Bothrops</i>	Mild: local edema in 1 or 2 of the 5 segments defined ^b ; cutaneous or mucosal bleeding; normal or altered coagulation test results
	Moderate: edema in 3 or 4 segments; light bleeding; normal or altered coagulation test results
	Severe: edema in all 5 segments; severe hemorrhage, hypotension/shock; normal or altered coagulation test results
<i>Crotalus</i>	Mild: barely perceptible myasthenic facies; no myalgia or dark urine; normal or altered coagulation test results
	Moderate: evident myasthenic facies; myalgia and dark urine; normal or altered coagulation test results
	Severe: evident myasthenic facies; intense myalgia and dark urine; difficulty breathing; normal or altered coagulation test results
<i>Lachesis</i>	Local signs and symptoms; occasional bleeding; no vagal manifestations
	Intense local signs and symptoms; occasional bleeding; evident vagal manifestations
<i>Micrurus</i>	All cases considered potentially severe

^aBased on the 1998 Brazilian National Ministry of Health Guidelines for the Diagnosis and Treatment of Animal Envenomation [85]

^bDivision of the upper and lower limbs into segments: segment 1 = foot/hand; segment 2 = distal half of the leg/forearm; segment 3 = proximal half of the leg/forearm; segment 4 = distal half of the thigh/upper arm; segment 5 = proximal half of the thigh/upper arm

- The antivenom should be administered intravenously.
- The number of ampules or vials required will vary according to the severity of the symptoms assessed on admission.
- Patients should receive the antivenom specific to the genus or family of snake that caused the envenomation.
- The antivenom can be diluted in 5% glucose or in saline solution. Although the dilution is typically between 1:5 and 1:10, the total volume to be administered should be evaluated on a case-by-case basis, taking into account patient weight and the presence of comorbidities that limit the administration of fluids.
- The antivenom should be administered in 30 min to 1 h; antivenom administration can be initiated slowly and increased gradually.
- In patients who present a hypersensitivity reaction to the antivenom during its administration (early adverse reaction), the infusion of the solution should be temporarily suspended and the hypersensitivity reaction should be treated in accordance with the type and intensity of the signs and symptoms. Epinephrine (adrenaline) is the drug of choice to treat anaphylaxis [86]. After treatment of the early reaction, antivenom therapy should be reinitiated, although the antivenom should be more diluted and infused more slowly.
- In cases of bites from snakes whose venom causes coagulopathy (*Bothrops*, *Lachesis*, and *Crotalus*), coagulation tests should be performed 12–24 h after antivenom administration, in order to assess the treatment. If there is no improvement of coagulopathy after 12 h (i.e., if blood still does not clot), the following possibilities should be considered: the antivenom was administered inappropriately (misdiagnosis of the type of envenomation); the quantity of antivenom administered was insufficient (error in the assessment of severity); or the antivenom was stored improperly or is out of date. However, in most cases in which the coagulation test results did not improve after antivenom administration, the etiologic diagnosis has been found to be incorrect.
- In patients with snake envenomation, it is important to achieve good peripheral venous access for antivenom administration. The venous access should not be obtained on the bitten limb, especially in cases of bites by snakes whose venom causes edema. In patients with coagulopathy, venous access via the peripheral jugular vein should be avoided because of the risk of loss of access and of hematoma, which can impair breathing by causing extrinsic airway compression.

Ancillary Treatment

Resuscitation

For snakebite victims requiring resuscitation, the airway-breathing-circulation approach should be employed. All vital signs should be checked.

Fasting

During antivenom administration, snakebite victims should fast, because there is a risk of nausea and vomiting as manifestations of hypersensitivity to the antivenom. After antivenom administration, the clinical condition of the patient should be evaluated before the decision to allow the consumption of food is made. Patients bitten by *Crotalus* and *Micrurus* snakes, whose venoms cause neuromuscular paralysis, should be carefully assessed before restarting an oral diet, given the possible progression of muscle paralysis to difficulty in swallowing and respiratory failure.

Fluid Resuscitation

Adequate crystalloid fluid resuscitation is necessary for proper hydration, the target hourly urine output being 1–2 mL/kg of body weight (BW) for children and 30–40 mL for adults. In individuals bitten by snakes belonging to one of the South American genera of *Crotalus* whose venom causes rhabdomyolysis, reversing the intravascular volume depletion is one of the most important measures to prevent AKI, because it restores proper renal perfusion and increases urine flow, preventing the formation of myoglobin pigment casts and the consequent tubular obstruction. In the setting of rhabdomyolysis, the goal of fluid

resuscitation is to maintain a urine output of 200–300 mL/h. Care should be taken to avoid volume overload, especially in children and individuals with heart disease or anuria [87].

Vasoactive Drugs

Snakebite victims who develop hypotension and do not respond to volume expansion with crystalloid solution should receive vasoactive drugs.

Atropine

In *Lachesis* envenomation, atropine administration should be considered if the patient develops bradycardia with hemodynamic instability.

Analgesia

To control the pain resulting from a snakebite, dipyrone, paracetamol, or opioids can be administered as necessary. The use of nonsteroidal anti-inflammatory drugs should be avoided.

Diuretics

In patients with snakebite envenomation who develop oliguria despite being adequately hydrated, a diuretic such as furosemide can be prescribed to stimulate urine flow. Diuretic administration can thus facilitate the management of volume overload in patients with AKI.

Urinary Alkalinization

In *Crotalus* snakebite victims who develop severe rhabdomyolysis, raising the urinary pH to above 6.5 can reduce toxicity and increase myoglobin solubility in the renal tubules. However, although urinary alkalinization is a common intervention in the management of rhabdomyolysis, there is little clinical evidence of its benefit [87]. The use of this measure should be avoided if the patient does not present a level of urine output sufficient to avoid alkalosis.

Mannitol

In *Crotalus* snakebite envenomation, which can lead to rhabdomyolysis, mannitol can be considered as an osmotic diuretic for the prevention of AKI, although its routine use is not recommended [87]. To avoid fluid overload and circulatory congestion, mannitol should be used only after the

blood volume has been corrected and the appropriate urine output has been achieved. The recommended dose of mannitol is a bolus of 0.5 g/kg BW per hour, followed by 0.1 g/kg BW per hour, in 0.45% saline.

Acetylcholinesterase Inhibitors

If a *Micrurus* snakebite victim develops respiratory failure and requires assisted ventilation, the use of acetylcholinesterase inhibitors such as neostigmine or edrophonium hydrochloride should be considered as a means of reversing the neuromuscular effects. Experimental studies and isolated reports support the use of acetylcholinesterase inhibitors for the treatment of bites from *Micrurus* snakes whose venom has predominant postsynaptic activity [88]. To prevent the muscarinic effects of acetylcholine (especially bradycardia and hypersecretion), patients can be injected intravenously with atropine – 0.5 mg for adults and 0.02 mg/kg per dose (maximum, 0.5 mg per dose) for children – prior to intravenous administration of neostigmine (0.05 mg/kg BW) or edrophonium hydrochloride (0.25 mg/kg BW for children and 10 mg for adults). Normally, the response is rapid, and a single dose is sufficient in some cases. If neuromuscular manifestations recur, the regimen should be repeated every 2–4 h or the acetylcholinesterase inhibitor should be administered as a continuous infusion (starting at 25 µg/kg BW per hour), the dosage being titrated according to the clinical response. If there is no response to this treatment, the acetylcholinesterase inhibitor should be discontinued.

Antibiotic Therapy

In cases of secondary infection after snakebite, as often occurs in *Bothrops* and *Lachesis* snakebite victims, the recommended treatment is with broad-spectrum antibiotics that are active against gram-negative bacteria (especially *Morganella* spp.), gram-positive bacteria, and anaerobic bacteria. Such antibiotics include chloramphenicol, clindamycin (in combination with ceftriaxone or ciprofloxacin), and ampicillin in combination with sulbactam. Whenever possible, the treatment regime should be reevaluated through the use of cultures and sensitivity testing.

Surgical Procedures

In snakebite victims, any abscess should be drained in a timely manner and areas of necrosis should be debrided. If there is suspicion of compartment syndrome, the patient should be carefully evaluated in order to determine whether fasciotomy is indicated. The use of fasciotomy should be limited to cases in which subfascial pressure remains elevated (>30 mmHg) or, more precisely, if the compartment perfusion pressure (mean blood pressure minus intracompartmental pressure) is ≤ 30 mmHg.

Use of Blood Products

Transfusion of fresh frozen plasma, cryoprecipitate, or platelets should not be used as a substitute for antivenom administration, in the correction of hemostatic disorders; spontaneous bleeding ceases a few hours after the initiation of antivenom administration. However, when there is a need to carry out invasive or surgical procedures after antivenom administration but prior to the reversal of coagulopathy, blood products can and should be used.

Renal Replacement Therapy

In some patients with AKI, dialysis should be considered.

Mechanical Ventilation

Patients with snake envenomation who present with neuromuscular manifestations, such as those with *Crotalus* or *Micrurus* envenomation, can occasionally progress to impaired respiratory function. Such patients require endotracheal intubation and mechanical ventilation.

Postural Drainage

If there is edema at the site of a snakebite, the affected limb should be elevated. However, in cases of compartment syndrome, that practice should be reevaluated.

Tourniquet Use

Tourniquets should not be applied in cases of snakebite, especially in those caused by snakes whose venom leads to intense local inflammation

(*Agkistrodon*, *Atropoides*, *Bothrops*, *Bothriechis*, *Bothriopsis*, *Bothrocophias*, *Porthidium*, or *Crotalus* in Central America, or *Lachesis*). If a tourniquet has been applied, it should be removed slowly and carefully, in order to avoid the abrupt release of vasoactive factors and the consequent shock [89].

Parenteral Medication

Medications should not be injected at the bite site. In cases of snakebites that might provoke coagulopathy (*Bothrops*, *Lachesis*, and *Crotalus* bites), intramuscular injections should also be avoided until clotting alterations are corrected.

Invasive Procedures

In snakebite victims, unnecessary invasive procedures, such as the use of a central venous catheter or urinary catheter, should be avoided, especially in those who have developed coagulopathy.

Tetanus Prophylaxis

If warranted on the basis of the vaccination history, the tetanus immunization status of patients with snake envenomation should be updated. In addition, the need for anti-tetanus serum or immunoglobulin should be evaluated. When tetanus prophylaxis is indicated, it should be administered after normalization of coagulopathy (typically 24 h after antivenom administration), in order to prevent hematoma formation.

Follow-Up Care

An individual who has been bitten by a venomous snake will require appropriate physical therapy in order to avoid contractures and deformities. Immobilization should be interrupted by frequent periods of gentle exercise, progressing from passive to active and including stretching, if indicated. Some patients might need to be followed up by a plastic surgeon, orthopedist, physiatrist, physical therapist, or occupational therapist. Furthermore long-term psychological consequences experienced by victims of snakebite are not known and needs investigation.

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Part XXIV

Natural Toxins: Spiders

Julian White

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Spiders are ubiquitous arthropod predators, common in all habitats occupied by humans, including modern urban environments. They may achieve high population densities – greater than one million per hectare [1]. Their primary interaction with humans is beneficial, as they act as biologic controls for arthropod pests, notably insects. Their medical interaction with humans is relatively minor, in comparison, but still significant because of the extent of exposure to risk.

Extent of Spider Bite as a Medical Problem

There are no accurate figures on which to gauge the global extent of spider bite. Logically, given the large numbers of spiders living in proximity to humans, bites should be common, but because most spiders are small and unlikely to inject more than miniscule quantities of venom compared with average human body mass, most bites could be expected to be trivial. Many spiders coexisting with humans are moderate to large in size, however, and at least a few of these are known to cause significant envenoming [2]. When spider bite is considered by the human population and a venue is provided to seek advice about bites, experience in Australia suggests that bites are reported frequently. Spider bite has been the most common or second most common cause of calls to Australian poison information centers at least since 1995, usually

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eclipsing every pharmaceutical class, including paracetamol/acetaminophen, until recent years [2]. In the USA spider bite has been a less frequent cause of calls to poison centers [3], though in the 1950s spider bite was reported to cause six to seven deaths per year [4] and a higher rate of significant bites than reported to poison centers is suspected [3]. In contrast, in Switzerland the reported incidence is just 1–10 bites/100,000 population, with mostly mild effects and universally good outcomes in studied cases [5]. When consciousness of spider bite is lower or the expectation that health services can assist is not present, it can be expected that the recorded incidence of cases will be lower, underestimating the extent of spider bite incidence. However, recent data from the USA appears to indicate that spiderbite results in more fatalities than snakebite in that country (70 vs. 59 in the 9 year study period), though detail on what type of spider and the cause of death is lacking [6]. This indicates spiderbite is not a universally benign phenomenon.

Medically Important Spiders

A few spider groups or effects of spider bite stand out as clinically important (Table 1) [2, 3]. Many other spiders occasionally or rarely have been reported to bite humans, although mostly with minor effects (Table 2). The former groups, few in number but global in extent, dominate the medical problem posed by spider bite. In Brazil,

despite a vast spider fauna, virtually all medically important spider bites are due to just three groups: banana spiders (genus *Phoneutria* – phoneutrimism (Fig. 1)), recluse or violin spiders (genus *Loxosceles* – loxoscelism (Fig. 2)), and widow spiders (genus *Latrodectus* – latrodectism (Fig. 3)). In North America, widow spiders and recluse spiders also are responsible for most significant bites. In Europe, Africa, Asia, and Australia, widow spiders are an important source of spider bite, whereas recluse spiders also cause significant problems in parts of Africa, Europe, and possibly Australia. In Australia, widow spider envenoming occasions more use of antivenom than all other causes of envenoming combined (including snakes), a remarkable finding, given that continent’s diverse, common, and highly toxic fauna. Another group of spiders also is of great relevance in Australia: the funnel-web spiders (*Atrax* and *Hadronyche* spp. (Figs. 4 and 5)), the most toxic of all the world’s spiders (not to be confused with North American funnel-web spiders, which are quite different and of minor importance medically).

Spider Taxonomy

Spider taxonomy is complex, and differentiating to species generally requires great expertise and the use of a microscope because it frequently involves detailed examination of male external genital organs [2]. Many spider species are yet to

Table 1 Spider groups of major medical importance

Spider group	Common name	Distribution	Clinical effects
Mygalomorphae			
<i>Atrax</i> and <i>Hadronyche</i> spp.	Funnel-web spiders	Australia	Excitatory neurotoxic effects, catecholamine storm, potentially lethal
Araneomorphae			
<i>Latrodectus</i> spp.	Widow spiders	Global	Latrodectism: excitatory neurotoxic effects, pain, malaise, rarely lethal
<i>Phoneutria</i> spp.	Banana spiders	Brazil	Phoneutrimism: excitatory neurotoxic effects, pain, malaise, rarely lethal
<i>Loxosceles</i> spp.	Recluse spiders	Global	Loxoscelism: local tissue necrosis, rarely major systemic effects, shock, hemolysis, DIC, occasionally fatal
Nonspecific	Various	Global	Necrotic arachnidism: spider bite resulting in local necrosis

DIC disseminated intravascular coagulation

Table 2 Spiders known to cause significant effects on biting humans^a [1–3, 7–21]

Family	Scientific name	Common name	Distribution
Mygalomorphs			
Ctenizidae	<i>Aganippe</i>	Trapdoor spider	Australia
	<i>Arabantis</i> spp.	Trapdoor spider	Australia, East Indies
	<i>Bothriocyrtum</i> spp.	Trapdoor spider	California
	<i>Dyarcycops</i>	Trapdoor spider	Australia, New Zealand
	<i>Ummidia</i> spp.	Trapdoor spider	North and Central America
Hexathelidae	<i>Atrax</i> spp. and <i>Hadronyche</i> spp.	Funnel-web spider	Australia
Theraphosidae	<i>Harpactirella</i>	Trapdoor spider	South Africa
	<i>Pamphobetus</i> spp.	Tarantula	South America
	<i>Aphonopelma</i> spp.	Tarantula	North America
	<i>Dugesia</i> spp.	Tarantula	North America
	<i>Selenocosmia</i>	Tarantula	East Indies, India, Australia
	<i>Lasidora</i> spp.	Caranguejeiras	South America
	<i>Poecilotheria</i> spp.	Ornamental tree spiders	India, Sri Lanka
	<i>Lampropelma nigerrimum</i>	Tarantula	Asia
	<i>Pterinochilus murinus</i>	Tarantula	Africa
	<i>Eumenophorus</i> spp.	Tarantula	Africa
	<i>Stromatopelma</i> spp.	Tarantula	Africa
Dipluridae	<i>Trechona</i> spp.	Funnel-web spider	Central and South America
Actinopodidae	<i>Missulena</i> spp.	Mouse spider	Australia
Araneomorphs			
Agelenidae			Europe, North America
	<i>Hololena</i> spp.	Agelinid spider	North America
Araneidae	<i>Araneus</i> spp.	Orb weaver	Worldwide
	<i>Argiope</i> spp.	Orb weaver	Worldwide
	<i>Neoscona</i> spp.	Orb weaver	Worldwide
			Worldwide
Clubionidae	<i>Chiracanthium</i> spp.	Sac spider	Worldwide
	<i>Liocranoides</i>	Running spider	Appalachia and California
	<i>Trachelas</i> spp.	Sac spider	North America
Ctenidae	<i>Cupiennius</i> spp.	Banana spider	Central and South America, West Indies
	<i>Elassoctenus harpax</i>	Hunting spider	Australia
	<i>Phoneutria</i> spp.	Banana spider	Central and South America
Desidae (Amaurobiidae)	<i>Ixeuticus (Badumna)</i> spp.	House spider	New Zealand, Southern California
Dysderidae	<i>Dysdera</i> spp.	Dysderid	Worldwide
Filistatidae	<i>Filistata</i> spp.	Hackled band spider	Worldwide
Gnaphosidae	<i>Drassodes</i> spp.	Running spider	Worldwide
	<i>Lampona</i> spp.	White-tailed spider	Australia, New Zealand
	<i>Herpyllus</i> spp.	Parson spider	North America
Loxoscelidae	<i>Loxosceles</i> spp.	Recluse spiders	Worldwide
Lycosidae	<i>Lycosa</i> spp.	Wolf spiders	Worldwide
	<i>Hippasa</i> spp.	Indian wolf spiders	Indian subcontinent
Miturgidae	<i>Miturga</i> spp.	Miturgid spiders	Australia, New Zealand
Oxyopidae	<i>Peuceetia</i> spp.	Lynx spider	Worldwide

(continued)

Table 2 (continued)

Family	Scientific name	Common name	Distribution
Salticidae	<i>Phidippus</i> spp.	Jumping spider	Worldwide
	<i>Holoplatys</i> spp.	Jumping spider	Australia
	<i>Mopsus</i> spp.	Jumping spider	Australia
	<i>Thiodina</i> spp.	Jumping spider	Americas
Siariidae	<i>Sicarius</i> spp.	Six-eyed crab spider	Africa
Sparassidae	<i>Heteropoda</i> spp.	Huntsman spiders	Worldwide
	<i>Isopoda</i> spp.	Huntsman spiders	Australia, New Guinea, East Indies
	<i>Olios</i> spp.	Huntsman spiders	Americas, Australia
Theridiidae	<i>Latrodectus</i> spp.	Widow spiders	Worldwide
	<i>Achaeranea tepidariorum</i>	Grey house spider	Worldwide
	<i>Steatoda</i> spp.	False black widow	Worldwide
Thomisidae	<i>Misumenoides</i> spp.	Crab spider	Americas
Zoridae	<i>Diallomus</i> spp.	Zorid spider	Australia

^aFor most (except those listed in Table 1), generally minor clinical effects only

Fig. 1 Banana spider, *Phoneutria nigriventer* (Copyright © Dr. Julian White, 2016)

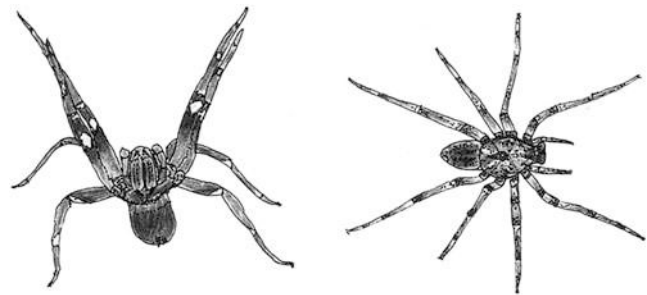


Fig. 2 Recluse spider, *Loxosceles reclusa* (Copyright © Dr. Julian White, 2016)

receive formal scientific description and naming. Scientists undertaking this task are few in number. Although previously described common spiders were thought to belong to a single taxon, more

recent research indicates that numerous species exist. This profusion of species and difficulty in assigning accurate nomenclature has ensured that the medical literature on spider bites and spider venom research is replete with inaccuracies that muddy understanding of this field.

Mygalomorphs

Order Mygalomorphae, together with the Araneomorphae (see later), currently contains most living spider species. Mygalomorphs are considered more ancient or primitive than araneomorph spiders, but neither group is recent, for spiders date back hundreds of millions of years. The basic distinguishing features are shown in Fig. 6. Mygalomorphs exist in a wide array of habitats globally, varying from small to large sized species, but in general these are mostly



Fig. 3 Female black widow spider, *Latrodectus mactans* (Copyright © Dr. Julian White, 2016)

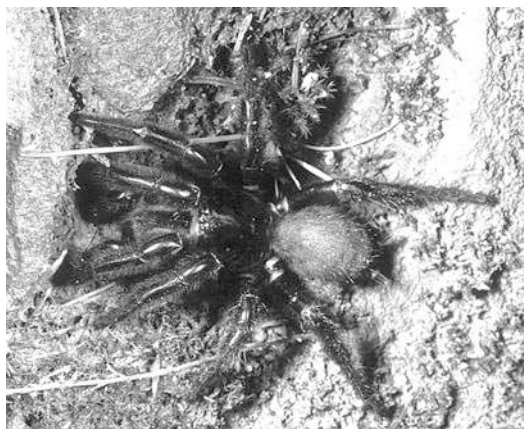


Fig. 5 Female Australian tree funnel-web spider, *Hadronyche formidabilis* (Copyright © Dr. Julian White, 2016)



Fig. 4 Male Australian Sydney funnel-web spider, *Atrax robustus* (Copyright © Dr. Julian White, 2016)

large terrestrial or occasionally arboreal spiders, living most of their lives in web retreats, often a burrow in the ground, usually with traplines radiating from the retreat, such that the spider rarely ventures far from the retreat except to mate. It is generally the male that explores in search of the female, which is at least one reason bites by mygalomorphs are more likely to be caused by male spiders. In some of the most deadly species, notably the Sydney funnel-web spider, the male has venom more toxic to humans than that of the female. This phenomenon is not universal,

because in some other funnel-web spiders, the female venom is as toxic as that of the male.

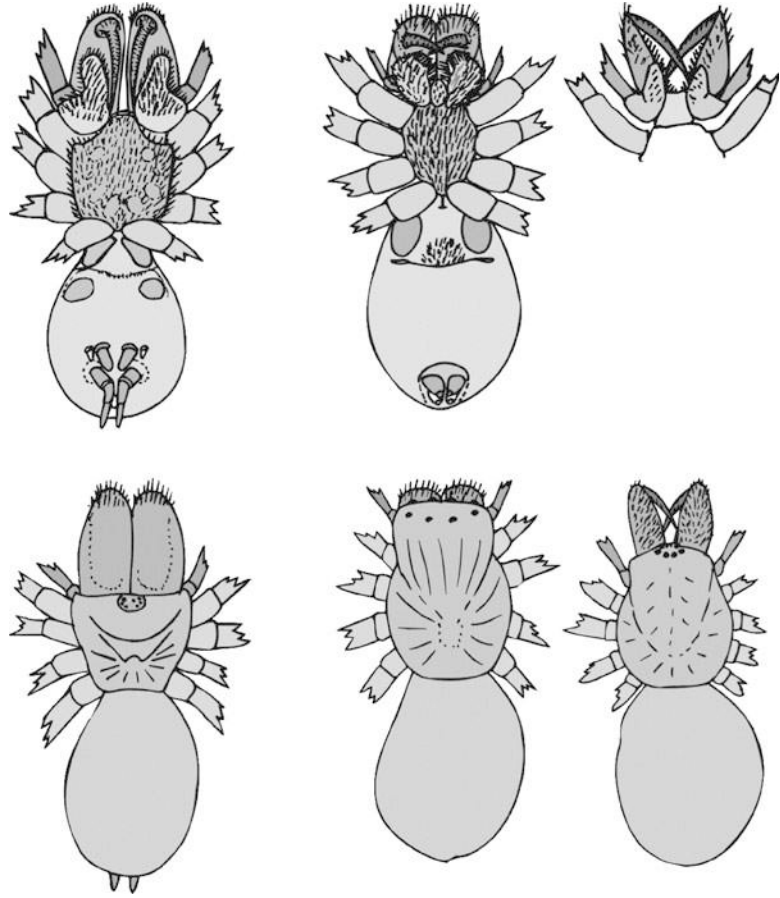
Araneomorphs

Araneomorph spiders, order Araneomorphae, are more diverse in numbers, range of species, size, shape, geographic distribution, and effects on humans. Their fang anatomy also is more diverse than mygalomorphs but can be distinguished from the latter moderately easily in most cases (see Fig. 6). Most medically important spiders fall into just three groups of araneomorphs: widow spiders, recluse spiders, and banana spiders.

Spider Venoms

As with most other venoms, spider venoms are usually complex mixtures of substances, with the most potent toxins being peptides or more complex proteins and generally falling within the class of neuroexcitatory toxins, with similarities in effect, if not structure, to the more potent scorpion toxins [2]. There is an important significant divergence from this characterization – the necrotoxins – which are best characterized from recluse spider venoms but possibly are present much more widely than recluse spiders are.

Fig. 6 Diagrammatic representation of the anatomic differences between mygalomorph spiders and araneomorph spiders



Effects of Spider Bite

The clinical effects of spider bite in humans fall into several broad categories. In most cases and for most spider species, the effects of a bite on humans are negligible. In the few cases and for the few spiders capable of inflicting injury on humans, two distinct patterns are seen: neuroexcitatory envenoming and locally necrotic envenoming [2, 3]. In general, these two patterns do not coexist in the same spider. Even for spiders capable of causing major envenoming in humans, the rate of dry bites is high and probably exceeds 80%. There are many factors affecting what symptoms are likely from a spider bite (Table 3).

Local Effects of Envenoming

For most spider species capable of causing a noticeable effect in humans, local pain, usually short-lived, sometimes accompanied by erythema or mild swelling is the only likely effect. Fang marks may not be apparent and are most likely to be direct punctures, not the minimal lacerations seen with some snakebites (caused by fangs dragging through the skin). Double punctures are likely, mostly close together, depending on the size and type of spider.

A few species cause more notable local effects, such as formation of distinct lumps or even blistering. Fewer still occasionally cause significant local tissue injury. Foremost among the latter are

Table 3 Spider and victim factors affecting the likely symptoms of a spider bite

Specific factors	Likely effect or influence
Spider-related factors	
Species of spider	Most species of spider are harmless to humans
Sex of the spider	For several species known to be toxic to humans, a specific sex is more toxic (e.g., for widow spiders, only the female is likely to envenom humans, whereas for Australian funnel-web spiders, both sexes are toxic, but only the male has caused fatalities)
Maturity of the spider	Usually only adult spiders are clinically toxic to humans
Individual spider	As with most other venomous animals, there is likely to be variation in venom components and toxicity between individuals of the same species and even for a given individual spider over time, depending on maturity, when venom was last expelled, and season
Quantity of venom injected	This varies greatly
Attack position	For any given species of spider, fang length is within a narrow range depending on the size of the spider, and angle of attack when biting a human victim determines how effectively the fangs may penetrate skin and inject venom
Gut secretions	For many species of spider, the fang tips at rest are close to the mouth parts, and it is possible that digestive secretions from the mouth may enter the wound caused by the act of biting a human with the fangs, with consequent effects being due to these digestive secretions and the venom. While this may be important in causation of some clinically significant local effects of spider bite, it remains unproven
Bacterial flora on the fangs, mouth parts, and adjacent structures	The act of biting a human with a fang has the potential to contaminate the wound with any bacteria on adjacent areas of the spider, with the consequence that clinically significant local effects of the bite may be due at least in part to secondary infection introduced by the act of biting. The bacterial flora on relevant areas of spiders is not known. However, evidence to date indicates that secondary infection following spider bite is uncommon to rare, with the possible exception of ulcerative lesions caused by some recluse spider bites
Number of times the spider bites the human victim	Multiple bites in general are more likely to result in clinically significant effects
Length of time the spider takes to make each bite	A brief glancing strike in general is less likely to result in clinically significant effects than would occur if the spider “hangs on,” taking some time to bite. This is only relative, however, because the toxicity of the spider concerned is of greater importance
Human victim–related factors	
Age of the human victim	In general, a child or an elderly adult is more likely to suffer clinically significant consequences of a spider bite than a normal healthy adult. This principle is not universal, however. In our experience in Australia with latrodectism (envenoming by widow spiders), often large, muscular men seem worst affected by the bite and require the most antivenom to reverse envenoming
Size of the victim	In general, the larger the human, the more body mass to dilute any venom and its effects; small children are usually at greater risk (but note above caveat for latrodectism)
Position of the bite	There are some areas of the body where it would be more difficult for a spider to penetrate the skin successfully and inject venom, such as where the skin is thicker or callused. For bites causing local tissue injury, bites on peripheral or dependent areas, such as the feet and lower legs, are more likely to result in problems
Preexisting health of the victim	Preexisting disease may make the results of any spider bite worse than might be expected in healthy people. Of concern are diseases either decreasing natural immunity to infection or reducing the capacity of local tissue at the bite site to withstand venom effects (e.g., peripheral vascular disease)
Allergic reactions	Individual inappropriate immune responses to venom may result in a far more clinically significant bite than otherwise would occur. This may be an anaphylactic-type reaction, which appears rare with spider bite, or a more localized reaction, which may result in significant and continuing tissue damage. A classic example of atypical local reaction to a bite is the development of pyoderma gangrenosum, which has been associated with loxoscelism

After White et al. [2]

the recluse spiders (see ► Chap. 130, “*Loxosceles Spiders*”), whose venom contains toxins that cause tissue necrosis, directly or indirectly [2, 3]. This process may begin soon after the bite but clinically is apparent only after several hours, whereas impending necrosis may take days to become discernible. There is growing, if generally inconclusive, evidence that spiders other than recluse spiders occasionally may cause tissue necrosis [22–28]. This area has engendered much speculative “science,” such as the speculation, raised to the level of “fact” by some, concerning tissue necrosis caused by spiders such as the wandering spider, *Tegenaria agrestis* in North America, and the white-tailed spider, *Lampona cylindrata* in Australia [24–28]. For these latter two species, at least, the current evidence indicates they do not cause necrotic bites. For a few other spiders, notably *Chiracanthium* spp., a reputation for occasionally causing necrotic bites appears to have limited supporting evidence [2, 22, 29].

General Effects of Envenoming

Some species capable of inflicting short-term local pain or erythema also may cause general systemic symptoms, manifested as one or more of the following: headache, malaise, nausea, vomiting, abdominal pain, flulike illness, or dizziness. The toxins responsible for such symptoms are not characterized, and the effects are generally not indicative of a particular species and so have little diagnostic value. The symptoms generally resolve over a matter of a few hours, less commonly over 1–2 days.

Neuroexcitatory Effects of Envenoming

Major neurologic effects generally are limited to species with potent neuroexcitatory toxins in their venom (widow spiders, banana spiders, Australian funnel-web spiders) [2, 3]. Their presentation depends principally on the type of spider. The details of each of these groups are found

in ► Chaps. 131, “Widow and Related *Lactrodectus* Spiders,” and ► 129, “Australian Funnel Web Spiders.” However, a growing list of other spiders, predominantly Mygalomorphs in the tarantula family (Theraphosidae), have been reported as causing medically significant, though nonlethal, envenoming that appears to be related to neurotoxicity [2, 7–9, 16]. A number of Theraphosid spider venoms have been examined and shown to contain potent peptide toxins, often with neurotoxic actions. As more cases are reported and more species have venom studied, it is likely the list of medically important Mygalomorph spiders will expand, but so far there is no evidence to indicate they will approach the overall medical significance of the already established spider groups of major importance, noted earlier.

Hemolytic and Related Effects of Envenoming

A subset of patients with loxoscelism after recluse spider bite develop major, potentially life-threatening systemic envenoming, in addition to the local necrotic effects typical of these spiders [2]. These systemic effects include hemolysis, disseminated intravascular coagulation, renal failure, shock, liver failure, multiorgan failure, and death. Death occurred in 30% of cases in the early loxoscelism literature from Chile, and fatalities still occur even in North America, although now rarely. More detailed discussion may be found in ► Chap. 130, “*Loxosceles Spiders*” [2].

Other Effects of Envenoming

For spiderbite overall, considering the many species recorded as at least occasionally biting humans, the predominant symptom, if any symptoms develop, is local short-lived pain at the bite site. Some larger spiders, such as huntsman (Araneomorphae: Sparassidae), have fangs large enough to cause distinct puncture marks which may result in local short-term bleeding [17].

A few tarantula spiders (Mygalomorphae: Theraphosidae) may cause irritation of skin and mucosal membranes through active shedding of abdominal hairs, the best known example being the Mexican orange kneed tarantula, *Brachypelma smithi*, popular in the pet trade [2].

First Aid for Spider Bite

Spider bite generally requires no first aid other than reassurance. For most of the remaining cases, use of local cold pack application is sufficient. Widow spiders require either no first aid or use of a cold pack [2] (Grade III recommendation). First aid is impractical for recluse spider bites because the bite is generally not apparent until many hours later [2]. Banana spider bites may respond to cold packs [2].

Australian funnel-web spiders are quite different from the other spiders; funnel-web spider bite is potentially lethal, and correct first aid not only can delay envenoming but also can reduce the extent of envenoming [2]. The reason for the latter is an observation that this venom is destroyed if restricted to the bite site for a prolonged period [30]. The correct first aid is use of a pressure bandage and immobilization by splint ("PBI"; see ► Chap. 122, "Australian and Pacific Snakes") [2, 30] (Grade III recommendation). Given that death may occur, at least in children, in 10 min after the bite, the importance of correct and prompt first aid is obvious.

Diagnosis of Spider Bite

The diagnosis of spider bite is sometimes straightforward, more commonly shrouded in some doubt, and frequently tenuous or uncertain. This situation relates to the ease with which a bite may occur without the culprit's being seen and the delayed nature of envenoming by certain species, notably species causing necrotic arachnidism, such as the recluse spiders. For certain species or groups of spiders, even in the absence of an identifiable specimen or reliable description of the

culprit, a diagnosis may be made with some confidence because of the distinctive nature of presentation and symptoms and signs [2, 31].

Significant envenoming by widow spiders classically is associated with a witnessed bite by a widow spider or a bite causing at least some immediate local discomfort, followed by the development of progressively more severe local pain, often with local sweating [2, 31]. The pain may move in focus from the bite site proximally to involve limbs or trunk, again often associated with sweating and hypertension, nausea, and malaise. The rate of progression in severity and area involved is variable, from 1 h to more than 24 h. Trunk pain may involve the abdomen or thorax and may mimic acute abdomen or myocardial ischemic pain. The diagnosis becomes more certain if treatment with sufficient amounts of appropriate antivenom results in clear resolution of the symptom complex.

Significant envenoming by an Australian funnel-web spider typically is associated with immediate pain, and the spider is usually seen and sometimes may need to be pulled off the victim [2, 31]. Systemic symptoms ensue rapidly, first manifested in 5–20 min by tingling around the lips and twitching of the tongue, rapidly followed by signs of catecholamine storm, with piloerection, hypersalivation and hyperlacrimation, hypertension, abdominal pain, nausea, and progressive severe pulmonary edema, with secondary hypoxia and impaired conscious state. The progression from first symptoms to lethal outcome may take 20–30 min or may take 1–3 h or occasionally longer. Without adequate antivenom therapy, death is likely.

Significant envenoming by a Brazilian banana spider typically is associated with a witnessed bite with marked local pain, with edema, erythema, and frequently sweating [2]. Systemic features include tachycardia; hypertension; nausea and vomiting; increased sweating and salivation; priapism in boys; and, in severe cases, pulmonary edema, cardiac arrhythmias, and shock. A fatal outcome is rare.

Significant envenoming by recluse spiders typically presents hours or days after the presumed

bite, which is usually not witnessed because the bite is painless and frequently occurs at night while the patient is asleep [2]. A spider is rarely available for identification. Even in most published series, a spider was positively identified in less than 10% of cases. In the first 24 h, the bite area becomes painful, erythematous, then mottled with hemorrhagic areas, often associated with systemic symptoms, such as fever, generalized erythema, and malaise. The diagnosis is usually apparent by the second day. After 4–7 days, an area of necrosis develops, with often severe pain. Less commonly in South American cases, rarely elsewhere, a severe systemic illness develops, with intravascular hemolysis, thrombocytopenia, disseminated intravascular coagulation, renal failure, potentially multiple organ failure, and death [2].

Treatment of Spider Bite

Treatment of spider bite most often consists of reassurance and short-term follow-up to exclude development of secondary infection [2]. For the few spiders capable of causing significant envenoming (e.g., widow spiders, Australian funnel-web spiders, Brazilian banana spiders, recluse spiders), treatment sometimes may be more significant, but even for these species most cases ultimately prove to be minor.

Approach to Treatment

Effective treatment of spider bite relies on early diagnosis of the likely culprit – in particular, defining if it is probably one of the few spider species of medical importance [2, 31]. If it is likely to be a potentially dangerous species, such as an Australian funnel-web spider, assessment is urgent, and specific treatment must be instituted as soon as systemic envenoming is apparent. For most other spiders, however, even widow spiders, it is practical to observe for a period before starting definitive treatment because many cases are minor, and a delay does not endanger life in most instances.

Specific Treatment: Antivenom

When available, antivenom is the most effective treatment for systemic envenoming; this is particularly true for significant bites by Australian funnel-web spiders, where major envenoming is likely to prove lethal without antivenom [2] (See ► Chap. 129, “Australian Funnel Web Spiders”). Widow spider bites rarely prove lethal but can cause prolonged and unpleasant symptoms, justifying antivenom therapy [2]. In Australia, where widow spider bites are frequent, antivenom is used routinely and has been considered effective and reasonably safe [2, 31]. Recently the RAVE II trial which was a double blind randomized control trial of IV antivenom versus placebo has cast doubt on the effectiveness of antivenom in latrodectism, resulting in some toxicologists no longer recommending this antivenom treatment [32]. However, there are some uncertainties about the validity of both the trial and its interpretation, particularly since it provided an answer (that antivenom is ineffective) that is at odds with more than 50 years experience with this antivenom in Australia [33]. Further, it failed to find an effective alternative treatment, noting that 70% of patients failed to gain significant symptom relief from analgesia alone, which is the current only alternative treatment. The author of this chapter has been treating Australian widow spider bites for nearly 40 years and has seen many cases respond rapidly and fully to antivenom, often after other treatment options have been tried and failed. It is therefore this author’s opinion that the RAVE II study alone should not result in change in treatment practice but that independent confirmation of the RAVE II study results should be undertaken (Grade III recommendation). Given that previous research has indicated an antivenom raised against one widow spider species is likely to be effective against other species of *Latrodectus* and that an increasing number of case reports, case series and trials have shown effectiveness, to varying degrees, of anti-*Latrodectus* antivenom, it appears the overall body of evidence supports the use of antivenom, despite the RAVE II study [2, 31, 33–44] (Grade I recommendation). Antivenom is used in moderate-to-severe cases of systemic

envenoming by Brazilian banana spiders, particularly in children and the elderly, but these cases represent only a small proportion of medically treated banana spider bites [2, 45–47]. Antivenom against recluse spiders is also available in Brazil, but its effectiveness at preventing necrosis is contestable, with evidence both supporting and refuting effectiveness and frequently patients present too late for antivenom to be likely to be effective [2, 3, 47–53]. Details of specific antivenom treatments for major spider bite may be found in their respective chapters.

Other Treatments

Details of specific nonantivenom treatments for major spider bite, such as loxoscelism, may be found in ► Chap. 128, “Overview of Spider Envenoming.”

Follow-up

All spider bites should be considered for follow-up, but not all require formal arrangements. For most cases, the significant and uncommon risk is secondary infection. Patients should be instructed on what symptoms and signs to look for, indicating such a complication, and to return promptly if these occur. All patients receiving antivenom should be followed, at least by phone call, to check for serum sickness.

Cross-References

- Australian Funnel Web Spiders
- Overview of Spider Envenoming
- Widow and Related Lactrodectus Spiders

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Australian funnel-web spiders are arguably the world's most dangerous spiders. As with most spider bites, the bites caused by funnel-web spiders are frequently minor, but in the approximately 10% of cases in which systemic envenoming occurs, the chance of fatality is significant [1]. Even modern interventions of intensive care medicine are insufficient to save a patient with a severe bite; only antivenom therapy is lifesaving in severe cases [2, 3].

Taxonomy and Distribution

The Australian funnel-web spiders of the genera *Atrax*, *Hadronyche*, and *Illawarra* are restricted to Australia, including Tasmania, as are the related mouse spiders of the genus *Missulena* [4–6]. All are mygalomorph spiders (Fig. 1) of the families Hexathelidae: Atracinae (*Atrax*, *Hadronyche*, *Illawarra*) and Actinopodidae (*Missulena*). They are quite distinct from the “funnel-web spiders” of North America. The Australian funnel-web spiders have recently been revised taxonomically, with names assigned to many species previously listed by number [6].

Funnel-web spiders live most of their lives in self-excavated or constructed silk-lined burrows or tubes, with traplines radiating from the entrance. The spider briefly leaves the burrow to catch prey crossing the traplines [5]. For mating to

occur, however, the male must leave the burrow and roam the surrounding area in search of a female. This biologic necessity ensures that males are more likely to interact with humans than female spiders. There is significant sexual dimorphism, with females being slightly larger, more robust, with larger abdomens, and often with different coloration (particularly mouse spiders) than males.

Atrax

Currently there are three recognized species of *Atrax*, the Sydney funnel-web spider, *Atrax robustus* (Fig. 2), *Atrax yorkmainorum*, and *Atrax sutherlandi*. *A. robustus* has caused the most severe bites and fatalities, partly because it is distributed within a major urban conurbation (Sydney and surrounding areas). All three species are restricted to eastern New South Wales (Fig. 3) [3, 4].

Hadronyche

There are 31 species of *Hadronyche*. They are found in eastern Australia from Cape York to Tasmania (Fig. 3). Several *Hadronyche* spp. have caused significant, potentially lethal bites (Table 1; Figs. 4 and 5) [4–6].

Fig. 1 Diagrammatic representation of the external anatomy of mygalomorph spiders (Copyright © Dr. Julian White, 2001)

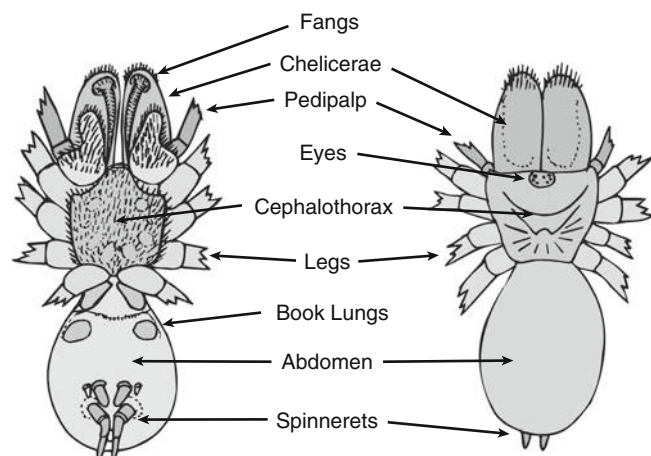




Fig. 2 Male Sydney funnel-web spider, *Atrax robustus* (Copyright © Dr. Julian White, 2001)

Illawarra

This recently erected monotypic genus of Australian funnel-web spiders has one species, *I. wisharti*, about which there is very limited information on venom. The information which is available, however, indicates similarities with *Atrax* and *Hadronyche* venoms. It was previously listed as an unnamed species of genus *Hadronyche* (species “20”) and it may be it has similarly toxic venom as other funnel-web spiders [8]. A few bites have been reported, under its previous identity, but none of these had documented clinical effects. Given the small number of reported cases, it is not possible to determine a level of dangerousness, as it is known that even for other funnel-web spider species that have caused fatalities, most bites do not result in detectable systemic envenoming.

Missulena

The mouse spiders, currently with 16 described species, are of uncertain medical importance [9–11], despite the Australia-wide distribution of these common spiders (Fig. 6) [10–12]. They have toxic venom similar to *Atrax* and *Hadronyche*, but there is only one case of significant envenoming in a human, which was nonfatal.

Venom

The venom of funnel-web spiders is a mixture of components, the most important of which is a class of excitatory neurotoxins, similar across species and potentially lethal for humans, but comparatively nontoxic for most other mammals [1, 8, 12]. This latter property has inhibited research and development of an antivenom. These neurotoxins act at voltage-gated sodium channels (Na_v) and are characterized as having an inhibitor cysteine-knot motif. Similar toxins have been isolated from a variety of other spider venoms and some marine venoms. These toxins isolated from funnel-web spiders, and also the related mouse spiders (genus *Missulena*), act on neurotoxin receptor site 3 at the Na_v and appear to inhibit inactivation of the channel, resulting in neurotransmitter release from somatic and autonomic nerve endings.

Atrax

Of the three species of *Atrax*, *A. robustus* venom has been examined in detail [8, 13–15]. The venom of male spiders is approximately seven times more toxic than that of females. The principal lethal component is δ -atractoxin (δ -ACTX; previously named robustoxin) [8, 14], a protein of molecular weight 4854 d, with 42 amino acid residues, four disulfide bridges, and subcutaneous median lethal dose of 0.16 mg/kg in newborn mice.

Hadronyche

The venom of several *Hadronyche* spp. has been examined, most notably *Hadronyche versuta*, with a principal lethal component similar to δ -ACTX, named *versutoxin* [16] (molecular weight 4852 d, 42 amino acid residues, four disulfide bridges, and subcutaneous median lethal dose 0.22 mg/kg in newborn mice). Venom from *H. formidabilis* and *H. infensa* appears similarly toxic, with equivalent toxicity in males and females, in contrast to *A. robustus*. A recent proteomics study of the venom of 18 species of

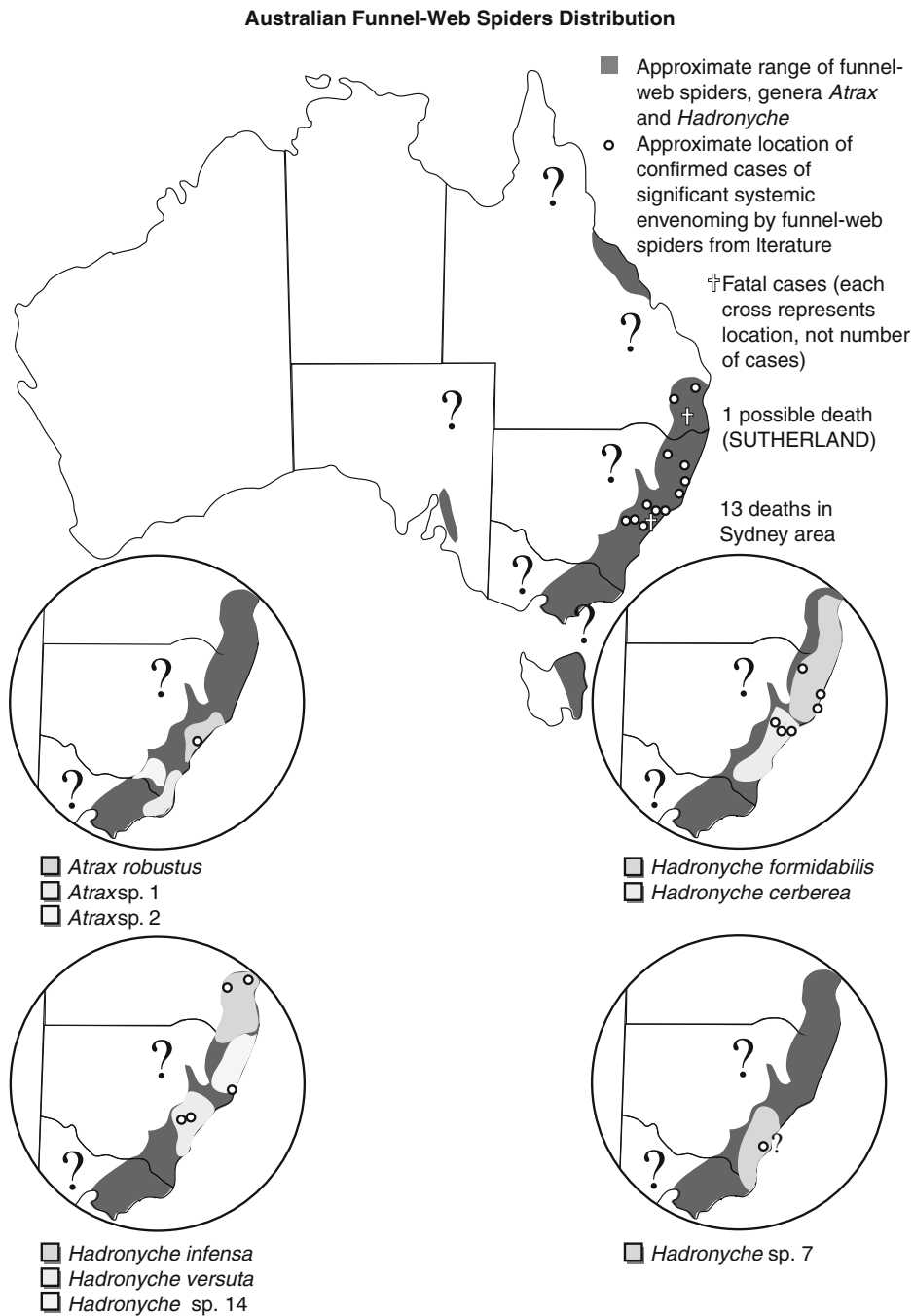


Fig. 3 Distribution of Australian funnel-web spiders (Copyright © Dr. Julian White, 2001)

Australian funnel-web spiders demonstrated similarities between all species, but also significant intra- and interspecies differences, and between males and females [15].

Missulena

Research has shown some *Missulena* spp. to have venom with δ -ACTX -like components

Table 1 Australian funnel-web spiders known to have caused significant envenoming in humans, based on confirmed bites by identified spiders. Note that this significantly underestimates numbers of mild bites by Sydney funnel-web spiders [7]

Species	Clinical effects	Number of cases with minor/local effects only	Number of cases with mild to moderate effects	Number of cases with severe effects (% of all cases severe)	Number of deaths reported
<i>Atrax robustus</i>	Major systemic envenoming, known lethality	20+	1	22	13
<i>Hadronyche cerberea</i>	Major systemic envenoming, potentially lethal	1	0	7 (88%)	0
<i>Hadronyche formidabilis</i>	Major systemic envenoming, potentially lethal	2	1	7 (70%)	0
<i>Hadronyche infensa</i>	Moderate-to-severe systemic envenoming, potentially lethal	6	6	3 (20%)	? 1
<i>Hadronyche versuta</i>	Moderate-to-severe systemic envenoming, potentially lethal	9	0	2 (18%)	0
<i>Hadronyche nimoola</i>	Mild to moderate envenoming, lethal potential uncertain	4	2	0	0
<i>Hadronyche macquariensis</i>	Moderate-to-severe systemic envenoming, potentially lethal	4	2	2 (25%)	0
<i>Hadronyche venenata</i>	Mild to moderate envenoming, lethal potential uncertain	8	1	0	0
<i>Hadronyche lynabrae</i>	Mild to moderate envenoming, lethal potential uncertain	2	1	0	0
<i>Illawarra wisharti</i>	Mild envenoming, lethal potential uncertain	5	0	0	0
<i>Other unspecified</i>		9	3	0	0
<i>Immature spiders</i>		8	0	0	0

and to be potentially lethal for humans, although no confirmed fatalities are known [17]. The similarities extend to antigenicity because antivenom against *A. robustus* appears likely to be effective against *Missulena* venom [17]. This statement is consistent with the only reported human case of major envenoming by this genus, in which *Atrax*-specific antivenom was reported to be beneficial [18]. An δ -ACTX-like toxin, δ -missulenatoxin-Mb1a (δ -MSTX-Mb1a)

has been isolated from male *Missulena bradleyi* venom [12].

Clinical Presentation

From a clinical perspective, the effects of *Atrax* and *Hadronyche* bites on humans are essentially the same [1, 7]. Because only one case of severe *Missulena* envenoming has been reported, the

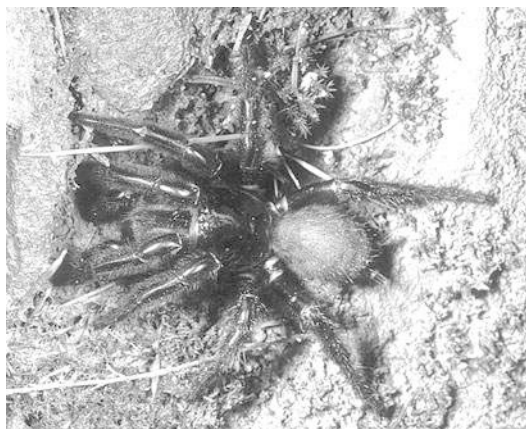


Fig. 4 Female tree funnel-web spider, *Hadronyche formidabilis* (Copyright © Dr. Julian White, 2001)

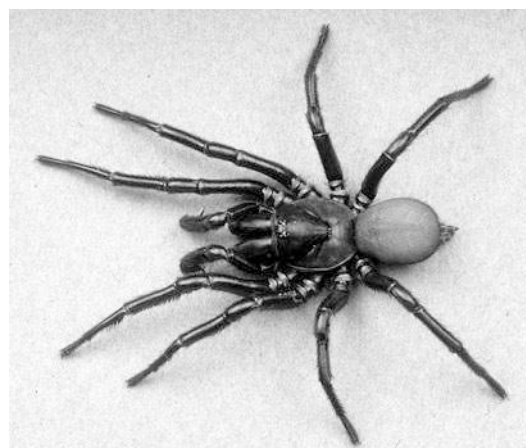


Fig. 5 Male funnel-web spider, *Hadronyche cerberea* (Copyright © Dr. I. Whyte, 2000)

clinical features of significant envenoming from these spiders are uncertain [10, 11, 18].

Atrax

The bite is usually painful, owing to the size of the fangs (5 mm) and the acidic (pH 4.5–5.0) nature of the venom. The spider frequently hangs on. Bite marks are usually present (Fig. 7). In the few cases in which systemic envenoming develops, there may be rapid onset of early



Fig. 6 Male mouse spider, *Missulena insigne* (Copyright © Dr. Julian White, 2001)



Fig. 7 Local appearance of funnel-web spider bite (From Miller et al. [19]. Copyright © Dr. I. Whyte, 2000)

symptoms, such as lip paresthesias and tongue fasciculation. Time from bite to first systemic symptoms may be 10 min, and deaths occurring in less than 1 h are recorded. Soon after onset of first symptoms, there is progression to more severe envenoming, which may include tachycardia, hypertension, hypersalivation and hyperlacrimation, piloerection, increased sweating, nausea, vomiting, abdominal pain, muscle fasciculation, cardiac dysrhythmias, and pulmonary edema. The venom causes a catecholamine storm effect and while atropine + phenoxybenzamine + propranolol largely abolished major envenoming effects in monkeys, allowing them to survive massive venom doses,

urinary catecholamines were still high. Monkeys surviving the initial envenoming phase then developed progressive hypotension with cardiomegaly and pulmonary edema, so quite distinct from the early phase of hypertension, intracranial hypertension, normal cardiac size, and pulmonary edema.

The pulmonary edema is, at least initially, noncardiogenic and therefore is an acute respiratory distress syndrome. It may develop quickly, be more severe, and result in hypoxia and impaired consciousness or coma. Death in this phase is usually secondary to pulmonary edema. The pulmonary edema is considered neurogenic in origin. Should the patient survive this first phase without antivenom therapy, the untreated clinical course may progress to the second phase, in which excitatory effects subside, secretions cease, and hypertension resolves, only to evolve into a progressive and terminal hypotension, apnea, and cardiac arrest.

Hadronyche

The clinical picture for *Hadronyche* spp. is essentially the same as for *Atrax* spp. except that the former spiders are larger and it is possible, although not yet proven, that the chance of envenoming and life-threatening envenoming may be higher [5, 11–13, 19–21]. Virtually all well-documented deaths after funnel-web spider bite were due to *A. robustus*.

Missulena

The clinical picture for *Missulena* bites is partially characterized, based on 40 confirmed bites by five different species [10, 11]. Experimentally, the venom is similar to funnel-web spider venom, with similar toxicity and effects. These spiders are common, however, and many bites have occurred without significant deleterious effects (R. Raven: personal communication, 1994). In nearly all cases there was either no reported effect

or only mild local or systemic effects [10, 11]. The single case of significant envenoming, in a 19-month-old child following a *Missulena bradleyi* bite, appeared similar to that of *Atrax* envenoming, including hypertension, muscle spasms, and loss of consciousness [18]. This case appeared to respond to funnel-web spider antivenom. Because of this case, and in light of the similarity between *Missulena* venom and that of *Atrax* and *Hadronyche* spp., bites by these spiders should be treated with great caution, using a similar approach to managing funnel-web spider bites [1, 7, 10, 11, 22].

Complications

The principal complications of funnel-web spider envenoming relate to the severity of direct venom effects. There may be hypoxic brain damage or other organ damage secondary to the pulmonary edema or cardiopulmonary or respiratory arrest [1, 2, 5]. There is a single case of prolonged status epilepticus after presumed *Hadronyche* bite, initially thought to be organophosphate poisoning (personal record; not published). In this case, there was no response to atropine, but rapid cessation of seizures occurred after administration of intravenous funnel-web spider antivenom (FWSAV) (CSL Limited, Victoria, Australia). By this stage, irreversible, ultimately fatal brain damage had occurred.

Diagnosis

The diagnosis of funnel-web spider bite is made on clinical symptoms and signs or presentation of a funnel-web spider; currently no venom detection is available [1, 22]. Occasionally, patients may present in confusing circumstances, with no history of a bite and apparent exposure to a chemical (notably, organophosphates), which may cause some similar clinical effects. The only known fatality due to

funnel-web spider bite since introduction of antivenom occurred in such circumstances (see above).

History

In most cases, there is a history of a witnessed bite by a funnel-web spider because the spider is large and the bite generally is painful. Although patients often cannot identify a funnel-web spider confidently, these spiders are distinctive, and within their range it is appropriate that all bites by spiders of this appearance (“big black spiders”) be managed initially as funnel-web bites [22]. Conversely, outside the common range of these spiders, other mygalomorph spiders, such as trapdoor spiders (*Aganipe* spp.) and wishbone spiders (*Dekana* spp.), are frequently misidentified as funnel-web spiders. There is no evidence that these species are dangerous to humans, although also no substantial research, such as venom studies, exists to prove that they are harmless. It is important to recognize that the known areas where funnel-web spider bite may occur, documented by cases, is expanding as better case reporting occurs [23].

After establishing that a bite from a possible funnel-web spider has occurred, it is important to determine if systemic envenoming has developed. Major envenoming is obvious, but in initially minor cases, the clinician should determine if there has been any perioral paresthesias, tongue fasciculation, piloerection, or increased sweating or salivation. The presence of any of the aforementioned signs is strongly suspicious of development of significant systemic envenoming.

Examination

The clinician specifically should look for evidence of autonomic stimulation, such as tongue fasciculation; piloerection; increased sweating, salivation, and lacrimation; tachycardia; hypertension; and particularly pulmonary edema.

Laboratory Tests

There are no tests specific for funnel-web spider envenoming. Experimentally envenomed monkeys have developed metabolic acidosis and elevated creatine phosphokinase concentrations [13].

Differential Diagnosis

No other terrestrial venomous animals are likely to cause a syndrome similar to funnel-web spider envenoming. Red back spiders (widow spiders; *Latrodectus hasseltii* [latrodectism]) can cause increased sweating and occasionally piloerection and commonly cause nausea and abdominal pain and hypertension, but they virtually never cause pulmonary edema [1]. Local, regional, or generalized pain is more prominent in most cases of latrodectism. Organophosphate poisoning may result in symptoms and signs similar to funnel-web spider envenoming – classically, tachycardia, hypertension (bradycardia and hypotension are also possible if muscarinic effects predominate), miosis, muscle fasciculation, excessive secretions, bronchospasm, vomiting, diarrhea, urinary incontinence, and occasionally pulmonary edema. The absence of bronchospasm and prominence of pulmonary edema should suggest funnel-web spider envenoming; conversely, the presence of bronchospasm and comparatively mild pulmonary edema (if present at all) should suggest organophosphate poisoning. Organophosphate poisoning is usually associated with a latent period of 1 or more hours between exposure and onset of symptoms.

Treatment

Treatment of funnel-web spider bite should focus on the needs of the few patients who develop systemic envenoming, because this is potentially lethal [22] (Fig. 8). All patients with definite or suspected funnel-web spider bite should be urgently hospitalized and assessed.

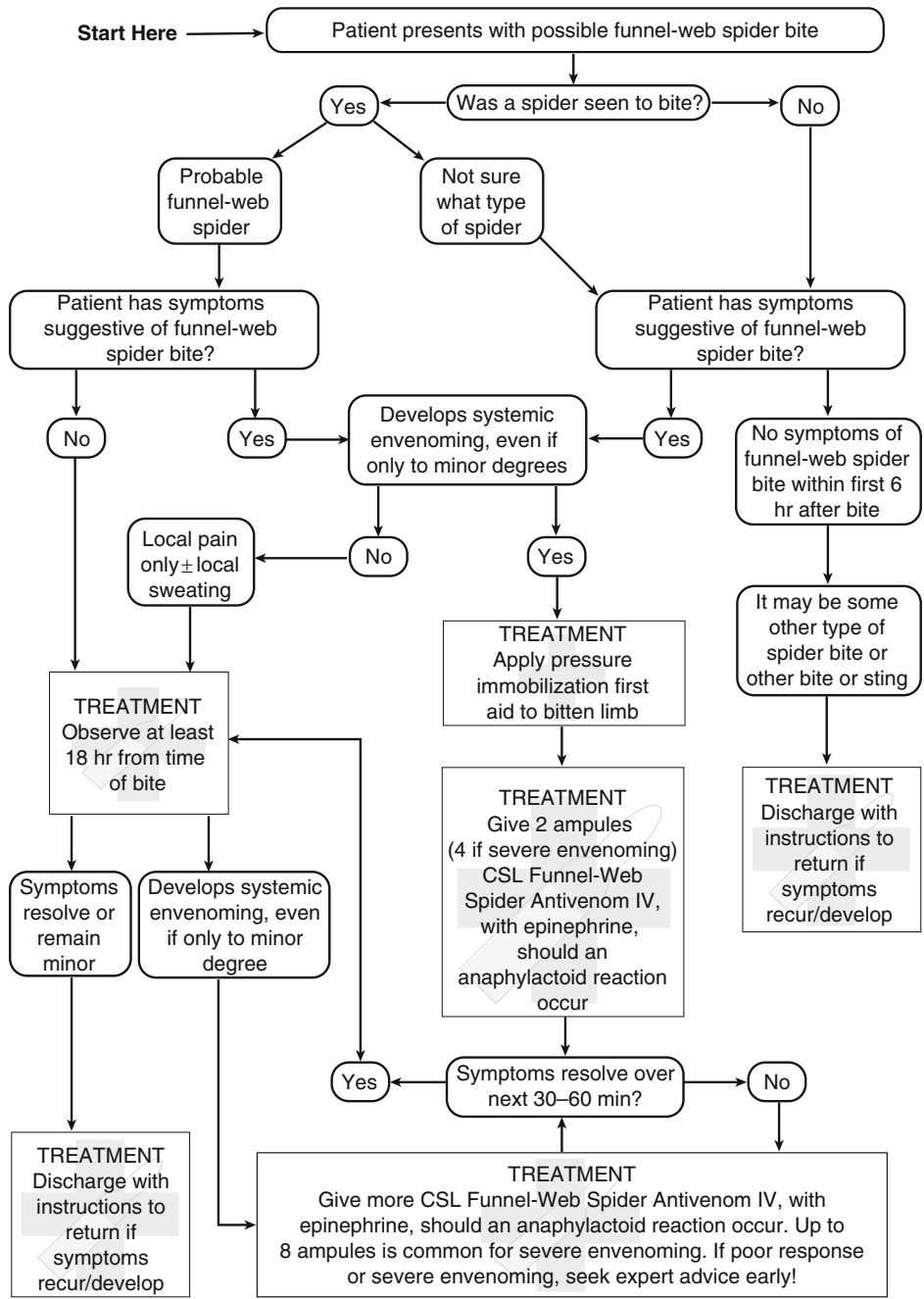


Fig. 8 Outline management plan for funnel-web spider bite (Modified from White [33]; and Miler et al. [19]. Copyright © Dr. Julian White, 2001)

At the first sign of systemic envenoming, anti-venom therapy should be started [22] (Grade II-2 recommendation). Most bites prove minor, however, and any patient presenting more than

6 h postbite without symptoms or signs of systemic envenoming is unlikely to develop envenoming subsequently [22] (Grade II-2 recommendation).

Most cases of funnel-web spider bite need no more than a period of observation because the bite is minor. Because late effects occasionally occur, observation is advisable, for at least 4 h from the time of the bite, or if appropriate first aid has been used, from time of removal of first aid [22].

First Aid

The recommended first aid for funnel-web spider bites is the pressure bandage and immobilization technique (PBI; see ► Chap. 122, “Australian and Pacific Snakes”) [22, 24, 25] (Grade II3_ recommendation). In contrast to snake venom, funnel-web spider venom is at least partially destroyed by prolonged immobilization at the bite site; this method not only delays envenoming but also may reduce the extent of envenoming [24, 26]. This technique is especially important given the rapidity of possible envenoming.

Urgent Measures

After stabilization of airway and breathing, good intravenous access is the next priority to allow rapid intravenous antivenom infusion, if indicated.

Antivenom

The only reliably lifesaving treatment in severe envenoming is intravenous antivenom therapy using specific FWSAV [1, 7, 19, 22, 26–31] (Grade II-2_ recommendation). FWSAV is lyophilized rabbit IgG against male *A. robustus* venom. Since its introduction in 1980–1981, there has been only one presumed death after funnel-web spider bite, and in that single case, death was due to late diagnosis not failure of antivenom. FWSAV is unlikely to cause major adverse immediate reactions, such as anaphylaxis, given the catecholamine excess that is characteristic of these envenomations, but serum sickness has occurred in at least one case (out of >50 treated cases) [7].

When to Use Antivenom

FWSAV should be used in all patients with systemic envenoming except patients who present late (>6 h) with no more than mild envenoming that has not progressed over several hours [22]. At the earliest evidence of systemic envenoming, it is appropriate to consider starting antivenom therapy because progression to life-threatening envenoming may be rapid, especially in children.

Dosage

The initial antivenom dose depends on the degree of envenoming. For mild envenoming, the clinician should consider starting with two vials; for more severe envenoming, treatment may be started with four vials [22]. In either case, if the response is incomplete, giving a further two to four vials may be considered after 15–30 min. Even severe cases usually respond to six to eight vials, but occasionally more vials are required; the maximum recorded dose was 18 vials. Readministration is generally prompted by recurrent episodes of pulmonary edema, each time responding rapidly to antivenom, but then recurring several hours later. There is mounting evidence that *Hadronyche* bites may require higher antivenom doses than *Atrax* bites. There are no clinical data on requirements for *Missulena* bites, but a single human case of severe envenoming appeared to respond to antivenom, consistent with experimental findings showing cross protection [10, 32]. The consensus among treatment experts is to keep giving antivenom until response is complete [22]. In a few cases, there is an initial good response to FWSAV, but several hours later the patient relapses with pulmonary edema. Although this situation occasionally may be due to intravenous fluid overload, it is more likely relapsed envenoming, and further antivenom administration is appropriate. One additional vial may be all that is required in such cases. Children require the same dose as adults. FWSAV is freeze dried, so has to be reconstituted. Because of this the usual dilution of liquid antivenom in Australia is generally not used for FWSAV. If you were treating a small child and had to give 18 vials (180 ml) then fluid overload might be an issue if

all given at once, but that is never the case. The starting dose is two to four vials.

Nonantivenom Treatment

In the absence of antivenom, the other therapeutic interventions for a patient with severe envenoming are of limited efficacy. In patients with severe pulmonary edema, intubation with intermittent positive pressure breathing and positive end-expiratory pressure has had some success [2, 3]. If early hypertension and tachycardia are clinically significant, α blockade has been and may be used, but β blockade is thought to be contraindicated [2]. Atropine has proved useful as a means of controlling secretions, as has diazepam as a sedative measure in the ventilated patient. However, it is not known if diazepam is superior to other standard sedating treatments during mechanical ventilation of funnel-web spider envenomed patients.

Special Populations

Pregnant and Breast-Feeding Patients

The mother and fetus may be severely affected by funnel-web spider envenoming, requiring robust antivenom therapy. There are insufficient reported cases to determine fetal prognosis. However, aggressive and appropriate treatment of the mother likely offers the best prognosis for fetal survival.

Pediatric Patients

Children appear to be at higher risk of rapid, severe, even fatal envenoming, requiring a prompt therapeutic response. If you look at a list of known fatalities, 8 of the 13 are children under the age of 15, and 5 of those are 5 years or younger and are the most rapid deaths. They require just as much antivenom as adults, but fluid overload from intravenous therapy is more likely. This situation may pose a diagnostic dilemma as to whether late-

onset pulmonary edema is due to relapsing envenoming or iatrogenic fluid overload. Clinical circumstances may provide the answer, but if in doubt, the treating physician should consider administering more antivenom.

Elderly Patients

The elderly are at increased risk from envenoming and secondary fluid overload.

Follow-Up

All patients receiving antivenom should receive follow-up, at least by telephone, to detect and monitor for development of serum sickness. All patients with even mild systemic envenoming should be monitored closely in an intensive care setting for at least 24 h or at least 12 h from complete resolution of all symptoms and signs of envenoming, whichever is longer.

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Loxosceles spiders, known as brown spiders, recluse spider, or violin spiders, are widely distributed in tropical and temperate regions. The envenomation caused by *Loxosceles*, known by loxoscelism, occurs mainly in the Americas, particularly in South America. Bites typically occur when a sleeping person rolls over on a *Loxosceles* spider in bed or while dressing when pressing a hidden spider between flesh and fabric. *Loxosceles* venom is a mixture of toxins consisting of proteins, glycoproteins, and low-molecular-weight peptides. The key components are members of the sphingomyelinase D/phospholipase D gene family, which activate complement, endothelial cells, and epithelial cells, as well as endogenous metalloproteinases, and are involved in the development of skin necrosis and hemolysis. The *Loxosceles* bite can evolve to skin lesions (cutaneous loxoscelism), which can be accompanied by intravascular hemolysis (cutaneous-hemolytic loxoscelism; also known as viscero-cutaneous loxoscelism). In the cutaneous-hemolytic form, acute kidney injury and, less frequent, disseminated intravascular coagulation can occur as complications of intravascular hemolysis. Treatments prescribed for loxoscelism include particularly antivenom, corticosteroids, and dapsone. However, there is no consensus regarding the best treatment for loxoscelism, and the standard treatment varies among the regions of the world where *Loxosceles* bites occur.

Taxonomy of *Loxosceles* Spiders

Spiders are in the phylum Arthropoda (jointed legs), the class Arachnida and further down the taxonomic tree, the order Araneae (spiders), suborder Araneomorphae. The medically important recluse spiders belong to the genus *Loxosceles* (pronounced *locks-AW-seh-leez*, similar to “isosceles” as in the triangle), derived from the Greek language meaning “crooked or slanted legs” for the way the spiders position their legs when at rest. The first *Loxosceles* species was scientifically described in 1820 from circum-Mediterranean specimens and is currently known

as *L. rufescens*. As of the writing of this chapter, there are 114 *Loxosceles* described worldwide [1] with about 60% being named by one luminary American arachnologist [2, 3]. The first North American species (*L. reclusa*) was named in 1940; earlier references to this species used extant European names which may cause confusion when one reads the older American *Loxosceles* medical literature [4].

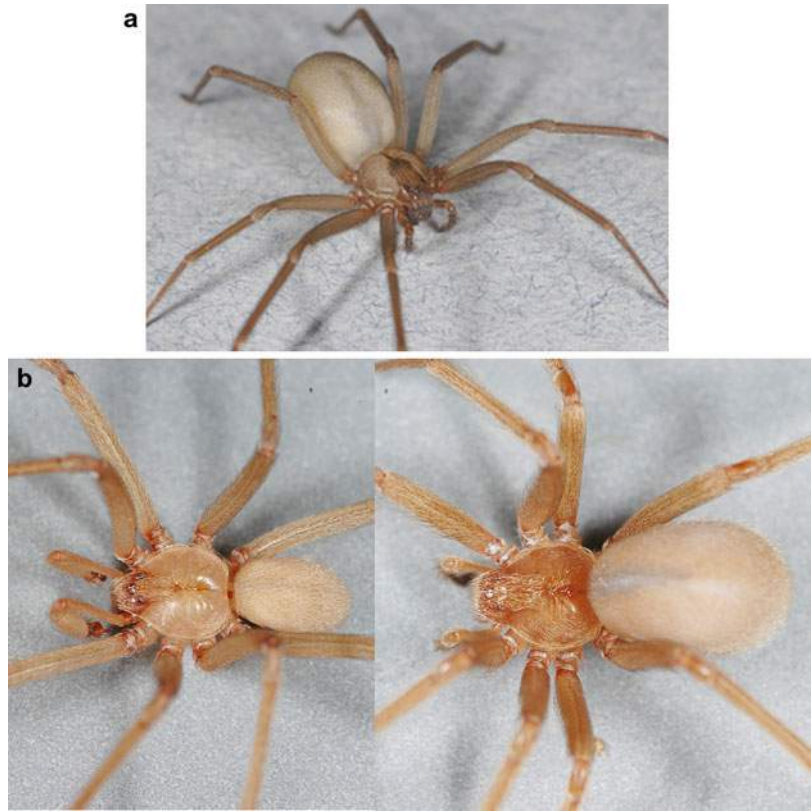
Spider Description and Biology

The most common appearance of a recluse spider is a rather nondescript brown spider with tan legs and 8–14 mm in body length when mature. Leg spans may be 2–4 cm. Several of the well-known species have a violin-shaped pattern on the dorsal surface of the cephalothorax (the major body part to which the legs attach) and may also be referred to as violin or fiddleback spiders (Fig. 1). Many North American medical publications have cited this marking as a diagnostic feature for identification. Although this pattern may be conspicuous for species such as *L. reclusa* (Fig. 2a) and *L. rufescens*, not all age stages of these species display such a distinct violin shape. Other species [e.g., *L. laeta* (Fig. 2b) in South America, *L. deserta* in the southwestern USA] have coloration which contrasts weakly with the rest of the



Fig. 1 Because of variability in coloration among the many species, the pattern of six eyes arranged in nontouching pairs is a better identification feature than the violin pattern common in several *Loxosceles* species

Fig. 2 The North American brown recluse spider, *Loxosceles reclusa* (a) and the South American spider, *L. laeta* (b)



cephalothorax such that a violin pattern is not readily apparent [5]. In addition, many harmless spiders have darkened patterns that nonarachnologists (including physicians) have misinterpreted as the violin pattern of a recluse spider [5, 6] resulting in misidentification and potentially excessive and incorrect medical treatment. The more reliable feature that should be used for identification is the eye pattern. Most spiders have eight eyes in two rows of four. The recluse spiders have six eyes with a pair of eyes anteriorly and a pair on either side separated by a space (Fig. 1). The recluse spiders are not the only spiders that have this pattern (e.g., spitting spiders of the genus *Scytodes*) but other features should eliminate those six-eyed nonrecluses from consideration.

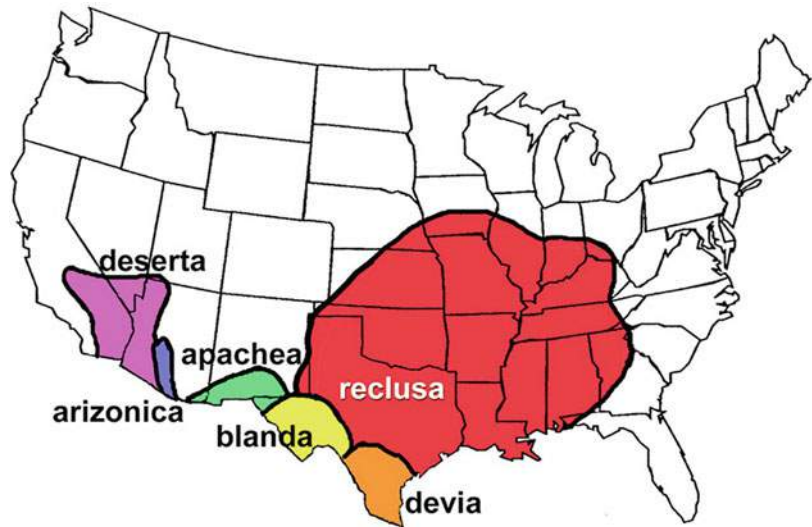
In addition, recluse spiders have monochromatic legs and fine recumbent hairs on their legs without conspicuous spines. Most Western Hemisphere *Loxosceles* species have a monochromatic abdomen which can vary from a light cream color

to a dark brown depending on the spider's diet so abdominal coloration is a nondiagnostic feature. However, South African species have boldly patterned tan and brown abdomens, looking very different from most of the other species of the genus.

Recluse spiders are nocturnal and in natural conditions are found under rocks and the loose bark of trees. In buildings, they are found in boxes, under tarpaulins, in holes and cracks in building structures, and behind paintings. They are active hunters where they prowl for their prey at night; but they also lay out silk as triplines from the opening of their retreat, waiting at the mouth of the opening for an appropriate sized prey to become entangled. Once prey is entangled, the spider rushes out to subdue it with a toxic bite.

Many *Loxosceles* species of medical importance are considered synanthropic, i.e., they increase in population in association with humans. Other synanthropic animals include rats, pigeons, and cockroaches. Recluse spider

Fig. 3 The distribution of widespread *Loxosceles* spiders in North America



populations can grow to hundreds or thousands in a single structure such as a house in Kansas (USA) where 2,055 *L. reclusa* spiders were collected in a 6-month period [7] and in a Chilean study where 29% of the inspected homes had *Loxosceles* spiders; the five most densely infested homes yielded an average of 163 *L. laeta* specimens [8]. These large populations develop despite the fact that *Loxosceles* spiders typically lay only 30–80 eggs per egg sac and only a few egg sacs during their lifetimes [4]. However, their behavior is such that they are very tolerant of conspecifics so there is little aggression among members of the same species [9, 10] allowing populations to swell.

Although large numbers of *Loxosceles* spiders in a structure would seem to correlate with greater threat of a bite, in the Chilean study mentioned above, no one in the five densely infested homes complained of a loxoscelism event [8], and the family in the Kansas house lived therein 11 years before someone received a probable recluse bite [4, 7].

Geographic Distribution

The greatest concentration of *Loxosceles* species is centered in Mexico and Central America with South America also containing many species

[2, 3]. There are 11 native species in the United States [4] with six having widespread distribution (Fig. 3). The Mediterranean recluse, is native to southern Europe and northern Africa, is a world-wide tramp found in many locations but is not extremely common outside of its indigenous range; one building may become greatly infested but the infestation typically does not spread beyond that structure unless connected by conduits and pipes. In addition, recent research implies that although *L. rufescens* has been considered one species throughout the Mediterranean area, it is actually several closely related cryptic species [11] which may eventually be separated into distinct taxa in future studies.

A dozen or so species occur in Africa although greater scrutiny may result in additional species being named. Some of the African species are found only in isolated caves which may be the ancestral condition and might explain why some *Loxosceles* species will profusely inhabit one building but not nearby structures. Recently taxonomic work has described several species in Asia. In Australia, the Mediterranean recluse lives in an extremely circumscribed distribution around Adelaide but poses only a mild medical threat there [5] especially when one considers the wealth of toxic organisms on that continent.

Epidemiology

In North America, the brown recluse, *L. reclusa*, has the greatest distribution [4, 5] and is the most likely candidate in loxoscelism. In South America, *L. laeta* is widespread through much of the continent [2] and is a considerable health threat as it is the largest of the *Loxosceles* species (being up to 14 mm in body length) and allegedly has the most toxic bite, due to either size or venom chemistry. Other species of widespread medical concern in South America are *L. gaucho*, *L. similis*, and *L. intermedia*, which are found in southern Brazil and Argentina.

Bites typically occur at night when a sleeping person rolls over on a *Loxosceles* spider in bed or in the morning while dressing when pressing a hidden spider between flesh and fabric. The bite is either painless or felt as a small prick of the skin.

Loxosceles bites are most common on the leg (35%), arm (17%), torso (12%), hand (9%), and foot (5%) with only 0.6–1.5% of the bites occurring on the face, neck, buttocks, shoulder, or genitalia [5].

Loxosceles Venom and Its Histopathophysiological Effects

Loxosceles venom is a mixture of toxins consisting of proteins, glycoproteins, and low-molecular-weight peptides [12–17]. The key components are members of the sphingomyelinase D/phospholipase D gene family, which activate complement, endothelial cells, and epithelial cells, as well as endogenous metalloproteinases, and are involved in the development of skin necrosis and hemolysis [18, 19]. Sphingomyelinases D (SMases D) catalyze the hydrolysis of sphingomyelin, which releases choline and ceramide 1-phosphate. Because SMases D are also able to hydrolyze a broad range of phospholipids, such as lysophosphatidylcholine (which releases lysophosphatidic acid), they are being reconsidered as phospholipases D. *Loxosceles* venom also contains numerous other enzymes including collagenases, alkaline

phosphatases, phosphohydrolases, hyaluronidases, and metalloproteinases. Hyaluronidase might facilitate the gravitational spread of the toxin through the tissue [20, 21].

Electrical stimulation of the cephalothorax of a brown *Loxosceles* spider yields only a few microliters (approximately 4 μ L) of venom. The amount and the content of venom depends on several factors related to the animal, such as size, sex, age, nutritional state, and particular species [12, 13, 16, 17]. Female *Loxosceles* spiders produce larger amounts of venom than do their male counterparts, which could be related to their differences in size and weight. In addition, venom from the females has been shown to induce more intense skin necrosis and hemolysis. Furthermore, the amount and content of *Loxosceles* venom has been found to vary among species. Among rabbits experimentally inoculated with *Loxosceles* venom, skin lesions are larger in those injected with venom from *L. laeta* than in those injected with venom from *L. intermedia*. Venom from *L. laeta* has also been shown to cause more hemolysis in vitro than does *L. intermedia* venom [22, 23].

The best laboratory animal model for the study of venom-induced skin lesions is the rabbit, which develops necrotic skin lesions with a gravitational spreading pattern similar to that observed in human envenomation [12, 23–25]. In envenomed rabbits, histopathological skin changes include endothelial thickening, edema, vasodilatation, vessel wall degeneration, hemorrhage into the dermis, dermal-epidermal dissociation, vacuolization of basal layer keratinocytes, and infiltration by inflammatory cells, especially by polymorphonuclear leukocytes (PMNs), all of which are time dependent. By 3 h after subcutaneous injection of venom, edema and subcutaneous hemorrhage are observed, as is PMN accumulation in and around venules. For more than 48 h, PMNs continue to infiltrate the affected area [12, 26–29]. The PMN infiltrate, in part recruited by indirect activation of the complement system, is considered a major contributor to tissue damage. When neutropenia is induced in rabbits, the development of the characteristic venom-induced lesions is inhibited: Biopsies taken at

3 and 6 h after leukocyte depletion in rabbits show slight edema, absence of PMN infiltration, and no vasodilation or hemorrhage. Similar treatment of guinea pigs to deplete complement also inhibits the formation of venom-induced necrotic lesions: Biopsies taken from injection sites at 3 and 6 h after envenomation show no PMN infiltration. However, although complement depletion prevents the influx of neutrophils in rabbits and neutrophil influx is also reduced in rabbits with genetic C6 deficiency, that does not prevent the hemorrhage and collagen injury [12, 30–32].

Loxosceles SMase D has been shown to induce expression of matrix metalloproteinases (MMPs) in rabbit skin, as well as inducing apoptosis and MMP expression of keratinocytes, which is inhibited by tetracyclines [33]. In addition, in erythrocytes SMase D induces activation of membrane-bound metalloproteinases, resulting in cleavage of glycophorins, which facilitate complement activation via the alternative pathway, resulting in cell lysis. Furthermore, SMase D activates the classical complement pathway in erythrocytes, probably by inducing a loss of membrane asymmetry, leading to exposure of phosphatidyl serine on the external lipid monolayer, which allows the binding of C1q, the first component of the classical complement pathway, followed by activation of that pathway, resulting in hemolysis [34, 35]

Clinical Presentation

In most accidents caused by *Loxosceles* spp., the spider responsible is not captured for identification, often not even having been seen. Therefore, the diagnosis is usually presumptive and can be incorrect. In the absence of a known agent, the diagnosis is based on epidemiological information (the spider is commonly found in the area where the bite occurred, or the circumstances of the accident are consistent with *Loxosceles* behavior) and on the clinical manifestations (skin lesion, systemic response, etc.) On the basis of clinical and epidemiological data, envenomation can be classified as follows [36]:

Putative: spider not known to be in area, atypical skin lesion

Presumptive: spider known to be in area, compatible lesion, typical clinical course

Probable: spiders found in area, patient may have felt bite, seen a spider, typical lesion, typical clinical course

Documented: spider found after bite, identified by qualified person, typical lesion, typical clinical course

Forms

The *Loxosceles* bite can evolve to skin lesions, which can (in rare cases) be accompanied by intravascular hemolysis. The clinical course depends on many variables, such as the amount of venom inoculated; the species, sex, and stage of development of the spider; the anatomical region affected by the bite; and the age, premorbid health status, and immune response characteristics of the patient. Depending on the clinical presentation, loxoscelism is classified as being in one of two forms: cutaneous or cutaneous-hemolytic.

Cutaneous loxoscelism is the more common of the two forms of loxoscelism, occurring in 87.0–99.9% of cases [37]. The victim develops a skin lesion with a relatively slow course that can progress to necrosis. In most cases, there is only one bite site, although there have been a few reports of cases in which there were two or more bites. The bite is mildly painful, reported as a pinprick or itching sensation, and some victims do not feel the bite, because they are bitten in their sleep. Approximately 2–6 h after the bite occurs, the intensity of the pain can increase and can be accompanied by edema and erythema at the bite site. In the first 24 h, a lesion characteristic of cutaneous loxoscelism can evolve, with a painful, irregular macula showing a mixture of violaceous and pale areas (Fig. 4), which is often surrounded by erythema (the hallmark “red, white, and blue sign”) (Fig 5). Serous, serosanguineous, or hemorrhagic vesicles can be seen, as can bullae (Fig. 6). The lesion evolves to induration and, roughly 7–10 days after the spider bite, progresses

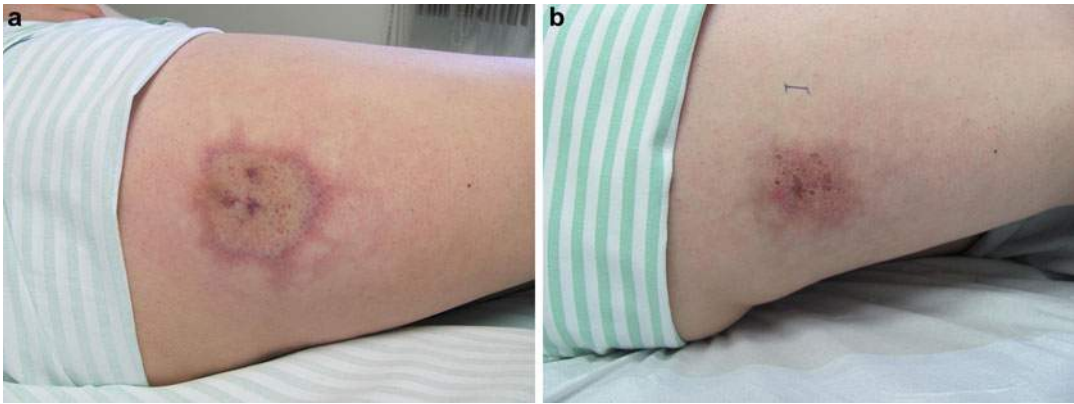


Fig. 4 Clinical course of cutaneous loxoscelism: (a) Lesion with ecchymosis and pale, 3 days after the bite. (b) Nineteen days after the bite

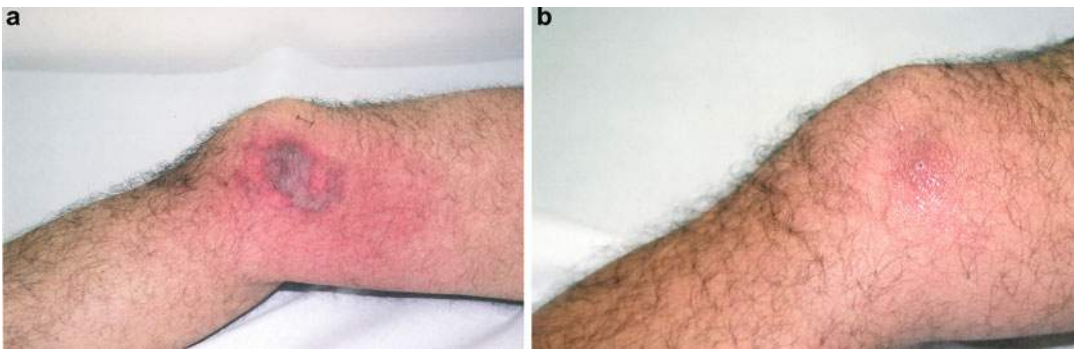


Fig. 5 Clinical course of cutaneous loxoscelism: (a) Violaceous lesion with erythematous halo observed around, 3 days after the bite. (b) Twenty days after the bite, patient evolved without necrosis/ulcer

to a dry, necrotic eschar with well-defined edges (Figs. 7 and 8). The necrotic tissue sloughs off in the second or third week, leaving an ulcer of variable depth and extent (Fig. 9). Lesions are typically more severe when the bite affects an area with a higher concentration of fatty tissue, such as the thigh, buttock, or abdomen. In areas such as the face and genitals, an edematous form, characterized by extensive edema and erythema with no progression to necrosis, can occur. When the face or neck is bitten, the edema can be so extensive that respiration is impaired. It is difficult to predict the depth, width, or evolution of skin necrosis. Not all bites evolve to violaceous/pale lesions (Fig. 10), and not all violaceous lesions progress to necrosis [38–43].

The cutaneous-hemolytic form of loxoscelism is also known as systemic or visceral-cutaneous loxoscelism. However, because systemic manifestations are also present in the cutaneous form, the denomination “systemic loxoscelism” is not an appropriate term to describe *Loxosceles* envenomation that progresses to hemolysis. Cutaneous-hemolytic loxoscelism is the most severe form of loxoscelism, characterized by intravascular hemolysis in addition to the skin lesion. It is less common than the cutaneous form and sometimes can be fatal. The frequency of the cutaneous-hemolytic form varies according to the species of *Loxosceles*: in areas endemic for *L. laeta*, the reported frequency of cutaneous-hemolytic loxoscelism 13–16% [38, 40], compared with up to only 10%



Fig. 6 Cutaneous loxoscelism; all cases are probable. (a) Three days after bite. (b): Five days after the bite. (c) Six days after the bite

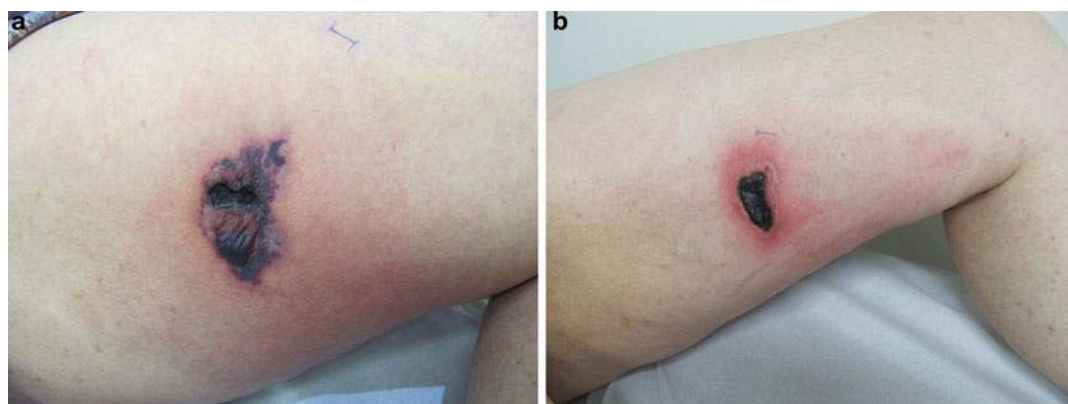


Fig. 7 Clinical course of cutaneous loxoscelism. (a) Cutaneous necrosis, 7 days after the bite. (b) Necrotic eschar, 19 days after the bite

in areas endemic for *L. gaucho* [43]. The cutaneous-hemolytic form is also rare in areas where *L. reclusa* is the predominant *Loxosceles* species [44], being very rare in areas where *L. intermedia* [45] and *L. rufescens* [46] are more

common. Cutaneous-hemolytic loxoscelism has also been noted with increasing frequency in children [40]. Glucose-6-phosphate dehydrogenase deficiency has been documented in some patients with the hemolytic form of loxoscelism

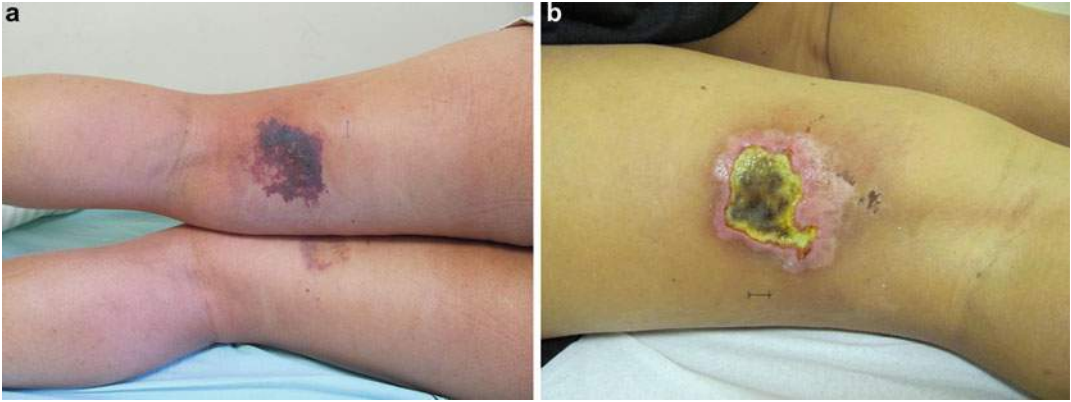


Fig. 8 Clinical course of cutaneous loxoscelism. (a) Lesion with ecchymosis and areas of pallor, 3 days after the bite. (b) Necrotic eschar, 39 days after the bite



Fig. 9 Clinical course of cutaneous loxoscelism. (a) Lesion with ecchymosis and areas of pallor, 26 h after the bite. (b) Skin ulcer, 35 days after the bite

Fig. 10 Skin lesion 1 day after bite by *L. gaucho*. Patients evolved without necrosis



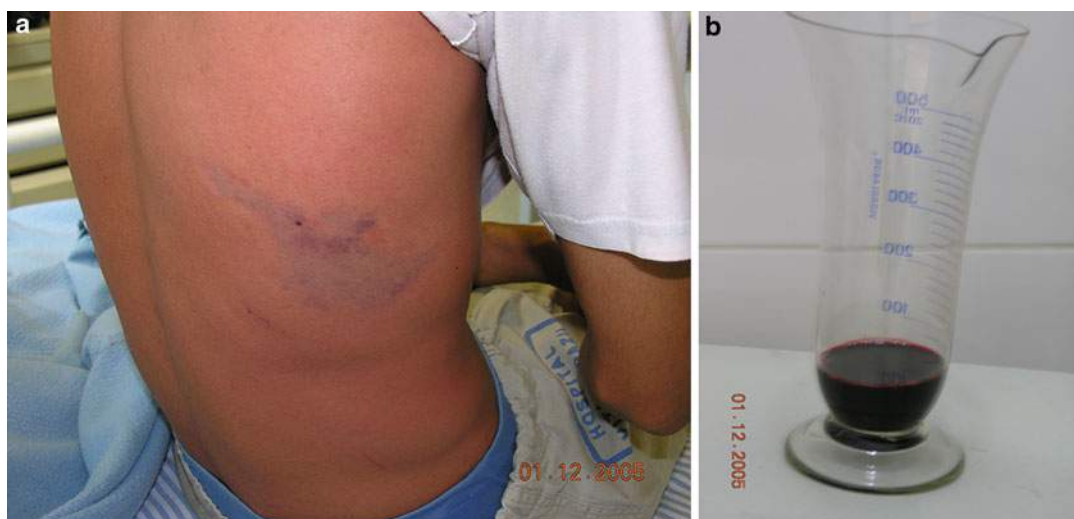


Fig. 11 Cutaneous-hemolytic loxoscelism, 24 h after the bite. (a) Cutaneous lesion. (b) Hemoglobinuria

[47]. Hemolysis can be acute or insidious, occurring between 48 and 96 h after the bite. However, the clinical signs of intravascular hemolysis, such as anemia, jaundice, and hemoglobinuria (Fig. 11), usually occur within the first 24 h after the bite [12]. Subclinical hemolysis has been reported in envenomation occurring in regions where most spider bites are attributed to *L. gaucho* [43]. No correlation exists between the severity of the local injury and severity of hemolysis.

In the cutaneous and cutaneous-hemolytic forms of loxoscelism, nonspecific systemic manifestations have been described, including papular and macular exanthema (Fig. 12), palmar and plantar erythema, pruritus, headache, weakness, malaise, lightheadedness, nausea, vomiting, and fever [12, 43]. Palpable purpura and pustular lesions have also been reported [48–51]. Systemic manifestations are relatively common (Table 1) and are generally noted within the first 48 h after the bite. When present, such manifestations help establish the diagnosis of loxoscelism. Some victims exhibit skin sloughing 2–3 weeks after the bite (Fig. 13).

Complications

Local: Secondary infection is infrequent and is attributable to host flora (streptococci or



Fig. 12 Macular-papular exanthema in patient with loxoscelism probable, 6 day after the bite

staphylococci); when such infection does occur, it does so during the necrotic eschar stage [43].

Systemic: In the cutaneous-hemolytic form, acute kidney injury (AKI) [52] and disseminated intravascular coagulation (DIC) can occur as complications of intravascular hemolysis. Experimental studies have shown structural changes in the kidneys of animals injected with *Loxosceles* venom or toxin [53–55]. However, in a case series of human loxoscelism, AKI and DIC were found to be

Table 1 Frequency of systemic manifestations in cases of loxoscelism in Brazil, by sign and symptom

Signs and symptoms	Entres et al. ^a (<i>n</i> = 810)	Malague et al., 2011[43] (<i>n</i> = 114)
Systemic manifestations, %	65	81
Exanthema, %	38	64
Fever, %	16	46
Malaise, %	NA	37
Headache, %	30	36
Myalgia, %	29	NA
Nausea or vomiting, %	NA	25
Lightheadedness, %	21	NA
Jaundice, %	0.08	10

^aCenter for Poison Control, Curitiba, Brazil
NA not available

infrequent, occurring only when there was massive hemolysis [43].

In the presence of massive hemolysis and AKI lung congestion, there can be electrolyte changes, cardiac arrhythmia, metabolic acidosis, hypoxemia, shock, and bleeding due to DIC.

Histopathological Alterations

Biopsies of skin lesion from patients with loxoscelism show vasodilation, edema, and thickening of the endothelium, together with thrombosis, vascular leakage, and accumulation of PMNs [12, 28]. Some authors have reported that the features most characteristic of loxoscelism are degenerative lesions and coagulation necrosis in sweat glands [56]. In the autopsy of a patient who died 31 h after a bite, most organs showed



Fig. 13 Sloughing of hands and feet observed over the course of loxoscelism

congestive and hemorrhagic phenomena, which were most pronounced in the kidneys [28]. A biopsy of an exanthematous lesion revealed necrotizing vasculitis without epidermal necrosis [49].

Laboratory Tests

There is no routine test to obtain a definitive diagnosis of *Loxosceles* envenomation. Although an enzyme-linked immunosorbent assay to detect the venom in samples collected from patient lesions (hair, aspirate, swab, or biopsy specimens) and a test to determine the circulating levels of antibodies to the venom have been studied, such tests have not been validated for clinical use [57–60]. However, certain alterations can be found in the laboratory test results of envenomed individuals with the cutaneous or cutaneous-hemolytic forms of loxoscelism [43]:

Hemoglobin: low in massive hemolysis

Leukocytes: leukocytosis and absolute or relative neutrophilia found in both forms

Platelets: normal in most cases; thrombocytopenia in some cases of the cutaneous-hemolytic form

Reticulocytes: elevated in the cutaneous-hemolytic form, especially in the second week after envenomation

Bilirubin and lactate dehydrogenase: bilirubin (total and indirect) and lactate dehydrogenase both elevated in the cutaneous-hemolytic form

Urea, creatinine, sodium, and potassium: normal values in most cases; abnormal values in cases of hemolysis with AKI

Alanine aminotransferase, aspartate aminotransferase, and creatine kinase: occasionally elevated in both forms; higher in cases of the cutaneous-hemolytic form

C-reactive protein: elevated in both forms; higher in cases involving hemolysis – even subclinical hemolysis

Fibrinogen: elevated in both forms; however, low fibrinogen level is found if there is DIC

Prothrombin time and activated partial thromboplastin time: normal in most cases; altered in cases involving massive hemolysis and DIC

D-dimer: potentially elevated in both forms

Blood gases: metabolic acidosis may be seen in massive hemolysis and AKI

Haptoglobin: low in massive hemolysis

Direct antiglobulin test: positive in some cases of the cutaneous-hemolytic form [61]

Urine: hemoglobinuria; hematuria in the cutaneous-hemolytic form

Differential Diagnosis

Over the decades, many spiders have been implicated as necrotic agents but subsequent rigorous evidence-based research has shown that many of these spiders were wrongly accused. Depending on the stage of the lesion, other causes of skin lesions are included in the differential diagnosis of cutaneous loxoscelism: insect bite, allergic dermatitis, infections (cellulitis, cutaneous abscess, necrotizing fasciitis, cutaneous leishmaniasis, and fungal infection), pyoderma gangrenosum, lymphomatoid papulosis, chemical burn, frost-bite, focal vasculitis, ischemic vascular disorders, factitious ulcers, and traumatic lesions [37, 62]. In patients with hemolysis, the diagnosis of loxoscelism is strengthened by the presence of a skin lesion with a typical clinical course.

Treatment

In cases of *Loxosceles* envenomation, the goals of treatment are to manage the skin lesion and prevent or minimize the hemolysis, as well as to provide symptomatic therapy, supportive therapy for complications, and wound care (when necrosis has already occurred). There is no consensus regarding the best treatment for loxoscelism, and the standard treatment varies among the regions of the world where *Loxosceles* bites occur. Treatments

prescribed for loxoscelism include antivenom, corticosteroids, dapsone, antihistamines, antibiotics, hyperbaric oxygen, electric shock, surgical excision, and vacuum-assisted wound closure [15, 63]. However, due to the lack of clinical trials, there is little evidence to indicate that any of those methods is superior to the others. In addition, the *Loxosceles* antivenom is available only in certain countries in South America. Tetanus prophylaxis is recommended for all *Loxosceles* bite victims.

Skin Lesion and Hemolysis

Antivenom

Antivenom has been used to reduce the size of the cutaneous lesion as well as to treat the hemolysis that occurs in the cutaneous-hemolytic form. However, there have been no clinical studies providing evidence of the effectiveness of antivenom in loxoscelism or regarding the timing of its use. Nevertheless, a controlled experimental study using *L. intermedia* venom in rabbits showed that the necrotic injury was approximately 90% smaller when the antivenom was administered within the first 6 h after venom injection. Even when the antivenom was administered as late as 48 h after venom injection, the lesion was approximately 30% smaller than the control lesion [25]. *Loxosceles* antivenoms are available in Brazil, Argentina, Peru, and Mexico. All except one (a whole IgG antivenom from Peru) are horse-derived F(ab')₂ antivenoms. The indications for antivenom therapy depend on the time of progression, the characteristics of the cutaneous lesion, and the clinical presentation. Unfortunately, delayed diagnosis of loxoscelism frequently restricts the use of the antivenom for preventing the necrotic lesion. The Ministries of Health of Brazil, Peru, and Argentina recommend the use of intravenous antivenom in cases of cutaneous or cutaneous-hemolytic loxoscelism [45, 64, 65]. In Brazil, antivenom administration is recommended in cutaneous-hemolytic loxoscelism patients who present with hemolysis, even if treatment is not given until 48 h after the bite.

Corticosteroids

Among clinical and experimental studies, there is no consensus on the efficacy of corticosteroids in the treatment of cases of cutaneous lesion or hemolysis caused by loxoscelism, and there have been no clinical trials evaluating their use in such cases. However, corticosteroids have been prescribed for the cutaneous-hemolytic form in Chile and in the United States [36, 41, 66, 67]. Short courses of systemic corticosteroids (5–7 days) are widely used for the treatment of loxoscelism in Brazil – with or without the antivenom in cases of cutaneous loxoscelism and with the antivenom in cases of the cutaneous-hemolytic form. For the cutaneous form, prednisone (40–60 mg/day) has been used. In cutaneous-hemolytic loxoscelism, corticosteroids have been administered intravenously (at doses equivalent to 1 mg/kg/day of prednisone) for 5–10 days [45]. It has also been recommended that adults and children with cutaneous-hemolytic loxoscelism receive intravenous methylprednisolone (or the equivalent) at a loading dose (based on ideal body weight) of 1.0–2.0 mg/kg, followed by doses of 0.5–1.0 mg/kg every 6 h, for 5–10 days [62]. Intralesional injection of corticosteroids is not recommended, because it could exacerbate the edema and pressure at the injection site, thus promoting necrosis [12].

PMN Inhibitors

Among the drugs that act on PMNs, dapsone is the most widely used, especially in the United States. Although experimental studies in envenomed guinea pigs showed that dapsone reduces the extent of cutaneous lesions [68], similar studies using a rabbit model found that the use of dapsone provided no benefit compared with the control condition [69, 70]. In addition, there have been no clinical studies showing that dapsone is an efficacious therapy for the cutaneous form of human loxoscelism. Furthermore, at therapeutic or supratherapeutic doses, dapsone is associated with hemolytic anemia and methemoglobinemia, especially in

children [71]. The adult dose of dapsone is 25–100 mg orally, twice daily.

Metalloproteinase Inhibitors

In addition to their antimicrobial effects, drugs such as tetracyclines and chemically modified tetracyclines have anti-inflammatory and immunomodulatory properties, including the ability to inhibit metalloproteinases. Tetracycline derivatives inhibit both the activity and production of MMPs. One experimental study demonstrated that the topical tetracycline, initiated 6 h after injection of venom or toxin with SMase D activity and administered twice daily thereafter, prevented necrotic skin lesions. However, there have been no clinical studies evaluating this form of treatment [72].

Other Treatment Modalities

Hyperbaric oxygen has been proposed as a means of preventing necrosis in loxoscelism. The results of experimental studies are inconclusive as to the effects of this treatment modality on the skin lesion [69, 73–75]. Although the findings of one uncontrolled clinical study indicated lesion improvement after hyperbaric oxygen use, the treatment has also been reported to worsen the lesion [76]. There have been no studies evaluating the effect that hyperbaric oxygen has on the healing of existing lesions caused by loxoscelism.

Topical nitroglycerin ointment was studied in rabbits experimentally injected with *L. reclusa* venom. The results show that this treatment modality is potentially harmful, increasing edema, inflammation, and creatine kinase concentrations [77].

It has been suggested that nonpharmacological therapies, such as electric shock and negative pressure, can prevent the necrotic lesion when used as the initial treatment for loxoscelism. The use of electric shock, based on previous experiences with snakebites, has been assessed in guinea pigs [68]. However, no beneficial effect of electric shock was observed in animals receiving the treatment 16 h after venom injection. An experimental study showed that negative pressure therapy, initiated early, improved the healing of cutaneous

lesions induced by the injection of *Loxosceles* venom in pigs [78]. However, additional experimental studies are needed in order to justify clinical studies of these types of nonpharmacological therapies.

Symptomatic Therapy

Analgesics

After a *Loxosceles* bite, analgesics are required, especially in the first week, when the pain is more intense. In general, either paracetamol or dipyrone is sufficient for pain control. However, opioids are required in some cases.

Antihistamines

There is no evidence that antihistamines influence the clinical course of the cutaneous injury in loxoscelism [70]. However, their administration is indicated in patients who develop pruritic exanthema.

Care of the Cutaneous Lesion (Eschar/Ulcer)

Antibiotics

In the United States, antibiotics have been administered as part of the initial treatment of the skin lesion resulting from a *Loxosceles* bite [36, 41, 44, 79]. However, infection is uncommon and, when present, occurs in the eschar stage, usually more than 2 weeks after the bite. Therefore, antimicrobial prophylaxis is not indicated and treatment should only be conducted with evidence of secondary infection. The selected antimicrobial spectrum should cover the skin flora.

Surgical Management

Early surgical intervention is not indicated for a skin lesion resulting from a *Loxosceles* bite, because surgery can amplify the inflammation and exacerbate the effects of the venom, thus protracting tissue injury and increasing lesion size, as well as worsening functional and cosmetic

outcomes [37]. The necrotic tissue should be approached only after its limits are well defined, which typically occurs more than 2 weeks after the bite. Following the debridement of the necrotic eschar, an ulcer containing fibrin and devitalized fatty tissue is often observed, in which case chemical debridement is indicated. Most victims of a *Loxosceles* bite present with small, superficial necrotic lesions that will heal completely with basic care. If major tissue loss ensues, the need for skin grafting will have to be evaluated.

Supportive Therapy for Hemolysis

Hydration

Victims of a *Loxosceles* bite should receive adequate hydration with crystalloid solution, in order to maintain a urine output of 1–2 mL/kg/h for children and 30–40 mL/h for adults. Adequate renal perfusion and increased urine flow are important measures to prevent AKI-induced pigment. Care should be taken to avoid volume overload, especially in children, in individuals with heart disease, and in individuals with anuria.

Renal Replacement Therapy

In loxoscelism patients with AKI, the need for renal replacement therapy should be assessed. Renal replacement therapy is usually indicated in patients with fluid overload that does not respond to diuretics, as well as in those with anuria, electrolyte disturbances, acid–base disorders, or uremia.

Packed Red Blood Cell Transfusion

Loxoscelism patients with severe anemia should receive packed red blood cell transfusion. In such patients, DIC is uncommon and there is rarely a need for transfusion of fresh frozen plasma or platelets.

Plasma Exchange

In patients with cutaneous-hemolytic loxoscelism plasma exchange is reported for management in case of refractory hemolysis [80–82].

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Widow spiders (Family Theridiidae; genus *Latrodectus*) are found throughout the world. Bites from these spiders may cause a neuroexcitatory envenoming with intense muscle spasm and autonomic dysfunction. This clinical syndrome, called *latrodectism*, is seldom fatal but may present a diagnostic dilemma and cause significant morbidity.

It is difficult to estimate the annual number of patients who experience clinically significant envenomation. Currently in the United States, approximately 2500 cases are reported to poison centers each year. Of these, approximately 900 require treatment in a health care facility [1–3]. Mortality is rare, but a number of deaths have been reported, particularly in the past and especially in the pre-antivenom era. In North America, data from 1950–1959 indicated 63 deaths ascribed to widow spider bite (at that time all would have been considered *L. mactans*) with highest numbers in some southern and eastern states, but little data on cause of death [4]. In this study, 31% of deaths were in children under 10 years of age and only 32% of deaths occurred in the first 24 h, which may indicate causes of fatality other than direct venom effects in at least some cases [4, 5]. In Australia, there are at least 13 reported fatalities associated with *Latrodectus* bites, all in the pre-antivenom era prior to 1956 [6]. In greater Europe at least some fatal bites have been reported historically and also numerous documented episodes of epidemic latrodectism dating back over a thousand years, notably in

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countries bordering the Mediterranean Sea and in Russia [5, 7]. In recent times there are two reported deaths associated with *L. geometricus* in Madagascar and one from a bite by *L. tredecimguttatus* in Greece [8, 9]. No verified cases of death due to latrodectus envenomation have been recorded in the USA in recent decades, and no deaths have been reported in Australia for 60 years. These figures exclude the exceptionally rare fatality associated with the use of antivenom to treat latrodectism. Australia may have the highest rate of latrodectism in the world. An estimated 5000–10,000 latrodectus bites to humans occur annually in Australia, but only 20% require antivenom therapy and no antivenom-related fatalities have been reported [10].

Widow spiders are present on all continents except Antarctica. Clinically significant spiders include *Latrodectus mactans*, *Latrodectus hesperus*, *Latrodectus bishopi*, *Latrodectus geometricus*, and *Latrodectus variolus* in North America; *Latrodectus hasseltii* (redback spider) in Australia; *Latrodectus katipo* in New Zealand; and *Latrodectus indistinctus* in South Africa. *Latrodectus geometricus* (brown widow) and *Latrodectus tredecimguttatus* are found on most continents. The Australian species, Australian species, *L. hasseltii*, has successfully colonized other regions including New Zealand, Japan, and parts of the Arabian Peninsula. These spiders appear to be environmentally adaptable and well able to spread through human activities. The taxonomy of the genus was the subject of debate throughout the twentieth century. Between five and forty species have been described with many allopatric (speciation that occurs when a population becomes segregated into two populations by a geographic barrier) populations being described by trinomials (e.g., *L. mactans hasseltii*) [5, 11].

Widow spiders are small with a protuberant abdominal section. Many species have specific but variable ventral or dorsal abdominal markings. The red hourglass marking is only present in the female of some species such as *L. mactans* and *L. hasseltii*. Male widow spiders are smaller

than females, reach maturity earlier than females, live only 1 or 2 months, and die soon after mating. Males have a small biting apparatus and generally are considered to be unable to envenom humans, though rare instances of mild envenomation have been claimed [12]. Female widow spiders are much larger, live several months, and are able to envenom humans. There is no scientific evidence to confirm the popular conception that the female spider routinely eats her mate. The term *widow* probably arose from the observations that males seldom are seen in the web. Widow spiders produce an irregular, untidy web to catch their prey, usually in a position where they can establish sticky drop lines to a flat surface with the spider residing high in the web. They are not aggressive and bite humans only when trapped against the skin. They often live in environments where they readily come into contact with humans. *Latrodectus* spp. bites to humans tend to occur in warmer months or just when the weather turns cool and the spiders migrate indoors [13].

Hundreds of therapies have been offered for patients envenomed by widow spiders, including warm baths, alcoholic beverages, opioids, various sedative-hypnotic agents, neostigmine, physostigmine, atropine, tubocurarine, methocarbamol, dantrolene, procaine, corticosteroids, magnesium, calcium, and antivenom, to name just a few [5, 7, 14, 15]. Therapies that are truly efficacious are described in the treatment section.

Biochemistry

Latrodectus venom contains a family of high-molecular-weight proteins that lead to transmitter release from nerve endings [16]. One study that compared the venoms of four black widow species (*L. mactans*, *L. variolus*, *L. bishopi*, and *L. geometricus*) showed that the electrophoretic patterns of all the venoms were similar, and one antivenom prevented the lethal effects of all venoms in a mouse model [17]. More recently,

the venom of *L. tredecimguttatus* has been studied in depth [16]. All *Latrodectus* species seem to produce α -latrotoxin, with a molecular weight of approximately 150,000 kDa [17–19].

Pathophysiology

It is thought that α -latrotoxin leads to the clinical envenomation syndrome in humans, whereas the latroinsectotoxins lead to venom toxicity in invertebrates. In vertebrates, the existence of calcium-dependent and calcium-independent binding proteins on the presynaptic membrane has been demonstrated [16]. Binding of α -latrotoxin to one or more of these proteins, notably latrophilin 1 or neurexin 1 α , facilitates the insertion of the α -latrotoxin tetramer into the membrane, with the formation of a central Ca^{++} permeable transmembrane pore, leading to presynaptic transmembrane influx of calcium or other ions [20]. This leads to vacuole release of neurotransmitters such as acetylcholine, dopamine, norepinephrine, glutamate, and gamma-aminobutyric acid, depending on the type of synaptic cleft involved. Uncontrolled release of neurotransmitters such as acetylcholine in the brainstem, spinal cord, and neuromuscular junction and possibly release of catecholamines in the brain, spinal cord, or autonomic ganglia, result in norepinephrine discharge and lead to the clinical manifestations of envenomation. The degree to which the various neurotransmitters are released in humans is uncertain and must be inferred from in vitro studies [18]. In addition it appears some actions of α -latrotoxin on vesicle exocytosis involve receptor binding and subsequent stimulation of intracellular signaling with Ca^{++} release [20].

Clinical Presentation

The clinical syndrome of latrodectism varies slightly depending on the species involved and the amount of venom injected [5, 7]. *L. mactans* is notorious for causing abdominal rigidity and



Fig. 1 Target lesion after the bite of a *Latrodectus* spider

back pain, whereas *L. hasseltii* seems to cause more diaphoresis. *L. geometricus* tends to cause local symptoms [21]. Mortality is currently rare and was never common, even in the pre-antivenom era, though myocarditis resulting in death has been reported with *L. tredecimguttatus* envenomation in Greece [9]. Two deaths have been reported in Madagascar where two species are known, *L. geometricus* and *L. menavodi*; in one case there was cardiovascular failure and in the other foot gangrene, though the latter is not readily explainable as a consequence of latrodectism, and the identity of the spider may be uncertain [8]. A number of other causes of death have been reported including pulmonary edema, a more likely sequelae of severe neuroexcitatory envenoming [5, 7].

The bite itself is often only minimally painful and may go unnoticed as some patients may not have progressive symptoms. Local pain becomes apparent within 10–60 min in most cases, though can be delayed in onset by many hours, and discomfort may spread to regional lymph nodes and beyond. A triad of local pain, diaphoresis, and piloerection may occur in addition to the presence of mild erythema around a central pale area, giving rise to the term *target lesion* (Fig. 1), though this is not a universal feature [5, 7]. In at least some series three quarters of patients develop only self-limiting local effects and do not subsequently develop systemic effects [13].

Systemic envenomation may take many hours to reach its full extent. Muscle pain occurs around the bitten area and then becomes generalized.

Patients may describe neck, chest, abdominal, lower back, and thigh pain. This pain often is associated with generalized diaphoresis and dysphoria. Associated features include low-grade fever, tachycardia, hypertension, tremor, paresthesias, headache, and occasionally vomiting. The use of a visual analog scale as well as a clinical grading system has been proposed to classify severity of envenomation [15, 22], based on the presence or absence of local and generalized signs and symptoms, but it has not been validated as a method to predict outcome or complications.

The term *facies latroductismica* describes the contorted grimace, general flushing, diaphoresis, trismus, and blepharoconjunctivitis sometimes seen in patients with full-blown latroductism [5, 7, 14]. Compartment syndrome, rhabdomyolysis, myocarditis, troponin elevation, and priapism have also been reported [8, 9, 23–26]. Altered mental status has been described, particularly in elderly patients. It is unclear whether this altered mental status is true delirium or a state of severe dysphoria. Generalized muscle weakness has been described up to 96 h after envenomation [27]. Chronic pain syndromes lasting weeks to months have been described [28]. In these cases, late antivenom therapy has been associated with resolution of symptoms. Whether this is a placebo effect or an actual action of the antivenom is unknown. Rare reported complications associated with latroductism include herpes zoster [29], priapism [24, 25, 30], and toxic epidermal necrolysis [31]. The degree to which these complications truly are related to latroductism is unknown because these are uncontrolled observations. However, priapism is a well-described feature of envenoming by the banana spider in Brazil, *Phoneutria nigriventer*, which has a broadly similar form of neuroexcitatory envenoming and clinical effects, and so is likely to be a true effect of latroductism envenomation [5].

Diagnosis

The diagnosis of latroductism is clinical and there are no specific confirmatory laboratory tests. The decision to order laboratory tests should be

dictated by the clinical situation for evaluation of sequelae resulting from envenomation. Case reports have described latroductism being mistaken for an acute abdomen with subsequent negative laparotomy, acute myocardial infarction, meningitis, psychosis, renal and biliary colic, peritonitis, malaria, porphyria, lead intoxication, and sickle cell crisis [5, 14].

Treatment

Treatment should initially focus on airway management and respiratory and circulation support as needed. Tetanus prophylaxis and wound care should also be addressed.

Treatment modalities advocated for latroductism have included opiates, benzodiazepines, muscle relaxants, calcium, and antivenom [5, 14]. Few studies have examined the efficacy of these treatments. The consensus among clinical toxicologists is that first-line treatment of patients with moderate latroductism in North America should be directed toward pain management with a combination of an opioid and a benzodiazepine, although this has not been studied prospectively (Grade II-2 recommendation). Severe systemic manifestations (e.g., severe muscle pain, diaphoresis, dysphoria, hypertension, prenatal labor) refractory to a combination of opioids and benzodiazepines in generous doses should prompt strong consideration of antivenom therapy (Grade II-2 recommendation). In Australia, a far lower threshold for its use has been accepted [5, 12]. It commonly has been given for regional or systemic envenoming, without first using an opioid and a benzodiazepine. One group of toxicologists have recently advocated a different view in Australia, with their research indicating the antivenom is ineffective and they no longer recommend its use [32]. However, this view is contested by others who point to significant problems with the study on which these recommendations were based [33–35]. Further, this study, while being interpreted as showing antivenom was ineffective, also demonstrated that analgesia failed to provide adequate symptom control in 75% of cases [32]. Thus in Australia, at the time of this writing,

there are two distinct and mutually exclusive views of best practice treatment of latrodectism.

Indications for ICU Admission in Envenomation by Widow and Related *Latrodectus* Spiders

- Requirement for continuous high-dose infusion of opioids and benzodiazepines in patients in whom antivenom is contraindicated
- Rare complications, such as electrocardiogram changes, acute myocardial infarction, or pulmonary edema
- Clinical monitoring during antivenom infusion (short-term admission) if safe monitoring cannot be achieved outside this setting
- Anaphylactic or severe anaphylactoid reactions complicating antivenom infusion

Though calcium was considered an important treatment modality for much of the twentieth century, one retrospective review of 163 patients concluded that calcium gluconate was ineffective for relief of pain when compared to IV benzodiazepines and opioids. Of the 24 patients with severe envenomation who initially received calcium gluconate, 23 reported no relief of symptoms [15]. Calcium should, therefore, no longer be considered to have antidotal properties for the treatment of latrodectism.

Dantrolene and methocarbamol have not been proven to be effective treatment modalities [36, 37]. Treatment of envenomation by *L. mactans* with intravenous calcium gluconate and methocarbamol was compared in a small ($n = 13$) prospective crossover study [36]. All four patients treated initially with methocarbamol required further treatment. In the series by Clark and colleagues [15] of 163 patients, 75 patients with severe envenomation received parenteral opioids. In this group, 55% of patients treated with opioids alone obtained symptomatic relief, whereas 70% of patients treated with combined opioids and benzodiazepines obtained symptomatic relief after initial treatment. It was concluded that benzodiazepines conferred an opioid-sparing effect when given with morphine. Antivenom was administered to 58 patients in Clark's series, one

of whom died, apparently to a hypersensitivity to antivenom. This patient had a history of atopy and asthma and the antivenom was administered as a bolus. Antivenom led to complete resolution of symptoms within 2 h (mean time 31 ± 26.7 min), and relapses did not occur, although seven patients (12%) required two doses. Patients who received antivenom had a shorter duration of symptoms (9 ± 22.7 h compared with 22 ± 24.9 h, $P < 0.05$) and were less likely to be admitted to the hospital (12% compared with 52%). Hypertension rarely required specific treatment, usually responding to supportive care or antivenom. Minor urticarial reactions occurred in four (7%) patients who received antivenom. Only nine of the 58 patients treated with antivenom were followed up by telephone at a later date; however, none of these patients reported symptoms suggesting delayed hypersensitivity reactions.

Antivenom Therapy

North America

The North American black widow antivenom is an equine IgG-rich preparation. The equine serum is pooled and partially purified to produce the lyophilized antivenom. Traditionally, the initial dose for adults and children is one vial (2.5 mL) diluted in 50 mL of saline. The generally accepted indication for antivenom is severe systemic effects (e.g., muscle pain, diaphoresis, dysphoria, hypertension) refractory to a combination of opioids and benzodiazepines and high-risk situations such as pregnancy (Grade II-2 recommendation). Based on our current state of knowledge, children, elderly patients, and pregnant patients are treated according to the same indications. Antivenom should be considered contraindicated in patients with known hypersensitivity to equine serum. Caution is indicated in patients with a history of severe asthma and atopy (Grade III recommendation). The two deaths that have been reported to date after intravenous administration of the antivenom occurred in patients with a history of asthma [15, 38]. The exact incidence of immediate hypersensitivity reactions is unknown.

Delayed type III hypersensitivity (serum sickness) may occur. The exact incidence is unknown.

If antivenom is considered, we recommend that:

1. The risks and benefits of this treatment be discussed with the patient.
2. The patient be placed in a clinical setting where acute allergic reactions can be managed.
3. Reliable intravenous access be achieved, and electrocardiographic and pulse oximetry monitoring be started.
4. The immediate bedside availability of invasive airway equipment, epinephrine and antihistamines be ensured.

There is no good evidence that skin testing reliably predicts reactions to antivenom; therefore, we do not support skin testing on medical grounds as positive and negative predictive values are poor [39].

The product information from Merck (West Point, PA), the manufacturer of the antivenom, recommends that it be given intramuscularly, unless it is administered to a critically ill adult or a child younger than 6 years old, in which case the intravenous route is recommended. However, the usual practice by medical toxicologists for many years has been to deliver the antivenom routinely to all patients by the intravenous route. This practice may relate to the hypothesis that the intravenous route is safer because the dose may be truncated if hypersensitivity signs or symptoms occur [40]. Premedication with subcutaneous epinephrine, antihistamines, or corticosteroids is controversial. It has not been part of routine practice for this antivenom in the United States. There is evidence that premedication with low-dose subcutaneous epinephrine reduces the incidence of acute allergic responses associated with the intravenous infusion of certain snake antivenoms with a high incidence of major adverse reactions [41], but premedication has not been studied in *Latrodectus* antivenom administration.

If the intravenous route is chosen, the most recent package insert recommends an initial dose

of 2.5 mL (one vial) diluted in 10–50 mL of saline administered over 15 min [42]. Despite the recommendations in the package insert, many toxicologists have advocated administration in greater volumes of fluid over a longer period of time as it is impossible to predict which patients will develop allergic reactions [43]. We recommend that the antivenom be diluted in 50–250 mL of normal saline and the infusion started slowly (e.g., 10 drops per minute). Provided that no allergic symptoms occur, we recommend that the infusion rate can be doubled every few minutes so that the total volume is administered over 60 min. The patient should be observed closely throughout the infusion and for 30 min thereafter. Acute allergic reactions are unlikely to occur more than 30 min after cessation of the infusion, and patients may be discharged as soon as they are clinically well. Routine admission to the intensive care unit of patients with uncomplicated antivenom-treated latrodectism, even if severe, may not be required.

Patients who receive the antivenom by the intramuscular route should be observed to exclude acute allergic reactions and to ensure clinical improvement. Although not formally studied, in our experience, 2 h of observation for allergic reaction is sufficient.

Analatro[®] is a purified F(ab)₂ *Latrodectus mactans* antivenom currently in clinical trials in the United States. It is expected to have fewer adverse reactions than the whole IgG product. It has been available in Mexico since 1998 and marketed under the name Aracmyn[®]. No serious adverse events were reported in a randomized double-blind, placebo-controlled trial of the highly purified equine F(ab)₂ antivenom though the data for safety is limited by the sample size of 24 subjects [44]. A subsequent larger Phase III randomized, double-blind, placebo-controlled trial of this antivenom has initially been reported as showing clear benefit of antivenom versus placebo, with no serious adverse events reported, and the rate of adverse events was similar in both study arms (antivenom and placebo) [35]. The researchers concluded that this antivenom was “effective in reducing moderate to severe pain caused by latrodectism” [35].

Australia

In Australia, redback spider (*L. hasseltii*) bite leads to signs and symptoms similar to those encountered in other parts of the world, including pronounced diaphoresis, tachycardia, hypertension, muscle cramps, tremor, but vomiting is uncommon. The Australian antivenom also is a purified equine-derived IgG-F(ab)₂ product that historically was usually given intramuscularly, though in the last 10–15 years it has commonly been given intravenously [12]. No deaths due to anaphylaxis have been associated with the use of *L. hasseltii* antivenom. In a series of 2144 patients treated over 13 years, the incidence of allergic responses was 0.5%, and there were no deaths [45]. Reactions are usually mild consisting of mainly urticarial and cutaneous manifestations. Incidence of serum sickness is less than 5%. All severe acute allergic responses in this series occurred in patients who received antivenom by the intravenous route, contrary to product recommendations. However, the efficacy of intramuscular administration has recently been questioned [32, 46, 47]. One prospective cohort study found that only 17% of patients treated with intramuscular antivenom had no pain at 24 h [48]. Another randomized controlled trial of intramuscular versus intravenous antivenom found no significant difference between the two routes of administration [46]. Further studies are needed to determine the appropriate use of antivenom and most efficacious route of administration. With the caveat noted earlier of controversy about best practice management of latrodectism in Australia, current Australian practice is to use antivenom for patients with severe local symptoms unresponsive to oral analgesics and in patients with signs or symptoms of systemic envenomation [12]. Benzodiazepines are used only in the rare situations when they are necessary while waiting for the antivenom to work. Most patients (66–97%) treated with antivenom require two vials given by intravenous infusion or intramuscular injection [13, 45, 49]. The remaining patients require additional doses [28].

Skin testing is not recommended in Australia [11, 12], and premedication is controversial [5, 12, 49]. Given the low risk of acute allergic reactions, it would seem reasonable to withhold

premedication, unless the patient has been sensitized to horse serum or has a history of atopy (Grade III recommendation). We recommend that patients should have reliable intravenous access and be placed in an environment where acute allergic reactions can be treated. If repeat doses are required, some authorities recommend the intravenous route using a technique similar to that described earlier for the North American product [12]. We recommend that patients who receive the antivenom by the intramuscular route be observed for 2 h to exclude acute allergic reactions and to ensure clinical improvement before discharge.

L. hasseltii antivenom has been administered by some unorthodox routes. Case reports have described local subcutaneous injection of antivenom to control severe prolonged local symptoms [50] and use of antivenom by a regional intravenous technique similar to the Bier block [51]. These kinds of approaches have not been validated and cannot be recommended.

The exact incidence of delayed-type hypersensitivity (serum sickness) associated with *L. hasseltii* antivenom is unknown, but it is thought to be low. Prophylactic steroid therapy is prescribed by some clinicians in an attempt to prevent serum sickness if multiple doses of antivenom are used [5]. This practice has not been validated experimentally.

New Zealand

The New Zealand katipo spider is similar to the Australian redback spider and should be treated as such [52].

South Africa

Three members of the genus *Latrodectus* are present in South Africa. *L. indistinctus* (black widow) and *L. geometricus* (brown widow) are thought to be chiefly responsible for human envenomation. All of these spiders have venom that contains α -latrotoxin. The relative toxicity of *L. indistinctus* and *L. geometricus* venoms has been studied using a mouse lethality model [53]. The venom of *L. indistinctus* (black widow) seems to be three to four times more potent than that of *L. geometricus* (brown widow). In a retrospective

series of 45 cases [21], *L. indistinctus* (black widow) caused more severe envenomation with systemic signs and symptoms. The presentations of brown widow bites were mild, and local symptoms predominated.

In South Africa, antivenom is administered in severe cases to prevent a protracted course [21]. The equine-derived F (ab)₂ antivenom is given as an intramuscular injection of 5 mL.

Reactions to Antivenom

As stated earlier, allergic reactions to antivenom are uncommon. During intravenous infusion of antivenom, mild isolated urticaria may be treated by slowing the rate of infusion and administering an intravenous antihistamine, such as diphenhydramine. In the setting of latrodoctism, clearly airway swelling, bronchospasm, or hypotension should prompt immediate abandonment of antivenom therapy and aggressive therapy.

The immediate priority of management is the assessment and management of threats to the airway, breathing, and circulation. Intubation and ventilation may be required. First-line therapy consists of oxygen, epinephrine, and intravenous fluids [54]. High-flow oxygen should be given to ensure adequate oxygen saturation. Epinephrine should be administered in all cases with hypotension, airway swelling, or bronchospasm [55] (Grade II-3 recommendation). Large volumes of crystalloid or colloid may be required to maintain circulatory volume and adequate blood pressure.

When the immediate threats to the airway, breathing, and circulation have been managed with airway control and first-line drugs, the use of second-line drugs, such as corticosteroids, antihistamine (H₁ and H₂) blockers, glucagon, and aminophylline, may be considered. Antihistamines should be used in combination with H₂ blockers, such as cimetidine or ranitidine [55, 56] (Grade I recommendation). Corticosteroids are indicated to prevent prolonged sign or symptom duration, especially bronchospasm [57] (Grade II-3 recommendation). Based on theoretical considerations and two case reports, glucagon has been advocated for patients taking

Table 1 First-line therapy for anaphylaxis

Treatment	Dosage
Oxygen	Apply high FiO ₂ oxygen via endotracheal tube or facemask to maintain oxygen saturation >92%
Epinephrine	<i>Early or mild anaphylaxis</i> – 0.3–0.5 mg (0.3–0.5 mL) 1:1000 epinephrine by intramuscular injection repeated every 5–10 min as required <i>Hypotension, dyspnea, airway compromise, or patient deteriorating</i> – 1:100,000 epinephrine 1–2 mL/min IV, repeated as necessary. 1:100,000 epinephrine may be prepared by drawing 1 mg of epinephrine (1 mL of 1:1000) in a 20-mL syringe and adding 9 mL of normal saline to make a volume of 10 mL. All but 2 mL is discarded (leaving 200 µg) before a further 18 mL of saline is added to make 20 mL (10 µg/mL)
Fluid	Give 10–20 mL/kg of crystalloid or colloid for hypotension

FiO₂ fraction of inspired oxygen Adapted from Brown [54], p. 640

β-adrenergic blocking drugs who have an increased risk of anaphylaxis and are resistant to treatment [54, 57] (Grade III recommendation). Aminophylline may be appropriate for patients with bronchospasm resistant to epinephrine and steroids [54] (Grade II-3 recommendation). Tables 1 and 2 provide suggested treatment doses.

Criteria for ICU Discharge in Envenomation by Widow and Related *Latrodectus* Spiders

1. For patients who have not received antivenom, high-dose opioid and benzodiazepine infusions should be ceased. Patients who feel clinically well and have normal vital signs 4 h after starting oral analgesia may be discharged.
2. After intravenous infusion of antivenom, patients may be discharged at the end of the infusion if there is a satisfactory clinical response (patient feels well) and there is no evidence of anaphylactic or anaphylactoid reaction.

(continued)

3. After intramuscular injection of antivenom, patients may be discharged 2 h after injection if there is a satisfactory clinical response (patient feels well) and there is no evidence of anaphylactic or anaphylactoid reaction.

Key Points in the Treatment of Envenomation by Widow and Related *Latrodectus* Spiders

1. Latrodectism is painful and associated with significant dysphoria. Initial doses of opioid and benzodiazepine should be generous and repeated as frequently as necessary.
2. Failure of opioids and benzodiazepines to control symptoms should prompt consideration of antivenom use. Antivenom may be given sooner if it is clear that high doses of opioids and benzodiazepines do not afford clinical relief.
3. Despite the small but finite risks associated with antivenom, prudent use in carefully selected patients is sound clinical practice. Known equine allergy or previous exposure to horse serum should be addressed. Use caution in patients with asthma and history of atopy.
4. Acute allergic responses occur at the time of antivenom administration. Prolonged inpatient monitoring for late reactions is not indicated.
5. Failure of antivenom to alleviate symptoms should prompt administration of an additional dose or may bring the diagnosis into question.

Table 2 Second-line therapy for anaphylaxis

Treatment	Dosage
Antihistamines	Diphenhydramine, 25–50 mg IV, or promethazine, 12.5–25 mg IV, <i>plus</i> cimetidine, 300 mg IV, or ranitidine, 50 mg IV, repeated every 6 h as required. Oral therapy may be started when able
Corticosteroids	Hydrocortisone, 5 mg/kg (≤ 200 mg) IV, followed by 2.5 mg/kg IV every 6 h, or methylprednisolone, 125 mg IV every 6 h. Oral prednisone, 40–50 mg daily, may be started when able
Glucagon	<i>For patients on β-adrenergic blockers</i> – 1 mg IV every 5 min until stable, then 5–15 μ g/min as an infusion
Aminophylline	<i>For refractory bronchospasm</i> – 5 mg/kg IV infused over 30 min followed by an infusion of 0.5 mg/kg/h

Adapted from Brown [54], p. 640

patients that have been treated with antivenom [24, 25]. Detailed physical examination may reveal evidence of a widow bite (e.g., localized diaphoresis, target lesion) (see Fig. 1), or a spider may be found in bedding, in clothing, or beneath the bed. Infants and children have been said to be at increased risk of severe morbidity from latrodectism, but there is little literature, confined to case reports, that specifically addresses the pediatric population.

Pregnant Patients

The effect of latrodectism on pregnancy is not clear. Pregnancy has been cited as an indication for antivenom therapy in case vigorous abdominal muscular contractions lead to fetal distress [58]. It is not known whether the α -latrotoxin crosses the placenta. Reported cases of latrodectism in various stages of gestation have not led to spontaneous abortion [58, 59], although there are reports of spontaneous abortion after latrodectism in nineteenth-century southern Russia [58]. Antivenom is not contraindicated in pregnancy. One observational study showed no pregnancy losses in the 97 cases studied [60].

Special Populations

Pediatric Patients

Infants may present with inconsolable crying, restlessness, generalized rash, and poor feeding [5, 12]. There are a few case reports of priapism associated with *Latrodectus* bites in pediatric

Elderly Patients

Elderly patients have been said to be at increased risk of severe morbidity from latrodectism. Patients with comorbidities, such as ischemic heart disease, might be more susceptible to the physiologic stress resulting from the high catecholamine state associated with latrodectism. Profound dysphoria may be mistaken for altered mental state. Latrodectism itself may cause chest pain, but widow bites also have been associated with elevated markers of cardiac injury [26]. The incidence and significance of these changes are not known.

Key Points in Envenomation by Widow and Related *Latrodectus* Spiders

1. *Latrodectism* refers to envenomation by the widow spiders (genus *Latrodectus*).
2. Latrodectism is similar throughout the world. There is structural homology of the venoms of the various *Latrodectus* species.
3. The diagnosis is made on clinical grounds. It is based on a history of possible spider contact; local pain that migrates to other areas; autonomic changes, such as diaphoresis and hypertension; and pain or discomfort that appears disproportionate to physical signs.
4. Mortality is negligible with good supportive care.
5. Opioids and benzodiazepines improve patient comfort. There is little evidence to support the routine use of calcium gluconate or muscle relaxant agents, such as dantrolene sodium and methocarbamol.
6. Patients with symptoms refractory to a combination of opioid and benzodiazepine should be considered for antivenom therapy, especially in parts of the world where safe antivenom products are available.
7. Most patients may be discharged from the hospital after treatment with antivenom; admission to the intensive care unit is rare, unless there are unusual complications of envenomation or treatment.

8. Antivenom raised against one *Latrodectus* species is likely to be effective treatment for envenomation by other *Latrodectus* species.
9. Known equine allergy or previous exposure to horse serum should be addressed. Use caution in patients with asthma and history of atopy.

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Part XXV

Natural Toxins: Miscellaneous

B. Zane Horowitz

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Botulinum toxin is the ultimate example of the core principle in toxicology that all substances are poisons, and it is only the dose that determines if a substance is therapeutic or toxic. Two forms of pharmaceutical products, onabotulinum toxin A (Botox) and rimabotulinum toxin B (Myobloc), are used as injectable therapeutic agents to induce local muscle paralysis to treat a growing variety of disorders from dystonia to bladder spasm, as well as cosmetic enhancer to flatten facial wrinkles. More botulinum-based products for these, and other, purposes are under development. As a toxin, botulinum, when ingested, is one of the most lethal on a weight per kilogram basis with a LD₅₀ of 0.001 ug/kg [1].

There are four *Clostridium* bacteria that elaborate a botulinum neurotoxin (Table 1). There are eight serotypes of *Clostridium botulinum*, designated A through H, and each produces a distinct neurotoxin designated BoNT/A through BoNT/H [2]. Subtypes of neurotoxins, which are differentiated by amino acid sequences, are designated by a number after the serotype letter for serotypes A, B, E, and F. Nearly all human cases of botulism are caused by *Clostridium botulinum* serotypes A, B, and E [3, 4]. Serotypes C and D produce disease in birds and livestock only. Occasional human cases of botulism type E, subtype E4 and E5, are caused by botulinum toxin from the anaerobic bacteria *Clostridium butyricum* [2, 5, 6], and very rare cases of subtype F7 toxin may be elaborated by *Clostridium baratii* [2, 7, 8]. Five cases of human disease from *Clostridium argentinense*, which

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Table 1 *Clostridium* bacterium and botulinum serotypes

Organism	Botulism serotype ^a	Serotypes
<i>Clostridium botulinum</i>	A,B,C,D,E,F,H	
<i>Clostridium butyricum</i>	E	E4, E5
<i>Clostridium baratii</i>	F	F7
<i>Clostridium argentinense</i>	G	

^a*Proteolytic serotypes*: (GROUP I)
All A serotypes (A1 to A10)
All B serotypes, except B6
All F serotypes, except F6 and F7
Type H
^a*Non-proteolytic serotypes*: (Group II)
B4 serotype
All E serotypes, except E4 and E5 (which are *C. butyricum*)
F6 serotype

produce type G neurotoxin, have been detected at autopsy from a series of unexplained deaths in Switzerland [9]. Additional “bivalent” strains produce dual toxins with the prevalent toxin type designated by a capital letter and the lesser type by a small case letter: Ab, Ba, Af, Bf, and an equal dominant type AB [10]. Type H neurotoxin has recently been identified in conjunction with a type B case (Bh) in an infant [10, 11].

History

A mysterious paralytic disorder was first linked to poorly prepared sausages in the late 1700s in Germany. The first documented cases occurred in 1793 in the village of Wildbad, in Wurttemberg. A serious outbreak of food poisoning related to “Blunzen,” a dish of blood sausage cooked in a pork stomach was responsible for 13 cases of food poisoning, of which six persons died [6, 12]. A decade later in 1802, the first warning about eating sausages was issued by the Royal Government in Stuttgart, when health officials offered a list of symptoms that included vomiting, double vision, and dilated pupils as a guide to local health practitioners [6, 13]. Professor Johann von Autenrieth, at the University of Tubingen, suspected that sausages were not boiled long enough during preparation which

led to their contamination with an as yet unidentified agent. In 1817 he summarized seven cases sent to him by two practitioners [6]. Six of those cases were submitted by Dr. J. Georg Steinbuch on a cluster from liver sausage in the town of Herrenberg. The only other case was submitted by a Dr. Justinus Kerner, the medical officer in Welzheim [12]. Steinbuch died a year later, but Justinus Kerner continued to collect and publish these “sausage poisoning” cases that for many years in Germany would be called “Kerner’s disease.” Within 3 years, in 1820 Kerner had published a monograph with descriptions of 76 cases he had observed, with details of their symptoms [13, 14]. Two years later, Kerner had summarized details of the 155 cases of botulism he had attended [13]. Kerner tried to discover the basic science behind the mysterious disease. He prepared extracts of the food and treated them with silver nitrate, mercuric chloride, and ferric chloride. He then fed these preparations to a wide range of experimental species including birds, mice, rabbits, and cats [11, 13]. In each of these mammalian species, he observed what would be the cardinal symptoms of botulism: vomiting, dilated pupils, ptosis of the eyelids, difficulty swallowing, and respiratory failure. Finally, as was common among the medical pioneers of that era, he experimented with a small dose on himself and noted a similar weakness. He placed a drop of the extract on his tongue and observed it caused “a great drying out of the palate and the pharynx” [13, 15]. He tried a larger dose and noted his “eyelids became tired, his vision blurry,” and then he developed pain in his abdomen and constipation. When his mentor Professor von Authenrieth heard of Kerner’s dangerous self-experiments, he wisely persuaded him to stop these experiments [12, 14]. Kerner’s conclusions from these experiments were that the toxin develops under anaerobic conditions and affects the autonomic nervous system [15]. In somewhat prescient speculation, Kerner thought that someday this toxin could have a therapeutic use in suppressing hyperactivity of the sympathetic nervous system such as sweating or oversecretion of mucous [13, 15].

Toward the end of the century, in 1895 in the Western Wallonian district of Hainaut in Belgium, another cluster of botulism cases occurred. Emile Pierre Marie van Ermengem of the University of Ghent was sent to investigate. He was a student of the noted microbiologist Robert Koch and had worked in Koch's Berlin Laboratory in 1883 [12, 16, 17]. He would uncover the cause of botulism and provide accurate descriptions of the progression of the disease. This larger cluster of cases originated from a funeral wake where pickled raw ham had been served. Within a day, twenty-three friends of the deceased who had eaten the ham fell ill with abdominal pain and vomiting. Their vomiting persisted and stomach pains grew worse, but few had any diarrhea and many began to complain of constipation and sought purgatives as a cure [17]. By the second day, some had visual disturbances, "veiling of the eyes," and "loss of clarity of vision over" short distances [17]. The next day, the patients had double vision, their throats were dry, and they were choked with thick viscous mucus; no amount of coughing could clear it. Their voices grew dull and articulation became difficult, and then it seemed as if the "tongue itself was paralyzed" [17]. By the end of a week, three had died and 10 were seriously ill [16]. Notably, none of them developed a fever, and their thinking remained clear until weakness and difficulty breathing overcame them in the last few hours before death.

On van Ermengem's investigation, it was discovered that one ham, uncooked but pickled in brine, lay at the bottom of the barrel from which the food was served at the wake. It did not smell of putrefaction. After initial slide preparations proved negative, anaerobic cultures were done, and he discovered a large spore-bearing bacillus [17]. Staining with Ziehl's solution revealed oblong ellipsoidal bodies within the muscle bundles of the ham that proved there were spores present [17]. In experiments similar to Kerner's, van Ermengem cut the ham up into small pieces and fed it to mice, guinea pigs, rabbits, cats, dogs, chickens, and monkeys. The cats and monkeys experienced a syndrome identical to human botulism [17]. It was van Ermengem who proposed giving the name *Bacillus botulinus* to the

Clostridium-like bacillus he found. The spore-forming bacillus was named for the Latin word for sausage – botulus.

In 1904, G. Landmann examined another cluster of poisoning cases from canned beans. Twenty-one people who had eaten salad made from waxed beans at a German cooking school became ill, of these eleven had died [11, 18]. This was a unique but important event, as up to this point in time, it was assumed that botulism was a disease only of meat and, in scarce Russian literature, of fish. Working at the German chemical house of Merck in Darmstadt, Landmann was able to culture the anaerobic bacillus [19]. In 1910, Dr. J. Leuchs from the Royal Institute of Infections in Berlin obtained some of the original samples of the *Bacillus botulinus* from the van Ermengem strain and from Landmann's outbreak of canned white beans. He injected these bacilli into horses and from this equine source harvested sera producing an antitoxin [12]. He found that each antitoxin only neutralized the bacillus-produced toxin from the strain from which it was derived, suggesting that there were two different toxins involved. It was not until 1919 that Georgina Burke at Stanford University would designate the Landmann strain as type A and the Van Ermengem strain type B, designations that remain today [12, 19].

Biochemistry and Clinical Pharmacology

The pathophysiology in classic food-borne botulism occurs through the ingestion of the preformed botulinum toxin from food [1, 3, 19–21]. In the gastrointestinal tract, the botulinum toxin is actively transported across the lumen of the intestinal tract via endocytosis and transcytosis. Serotypes A and B are the most efficiently transported across the intestinal lumen [2, 22]. Once in the systemic circulation, botulinum toxin is distributed to sites of acetylcholine-mediated neurotransmission where it causes toxicity [20, 22]. The large molecular mass (15,000 Da) of the botulinum toxin renders it incapable of crossing the blood–brain barrier. Botulinum toxin inhibits cholinergic transmission at

sympathetic and parasympathetic ganglia, at parasympathetic postganglionic sites, and most importantly at the presynaptic cholinergic nerve terminal at the neuromuscular junction [22]. Anticholinergic symptoms tend to be mild, and victims will manifest dry mouth, dilated pupils, and decreased bowel and bladder motility.

All botulinum toxins consist of a linked heavy chain and light chain. The heavy chain binds to the presynaptic neuronal surface, where the toxin is taken up by endocytosis. From within the endocytosed vesicle, the light chain translocates from inside the vesicle into the presynaptic cytosol [2, 19, 22]. The light chain is cleaved from the heavy chain by reduction of a single disulfide

bond, in order to enter the neuronal cytosol, where it acts as a zinc-dependent endopeptidase. The light chain inactivates one of three SNARE proteins (soluble N-ethylmaleimide-sensitive fusion protein attachment receptor) in the neuronal cytosol [2, 19, 23] (Table 2, Fig. 1). The SNARE protein complex allows acetylcholine-

Table 2 SNARE protein inhibition by botulinum serotype

Botulinum type	Cytosol SNARE protein inhibited
A, E	SNAP-25
B, D, F, G	Synaptobrevin
C	Syntaxin and SNAP-25

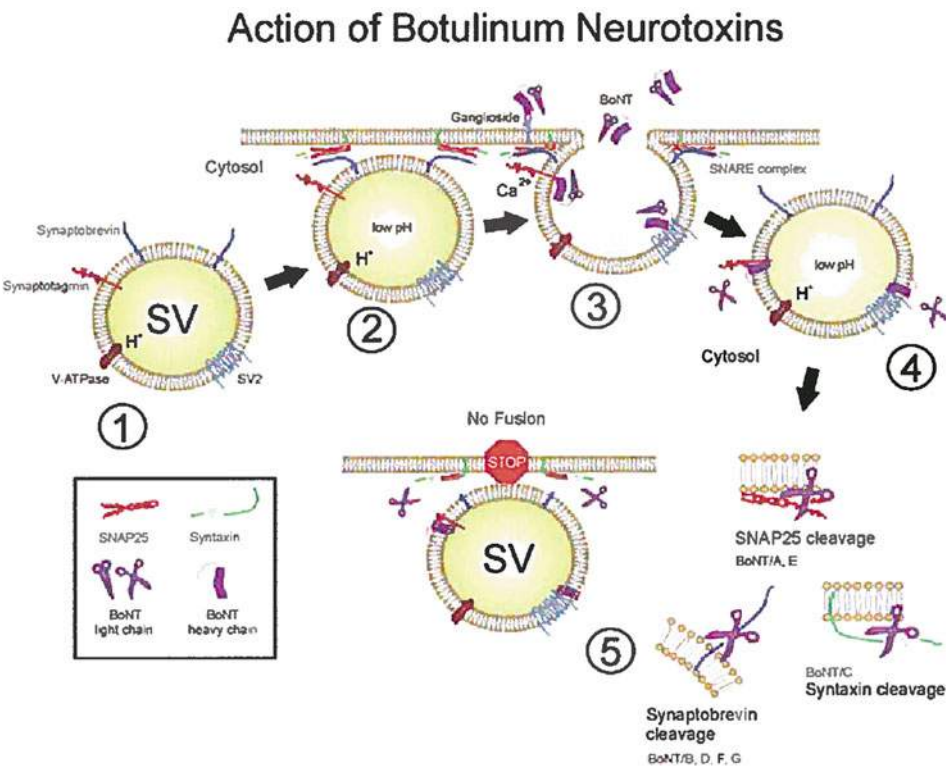


Fig. 1 Botulinum neurotoxins (BoNT) prevent exocytosis by cleaving synaptic proteins. Synaptic vesicles (SV) approach the synaptic membrane and form the SNARE complex as a prerequisite for the fusion pore and exocytotic transmitter release. During this step, BoNT bound to gangliosides at the extracellular side can be taken up into the vesicle by binding of the heavy chain to specific target proteins synaptotagmin or SV2. Following retrieval from the plasma membrane, recycling vesicles

become acidified again by means of the vacuolar proton pump (V-ATPase). This results in incorporation of the N-terminus of the heavy chain into the vesicular membrane, partial unfolding, and translocation of the light chain into the cytosol to target the specific synaptic proteins involved in the exocytotic machinery (From: Current Topics in Microbiology and Immunology, Botulinum Neurotoxins, Synaptic Vesicle Proteins: Targets and Routes for Botulinum Neurotoxins, 2013)

Table 3 Clinical forms of botulism

Gastrointestinal types
1. Adult botulism
2. Infant botulism
3. Adult intestinal toxemia botulism
Wound botulism
Inadvertent or iatrogenic injection of botulism toxin
Inhalational botulism

containing vesicles in the presynaptic nerve terminus to fuse with the neural cell wall in preparation to be released into the synaptic cleft [1, 2, 4, 22, 24]. Both serotypes A and E inhibit the function of SNAP-25 protein, while serotype B inhibits synaptobrevin [2, 25]. Without the ability of acetylcholine vesicles to fuse and dock with the distal neural cell wall in the absence of functional SNAP-25, release of acetylcholine does not occur, and no muscular contraction can occur. The result is a progressive descending flaccid paralysis.

Clinical Presentation and Life-Threatening Complications

There are six clinical forms of botulism, three of which occur through the gastrointestinal route (Table 3).

Adult Botulism

All adult-type forms of botulism manifest symptoms similarly [1, 26–29]. The gastrointestinal forms usually have a prodrome of nausea and vomiting within a few hours of ingestion of a contaminated food source, but often it is not bothersome enough for most people to seek medical care. Diarrhea that occurs with other food-borne illnesses may not occur with botulism. A variety of food sources around the world have been implicated in food-borne botulism outbreaks [3, 26] (Table 4). Typically these foods have low acidity, low salinity, and were canned without adequate heating to kill the botulism spores, which are often introduced via soil contamination.

Onset of symptoms after exposure is variable, even within common source outbreaks, but with

Table 4 International foods associated with cases of botulism by country

Ashbal (salted carp eggs) – Iran
Canned Mushrooms – Russia
Chopped garlic in soybean oil – Canada
Chou dou fu (fermented bean curd) – China
Cinkrugan (fermented raw goat meat) – Taiwan
Faseikh (fermented mullet) – Egypt
Gefilte fish – US Jewish community
Hazelnut yogurt – United Kingdom
Heart of palms – Brazil
Inlagd sill (pickled herring) – Sweden
Izushi (fermented sole preserved in rice) – Japan
Kapchunka (uneviscerated salted whitefish) – Israel, Russian immigrants, United States
Kunzha (smoked fish) – Russia
Ladoo (sweetened flour) mixed with buttermilk curd – India
Mascarpone cream cheese, tiramisu – Italy
Matambre (rolled stuffed meat) – Argentina
Muktuk (whale blubber) – Alaska, United States
Octopus escabeche (pickled octopus) – Argentina
Olives – Spain
Pruno – US prison wine
Palani (surgeon fish) – Hawaii, United States
Rakfisk (fermented char) – Norway
Salchipapas (Fried potatoes, hot dogs, and eggs in mayonnaise) – Peru
Seal oil – Alaska, United States
Scallops – France
Skordalia (Baked potato in garlic oil) – Greek food, United States
Suzme yogurt – Turkey
Vacuum packed whitefish – Canada
White ants – Kenya

food-borne botulism onset of symptoms occurs usually within 1–5 days of ingesting the contaminated food product [26–29]. Type F cases may occur more rapidly within 48 h [7]. Once the botulinum toxin acts at the neuromuscular junction presynaptic nerve, signs and symptoms of a flaccid paralysis occur in a descending fashion. Bulbar palsies of the cranial nerves with motor function present first [29]. Initially it affects the oculomotor muscles, progressing to facial muscle paralysis and then to muscles of mastication, swallowing, and eventually the larger muscles of the arms and legs. Ultimately, if unrecognized and

Table 5 The twelve “D” s (Horowitz Dodecad): symptoms of botulism in order of appearance [21]

Dry mouth
Diplopia
Dilated pupils
Droopy eyes (ptosis)
Droopy face
Diminished gag reflex
Dysphagia (difficulty swallowing)
Dysarthria (difficulty articulating speech)
Dysphonia (difficulty phonating/whispered speech)
Difficulty lifting head
Descending paralysis
Diaphragmatic paralysis

A shortened version of this is taught in Alaska as the “pentad” [6]:
Dilated pupils
Diplopia
Dry throat
Dysphagia
Nausea and vomiting

untreated, the intercostal muscles and the diaphragm are compromised, and respiratory insufficiency occurs. Once allowed to progress to respiratory failure, the patient will need ventilator-assisted support, potentially for several months, until the motor end-plate recovers [30]. A constellation of symptoms called the dodecad or 12 “D” s has been used as mnemonic (Table 5).

Notably absent in this clinical presentation are any central neurologic manifestations or any sensory impairment. Since botulism is not an infection with *Clostridium*, but rather a manifestation of elaboration of botulinum toxin from its spores, fever is not part of the presenting symptoms. Even in cases of wound botulism, the wound does not always appear to have a significant inflammatory component, fever may be absent, and evidence of systemic infection, such as leukocytosis, may not be found [31].

The US Centers for Disease Control and Prevention (CDC) recognizes another adult gastrointestinal form, previously referred to as undefined adult botulism and also referred to as adult-type infant botulism, now classified as adult intestinal toxemia [32–34]. This very rare form of botulism

has a delayed onset from clostridial colonization in an abnormal gastrointestinal tract and may take 40–60 days for stools to clear. In a case series from Ontario, Canada, in 2006, two patients had Crohn’s disease and a prolonged course [33]. It has been associated with peptic ulcer disease, Billroth surgery, and Crohn’s disease [34].

Infant Botulism

Infant botulism presents differently from adult-type botulism. 95% of cases occur in children less than 6 months, and its occurrence after 1 year of age is rare [35–46]. Almost all cases are caused by *Clostridium botulinum* serotypes A and B. Case reports of *Clostridium baratii*, type F, and *Clostridium butyricum*, type E, have occurred [7, 8, 41–43]. An epidemiologic investigation initially linked infant botulism to parental feeding of raw honey to the infant [46], but since the initial reports most cases occur without being fed honey. Breast-feeding may be an unappreciated risk factor. Infants fed formula usually present within 2 months of life suggesting a narrow window of susceptibility, while breast-fed infants present up to 1 year old [37]. It is rare for an infant botulism case after 2 months old to not have been breast-fed [37, 43].

The pathogenesis is linked to the fact that infants have both immature intestinal flora and decreased bile acids that allow the *Clostridium* spores to colonize the bowel, germinate, and elaborate the toxin [44, 46]. Both the toxin and the bacteria can be obtained from fecal samples, sometimes requiring a saline enema in order to obtain a sample. Symptoms begin with bulbar weakness such as a poor suck or weak cry due to inhibition of phonation muscles and inability to hold the head upright [44]. Constipation in a young child is a prominent complaint of parents bringing a child to a clinic or emergency department for evaluation of an infant that ultimately is proven to have infant botulism [44]. This nonspecific presentation often causes misdiagnosis early in the natural course of the disease. As infant botulism progresses over a

few days to a week, a more generalized muscle weakness occurs with a hypotonic or “floppy” baby with poor head and neck control. A weak hoarse cry, ptosis, and diminished deep tendon reflexes all may be noted [44]. Most cases do not progress to respiratory failure; however, missed cases are speculated to be responsible for possible sudden infant death syndrome [38]. Once the diagnosis is considered, hospitalization is required in a pediatric intensive care setting, as secondary complications such as pneumonia and sepsis can occur [37, 38, 44]. Hyponatremia due to syndrome of inappropriate antidiuretic hormone release has been reported in hospitalized cases [36].

Wound Botulism

Wound botulism occurs when a wound is colonized with *Clostridium botulinum*. Early cases prior to the 1980s were often due to surgical wounds with retained packing [47]. After 1982, clusters of cases associated with injection drug users who had “skin-popped” black tar heroin appeared [31, 47–53]. On presentation, their injection sites did not have the appearance of wound infections and only displayed the typical scarring from multiple intravenous or intramuscular drug use. Some cases had asymmetric bulbar palsy on initial presentation, but progressed with symmetric descending paralysis [48]. Since food contamination was not the source of *botulinum* toxin, gastrointestinal symptoms were absent. Delays to diagnosis, especially early in a clustered outbreak, meant delay to administering the antitoxin and a prolonged ventilator-dependent clinical course [53]. The vast majority of the cases occurred in California, and the few others were all on the West Coast, where type A *botulinum* toxin was implicated [47–51]. In addition to the standard supportive care and early antitoxin administration, debridement of wounds is critical to management. It is frequent that such injection drug users have multiple wounds and all wounds should be explored for signs of necrotic tissue to

be debrided. Any signs of adjacent skin infection should be treated with antibiotics.

Inhalational Botulism

Inhalational botulism is a potential biologic weapon, but this form of exposure has only been described in humans after an accidental laboratory exposure [54]. Three days after performing an autopsy on a lab animal that died of botulism, three technicians developed tightness in the throat, difficulty swallowing, and symptoms characterized as a cold without a fever [54]. They developed ocular paresis, rotatory nystagmus, dilated pupils, dysarthria, ataxia, and generalized weakness. All recovered within 2 weeks with antitoxin treatment [54]. If a terrorist attack occurred with inhalation botulism, there would likely be an irritant upper airway prodrome with the initial contact, followed by a variable onset of different degrees of paralysis in exposed victims. By 3 days postexposure, those maximally affected might present to a variety of outpatient and emergency department sites with the classic syndrome of descending bulbar palsies. The issue which makes this scenario most worrisome is that delayed diagnosis in a large number of patients, and the limited availability of the antitoxin, would lead to a significant number of ventilator-dependent victims immobilizing intensive care unit (ICU) care for months.

Botulinum toxin had been investigated as a biologic weapon earlier by British, the US, Canadian, Japanese, and Soviet military since World War II. Japan’s infamous Unit 731 during World War II experimented with botulism by feeding it to prisoners in Manchuria [19, 54]. Botulism’s sole link to a purposeful use as a weapon is that it is thought that Paul Fildes, a high-ranking British specialist in bacterial weapons development during World War II, alluded to the fact that he contributed to the assassination of Reinhard Heydrich, head of the Gestapo [54]. The British supplied the Czech underground with a modified hand grenade, with a glass vial containing

botulism attached to it, that was used in the ambush of Heydrich's car.

As far as an aerosolized weapon, the Russians have exposed animals to botulinum toxin at their Vozrozhdeniye Island site in the Aral Sea [19]. In the early 1990s, prior to their attack with Sarin on the Tokyo subway system, the Japanese doomsday cult *Aum Shinrikyo* had released an ineffectively produced *Clostridium botulinum* preparation in Japan targeting a US military installation and planned a release during the prince's wedding [19].

During the United Nations inspections of Iraq's capabilities for biologic warfare in 1991 after the first Gulf War, botulinum toxin was found to be one focus where Iraqi research efforts had been directed. Iraq had produced more botulinum toxin than any other weaponizable agent. Approximately 19,000 l were produced of which approximately half was already loaded onto warheads [19, 55]. When General Hussein Kamal Hassan defected from Iraq in August 1995, he verified that he was personally aware of 100 bombs, 13 SCUD/Al Hussein missiles, and 122 mm rockets that were loaded with botulinum toxin as part of Iraq's biologic weapons program [54, 55]. As a response to these events, the US Strategic National Stockpile has the new botulism heptavalent antitoxin cached throughout the United States as part of their disaster and bioterrorism preparedness.

Inadvertent/Iatrogenic Injection of Botulinum Toxin

Therapeutic injection of botulism, as Botox or Myobloc, for the variety of motor disorders has on a few rare occasions resulted in local muscle toxicity. However, a bizarre event occurred in November 2004 when an osteopathic physician, who had previously had his license revoked but operated a cosmetic clinic in Florida, and his girlfriend were admitted to hospitals in New Jersey in ventilatory failure. Simultaneously another married couple – a chiropractor and his wife – who were treated at this physician's clinic were admitted to a different hospital in Florida

[56]. Investigation of this event revealed that the physician purchased large quantities of research grade botulinum toxin, not intended for human use. He then attempted to compound it on his own to a more dilute concentration equivalent to "Botox." Pharmaceutical Botox was not involved. All four victims ended up on ventilators for several months, with 3 of these cases confirmed as botulism [56]. This gap in the tracking of high-grade botulinum toxin highlighted a loophole in the surveillance of sale and distribution of this product, which could lead to its use as a terrorism agent, which theoretically could be dispersed as an aerosol.

Diagnosis

Differential Diagnosis

Although a long list of neurologic and metabolic causes for motor neuropathies is frequently considered [19, 21, 25, 27], only two important diagnoses seem to cause the majority of misdiagnosis of botulism and accordingly delay to treatment [21, 28, 57]. Myasthenia gravis is frequently considered in new onset bulbar palsies without sensory findings, especially when isolated bilateral ptosis is the presenting complaint. In fact the edrophonium challenge test, thought to be specific for myasthenia, may be equivocally positive in some botulism cases owing to its subjective interpretation [48, 58]. The other often considered diagnosis is the Miller Fisher variant of the Guillain-Barre syndrome. This is an exceedingly rare disorder, usually having a viral prodrome with fever and more likely would present with ataxia [59, 60]. Even if the Miller Fisher variant of the Guillain-Barre syndrome is considered in the differential diagnosis, treatment for the more common botulism should be started, as time to antitoxin administration is critical for botulism.

Hypokalemic periodic paralysis and tick paralysis, two other common causes of symmetric myopathies, predominantly affect the proximal large muscles rather than cranial nerves. Unlike botulism, tick paralysis usually presents as an ascending paralysis, sometimes with an initial

Table 6 The motor exam for bulbar palsies

CN III	Can't move eyes left and right, lids droop
CN IV	Can't look downward symmetrically
CN V	Can't bite down
CN VI	Can't look outward
CN VII	Can't close eyes against force, purse lips, or smile
CN IX	Stylopharyngeus muscle only
CN X	Diminished gag reflex and difficulty swallowing, saying "ah"
CN XI	Diminished strength trapezius and sternocleidomastoid
CN XII	Difficulty moving tongue side to side

ataxic gait. Some venomous snakes, mostly elapids (cobra-type) can cause a botulism-like descending paralysis, though usually of more rapid onset. A history of snakebite may not be available, as bites of some species may go undetected and bites to sleeping humans may result in a severely paralyzed patient by morning, with no clear history of snakebite; the latter is classic for krait bites in parts of Asia. The similarity between snakebite paralysis and botulism is not surprising, as some of the snake presynaptic neurotoxins share similarities in site and mode of action with botulinum toxin. Most other central neurologic lesions, such as strokes, carotid dissection, tumors, and trauma, present with unilateral findings and some degree of central symptoms such as altered level of consciousness.

A high clinical suspicion based on the motor exam should be all that is needed for the treating physician to initiate the request for the release of botulism antitoxin, which in the United States is from the CDC. A young person presenting with ocular muscle findings who has not suffered a cerebral vascular accident is most likely to have botulism [21]. Bulbar palsies of the cranial nerves usually involving cranial nerves III and VI are the most common early finding [21, 60] (Table 6). Notably absent in the clinical assessment is any change in mental status, sensory findings, tremor or motor hyperactivity, fever, leukocytosis, or electrolyte abnormalities.

An assessment of impending respiratory failure should include bedside pulmonary vital capacity or negative inspiratory force, which should be

assessed early and repeated frequently [21]. Adjunct monitoring with end-tidal CO₂ may also be a vital clue to impending respiratory compromise.

Depending on the suspected site of entry samples of stool, gastric content, serum, wound aspirates, or sputum may be sent in anaerobic transport media for culture of *Clostridium* species [20]. The samples ideally should be obtained before treatment with antitoxin. In the constipated infant botulism patient, a gentle saline enema may be needed to obtain a stool sample [44]. Early growth in the anaerobic culture media of the typical gram-positive bacillus suggests a clostridial species, especially if they have oval-shaped subterminal spores and beta-hemolytic activity [1]. Specimens should be handled with a biosafety level 2 containment in the microbiology laboratory [20].

In the United States, serum, stool, and suspected contaminated foods can be sent to the health department or the CDC for a mouse bioassay. In the event of a bioterrorist event, contaminated surface swabs should also be sent for a mouse bioassay or an ELISA test [61]. The mouse bioassay is the most widely utilized test by health departments. While crude in its design, it is considered the most sensitive test for the diagnosis of botulism. Either serum or a biologic fluid supernatant is injected intraperitoneally into two sets of mice, one set pretreated with botulinum antitoxin and a control group [10, 61]. In a positive test, the mice with the antitoxin pretreatment all live, and the untreated mice all die. A definitive result may take as long as 4 days [61]. Since there is a long turnaround time on this assay (not counting additional delays in transport to an appropriate lab), **treatment of the patient should be instituted on clinical suspicion** and never await the results of this assay, which is used only to confirm and to serotype the botulinum toxin involved [61]. The ELISA test is not available outside of research facilities but has a shorter turnaround time and may be as sensitive for detection of the botulinum toxin [61].

While awaiting the delivery of antitoxin, other ancillary tests may be helpful to eliminate other diagnostic possibilities. A complete set of

electrolytes should help exclude potassium and magnesium disorders. A computerized tomographic scan should help eliminate central nervous system tumors or bleeds, although a magnetic resonance (MR) image or a MR angiogram may be necessary to exclude a brainstem lesion. A lumbar puncture can be obtained if infectious or postinfectious etiologies are considered, and an elevated cerebral spinal fluid protein suggests the Miller Fisher variant of the Guillain–Barre syndrome [59]. If myasthenia gravis is considered, the edrophonium (Tensilon) challenge test may be administered with a saline injection given first and the time to fatigue of upward gaze timed and then repeated after slow injection of edrophonium. If ptosis unequivocally improves, myasthenia gravis may be considered, but false-positive tests have been reported in cases of botulism [28, 54].

Other adjuncts such as electromyography are best reserved until after treatment with antitoxin. Botulism causes brief small amplitude motor potentials on repetitive nerve stimulation at 20 to 50 Hz, with an incremental response to repetitive stimulation [49].

Treatment

As early as possible, based on history and physical exam, the treating physician should contact their local and/or state health department to report a suspected case and seek their assistance in acquiring the antitoxin as quickly as possible.

The trivalent antitoxin (against serotypes A,B, E) was once the mainstay of treatment in the United States [1, 4]. It contained 7500 IU type A, 5500 IU type B, and 8500 IU type E antitoxins [21] (see Box 1). An older formulation of a bivalent antitoxin against only A and B serotypes was also used [21, 62], and in Alaska and Canada, a monovalent type E antitoxin was available. A specific monovalent antitoxin against serotype F is also produced. All these antitoxins were officially retired on March 12, 2010 when the CDC announced the release of a new heptavalent botulinum antitoxin (HBAT, Cangene Corporation) that replaces previously licensed

Table 7 Composition of each single use vial of HBAT

4,500 IU anti-A
3,300 IU anti-B
3,000 IU anti-C
600 IU anti-D
5,100 IU anti-E
3,000 IU anti-F
600 IU anti-G

trivalent ABE, bivalent antitoxin AB, and investigational monovalent botulinum antitoxin E (BAT-AB and BAT-E, Sanofi Pasteur) [63]. HBAT thus became the only botulinum antitoxin available for adults in the United States, although requiring an Investigational New Drug (IND) protocol. The HBAT antitoxin is currently part of the American Strategic National Stockpile that is kept in cached quarantine sites in the United States at large hub airports. The current amounts of serotype-specific antitoxin in HBAT are listed in Table 7 [6].

The US Army originally developed this equine-derived heptavalent (A-G) antitoxin [63–65]. The retired funeral procession horse, First Flight, was used for production of this equine-based antitoxin between 1978 and 1992. In a report of a case of botulism type F in California in 2004, it was first released on a compassionate use basis [8]. In 2006, the US Department of Health and Human Services contracted with Cangene Corporation in Canada, which evolved from Connaught Laboratories, the original manufacturer of the older trivalent antitoxin, to produce a heptavalent antitoxin. The current product is designated HBAT. In earlier literature, the heptavalent antitoxin was sometimes referred to as a “despeciated” product but is in fact an equine-derived IgG immunoglobulin that has been cleaved by pepsin removing the antigenic Fc component and leaving the F(ab’)² botulism immune globulin fragments, with some Fab fragments [65, 66]. This product was first assessed in an outbreak of type E food-borne botulism in Egypt in 1991 [65, 66]. In the Egyptian outbreak, forty-five patients received the US experimental F(ab’)² fragment antitoxin, and 5 others received it with

other antitoxins. Of the 45 patients who only received the US experimental F(ab')² fragment antitoxin, 31 were interviewed in a follow-up, and only one case whose symptoms could be construed in retrospect as serum sickness occurred [64, 65]. None of the patients treated with this new antitoxin died, although the more severe cases that were responsible for deaths occurred earlier in the outbreak [65]. A second outbreak assessment of HBAT was made in 2006. Twenty doses of HBAT were used in the bamboo shoot-related outbreak of food-borne botulism in Thailand, as part of an international mobilization of botulism antitoxins, and were assessed to have a good safety profile [67].

The current recommended dose for HBAT for adult botulism of all types is a single 20 ml vial diluted 1:10 in normal saline and administered over 60 min for all age groups above 12 months [63]. It has been used in children; if weight is < 30 kg, the recommended dose is to use a percentage of the adult dose equal to twice the patient's weight in kilograms (HBAT package insert, Cangene Corp., Winnipeg, Manitoba, Canada). In the continental United States, the HBAT antitoxin is cached in quarantine sites at designated large hub airports. It is necessary to have the treating physician call the local health department who then must call the CDC botulism emergency operations center (770-488-7100) to authorize the release of this product. In Canada, the responsible agency is the Botulism Reference Service (613-957-0902).

Alaska is the one US state that uses a faster distribution system. An educational outreach for the health aide program in over 180 individual villages has stressed the diagnostic mnemonic of the "pentad" for suspecting a diagnosis of botulism [68] (Table 5). Suspected cases can be air-evacuated from the villages to several regional hub hospitals where the antitoxin is kept at the hospital pharmacy. To release the antitoxin for use on a patient, a call to the Alaska State Section of Epidemiology (1-800-478-0084) starts the process [68]. An outbreak in December 2014 due to seal oil consumption involving 25 patients in remote villages was successfully managed this way.

Adjuncts to the critical care treatment of the botulism patient include all the special features of caring for any patient with severe neurologic impairment without cognitive impairment. Early in the course, a means of communication should be established through whatever preserved body movements the patient may still have. A limited group of nurses who are aware of the patient's ability at communicating will perhaps ease the frustration and depression these patient's experience. Frequent inquiries as to pain and discomfort caused by body position are important. Anecdotal experience suggests that patients may have headaches that go unnoticed and can be debilitating. Although reverse Trendelenburg position to 20–25° has been advocated in patients not requiring intubation, the more important adjunct is frequent measuring of vital capacity in these individuals to see if intubation is required [1, 69].

Once paralysis occurs, a collaborative effort by nursing, physical therapy, and respiratory therapy is needed to try to prevent the risks of infection, ventilator mishaps, and nutritional depletion that these patients experience. In one early series, a surprising number of deaths were due to unrecognized ventilator malfunctions [69]. Nosocomial pneumonia, urosepsis, skin breakdown and decubitus ulcer infections, and stoma infections of tracheostomies are common once the patient becomes ventilator dependent. The anticholinergic effect of the botulinum toxin may also contribute to bladder atony and thick viscid mucus secretions [29]. Muscle wasting and nutritional depletion will ultimately be impediments to weaning from the ventilator. Daily physical therapy of all paralyzed muscle groups will aid in the patient's rehabilitation. Frequent turning of the patient to prevent skin breakdown and pressure effects of immobilization is also important.

Treatment of Infant Botulism

In the United States, there is a human-derived antitoxin that is used only for cases of infant botulism. Human Botulism Immune Globulin (H-BIG) is only available through California State Department of Health Services (Telephone

510-540-2646) [35]. This product is derived from plasmapheresis from human donors who have received at least five doses of the pentavalent toxoid vaccine, usually given to at-risk laboratory workers [35, 70]. Since this is a pentavalent immune globulin against types A,B,C,D,E, it does not cover the rare occurrence of infant botulism serotype F disease [35, 41]. BabyBIG, as the US Food and Drug Administration (FDA) approved product is called, has a long biologic half-life and a greatly decreased risk of hypersensitivity reactions [35]. A single dose is given IV without any repeat dosing recommended. While potentially it could be used for adults who had an early and severe anaphylactoid reaction during the infusion of the equine-derived HBAT antitoxin preventing a full dose from being administered, it has never been released for this indication.

Botulism Vaccines

The Soviet-era biological weapons program experimented with a botulism vaccine in the 1930s and had the first human trials at the Vaccine-Sera Laboratory in Vlasikha in 1934 [71–74]. A bivalent vaccine was developed in 1946 (against types A and B) by the US Department of Defense, and C.E. Rice developed a similar vaccine in Canada in 1947 [72]. Subsequently, a pentavalent botulinum toxoid (PBT) vaccine was developed by at the US Army Medical Research Institute of Infectious Diseases (USAMRIID) in 1957 at Fort Detrick and manufactured by Parke-Davis between 1958 and 1981 [19, 73]. Since 1978, a comparable vaccine, from five monovalent vaccines, was produced by the Michigan Department of Public Health [19, 72–74]. It is effective in producing immunity in vaccinated laboratory workers against serotypes A to E. (It is not effective against F and G.) The original dosing schedule was three subcutaneous injections at 0, 2 weeks, and 12 weeks with subsequent annual boosters, based on antitoxin titers. Prior to 1969, fifty individuals who received this vaccine and were subsequently accidentally exposed to botulism did not develop any clinical symptoms of the disease [19, 72]. Between 1998

and 2000, the Michigan Department of Public Health monitored titers at 6 months after the three-dose immunization schedule and found they varied from a low of 19% for type E to 60% for type B and C [72, 74]. In a similar study at USAMRIID, type E titers were inadequate in 80% of vaccinated individuals with a three-dose regimen and in 60% with a four-dose regimen [73, 74]. Since titers against only types A, B, and C achieved an adequate level in greater than 50% of those vaccinated, the dosing regimen was changed to add a 6-month and 12-month booster vaccine dose, and since 2004 the recommended regimen is a five-dose schedule at 0, 2 weeks, 12 weeks, 24–26 weeks, 1 year, and annually thereafter [19, 73].

The pentavalent PBT was used in over 20,000 laboratory workers and in 8,000 soldiers deployed in the Gulf War [73]. Moderate local reactions occur in 7% of healthy vaccine recipients, and severe local swelling greater than 120 mm or lymph node swelling occurs in less than 1–2% [74]. Systemic reactions of fever, malaise, headache, myalgia, neck or back stiffness, hives, or pruritus occur in 5% [73, 74]. The pentavalent vaccine was not approved by the FDA and was part of the Strategic National Stockpile. It was retired from use in November 2011 due to loss of antigenicity of existing stocks, but persons in the middle of a vaccination series were allowed to complete it by May 2012 [75]. Individuals who have received the full five-dose vaccination schedule and have adequate titers are the source for BabyBIG [72–74]. Since the immunogenicity of the PBT vaccine is declining as subsequent lots are produced, research continues into candidates for a replacement vaccine. Japan has developed a tetravalent vaccine against all the human disease-causing serotypes, A, B, E, and F, but its immunologic response declines by 90% at 9 months after a 3-dose regimen [71]. Investigations of recombinant vaccine products, based on an immunologic response to the C-terminal end of the botulinum heavy chain (Hc), are underway at USAMRIID. The bivalent recombinant anti-AB vaccine based on this technology has shown good titer response and safety in phase I human trials and is in phase II trials [74].

Prognosis

Delay to administering the antitoxin is the most important factor affecting clinical course and outcome. In one study, mortality was 10% in those who received the antitoxin within 24 h of onset of symptoms, 15% when it was administered later than 24 h, and 46% when not given at all [76]. However, these statistics must be tempered within the time period when the data occurred, as four out the 19 deaths in this series occurred due to ventilator malfunction or accidental extubation. The fatality rate in those over 60 years of age was twice that of those patients younger than 60 [76].

The more rapid the onset, the more likely intubation was needed [57, 77]. Type A patients typically have a faster onset than type B. In a review of CDC cases in 1999 and 2000, 83% of type A required intubation, where as only 33% of each type B and E required intubation [27, 57]. In another study, the mean time on a ventilator was 58 days for serotype A cases and 26 days for serotype B cases [27]. Ventilator dependence can last as long as 142 days [29].

When there is an outbreak, usually the index case is most severely affected and may have early misdiagnosis and hence delay in treatment [62]. Subsequent cases, once the clinical suspicion is raised in outbreaks, uniformly do better [78].

Delays in access to the antitoxin on the continental United States are often a result of the need for clearance from the CDC, before the antitoxin is released. Additionally antitoxin is not kept in health-care facilities, but rather is cached in nonhospital storage facilities at major airports. This cumbersome process to access the antitoxin has resulted in delay to administering it to patients and in longer hospital stays [6, 53]. In the United States, the next logical step to reduce delays to treatment would be to adopt a distribution plan similar to Alaska's for the rest of the country and have this product available in major hospitals.

It is difficult to compare outcomes between studies that have spanned many decades as substantial improvements in critical care have

reduced the mortality in cases once the disease is recognized and treated appropriately. One group which studied long-term follow-up indicated that normal pulmonary function is regained, but diminished respiratory muscle function and easy fatigue may persist in some patients at 2 years after recovery [69, 77].

The prognosis for recovery from infant botulism is excellent with supportive care. There has been a 20-year study and a 30-year study of infant botulism conducted at a single children's hospital [79, 80]. All 66 children survived, both before and after the time period when BabyBIG was utilized, although mean length of stay was reduced from a mean of 36 days to 15 days, once BabyBIG was available after 1990 [80]. Type A serotype caused longer lengths of stay and slightly longer, but not statistically significant, ventilator-dependent days than serotype B [79]. All children had normal neurologic function on follow-up. In the largest study of infant botulism with 122 children randomized to treatment with or without BabyBIG, the BabyBIG-treated cases had a mean length of stay of 2.6 weeks compared with 5.7 weeks in the non-BabyBIG-treated cases [35]. This translated into fewer days in the ICU, fewer ventilator-dependent days, fewer tube-fed days, and lower costs for the BabyBIG-treated cohort [35]. The only side effect was a single case of a transient rash.

Box 1: Older Antitoxins [81]

The trivalent antitoxin (against serotypes A, B, E) was the mainstay of treatment in the United States and Canada from 1969 to 2010. It contains 7500 IU type A, 5500 IU type B, and 8500 IU type E antitoxins. Production of trivalent antitoxin ended in 2001, as adequate levels of antitoxin E in the production process could not be assured, but existing stores continued to be used. From 2001 to 2010, most cases in the United States were treated with the FDA-approved bivalent antitoxin against only types A and B. However, in Alaska, a monovalent type E antitoxin had been available from Canada and was used along with the bivalent

(continued)

FDA-approved antitoxin with an IND protocol in Alaska until 2010. Type E antitoxin is rarely used by itself. It was first manufactured at the University of Toronto by Connaught Medical Research Labs and used experimentally in Hokkaido, Japan, in the 1950s and 1960s and in Labrador in the 1961. The case fatality ratio after type E antitoxin was instituted in Japan fell from 29% prior to the availability of the type E antitoxin to 3.5% in 85 patients treated with the type E antitoxin. Shortly after the initial success of the Canadian antitoxin in Japan, the Japanese National Institute of Health created their own type E antitoxin.

Dosing recommendations for the trivalent or bivalent antitoxin are to give a single vial diluted 1:10 in normal saline intravenously over 30–60 min.

Indications for ICU Admission

All suspected cases should be considered for ICU admission for observation of neurologic progression and frequent assessments of pulmonary vital capacity.

Criteria for ICU Discharge

Stabilized respiratory status. Some patients may be discharge to skilled facilities where specialized ventilator-dependent patients receive care.

Otherwise, patients will need to be extubated and demonstrate adequate respiratory functional capacity on repeat assessments.

Key Points

1. Botulism is a neurologic disease caused by the botulinum neurotoxin.
2. Food-borne and wound botulism predominate in adults.

3. A clinical finding of symmetric cranial nerve palsies in an adult should raise the suspicion for the presence of botulism.
4. HBAT antitoxin should be administered based solely on clinical findings and not await confirmatory assays or EMG testing (II-3).
5. In the United States, the CDC botulism emergency operations center telephone number is (770-488-7100).
6. Infant botulism is the most prevalent form of botulism in the United States, but it should be considered a separate entity characterized by subtle findings of poor feeding and muscle weakness.
7. Suspicion of a case of infant botulism requires treatment with BabyBIG (II-2), obtained from the California State Department of Health Services (510-540-2646).

Treatment Recommendations and Level of Evidence

1. Use of HBAT for adult and wound botulism: II-3
2. Use of BabyBIG for infant botulism: II-2
3. Use of HBAT for iatrogenic botulism: III
4. Use of HBAT for adult intestinal toxemia botulism: III

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Hymenoptera is a large order of the class Insecta and comprises the social honeybees (family Apoidea), wasps, hornets, yellow jackets (Vespoidea), and ants (Formicidae). Honeybees (*Apis* species) are social insects that live in well-organized communities and have received more attention due to the massive attacks these insects can provoke. The species *Apis mellifera* includes several subspecies, with *A. m. mellifera* and *A. m. ligustica* being the most common in Europe and *A. m. scutellata* in Africa [1].

African honeybees were introduced into Brazil in 1956 with the aim of developing a strain better adapted to South American conditions than the European forms. However, in the following year, swarms of African bees escaped from a research facility in Rio Claro in the state of São Paulo and hybridized at random with the local European bees, forming the so-called Africanized bees [2] (Fig. 1). This accident dramatically changed the incidence and pattern of massive bee attacks in the American continents.

Although the Africanized and the European bees are similar in appearance [3], the former are peculiarly aggressive, attacking in swarms with high tenacity after minimal provocation [4]. They are able to sting using a modified ovipositor found on the terminal end of their abdomen (Fig. 2). After stinging, the stinger and the venom sac (Fig. 3) are pulled out of the bee's abdomen and remain in the victim's skin. The sting occurs only once and the insect dies following the evisceration.

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Fig. 1 Africanized bee specimen from São Paulo, Brazil



Fig. 2 Bee stinger

Africanized bees rapidly spread throughout the American continent [5] and reached the USA (Texas, New Mexico, Arizona, and California) in the early 1990s [6–8], where their aggressiveness earned them the name “killer bees” [9, 10].

Massive bee envenomation is a public health issue in many countries in the Americas (South, Central, and North America). However, since reporting of beestings generally includes both allergic reactions to beestings, often from solitary stings, plus massed beesting attacks, with the former likely to be a significant majority of the total case load, such statistics cannot be easily separated and should be interpreted as an indirect evidence of the frequency, or rising frequency, of massed beesting attacks.

Most deaths are associated with few stings and occur as a result of immediate hypersensitivity



Fig. 3 Stinger and venom sac, pulled out of the bee

reactions (Type I) causing anaphylaxis. Severe local reactions, particularly those involving airway swelling and obstruction, may also be a cause of death.

Bee Venom

The venom apparatus of honeybees has an important role in the defense of the colony. Pheromone secretion is one of the main stimuli for inducing aggressive attitude in bees and guiding other bees to the victim. The quantity of venom protein released in a sting ranges between 50 and 140 μg [11], so an attack with 500–1,000 stings would deliver approximately 0.7–1.4 mg/kg of venom in an individual of 70 kg. The bee venom consists of several powerful allergens and pharmacologically active compounds, including a complex mixture of biologically active components, primarily enzymes, peptides, and amines, with some variability in toxic components between different colonies and species [12].

Phospholipase A_2 (PLA $_2$) is one of the major allergenic components of bee venom and is an enzyme that represents 10–12% of total venom [13]. It is able to destroy phospholipids, disrupting the integrity of lipid bilayers and thereby making cells susceptible to further degradation. Phospholipase A_2 also produces a series of pharmacological effects: contraction of smooth muscles, lowering of blood pressure, increase of

capillary permeability, and destruction of mast cells [14]. The synergistic action between phospholipase and bee venom melittin results in tissue damage to erythrocytes and mast cells. Phospholipase B, also known as lysophospholipase, another enzyme constituting only 1% of the venom, acts in combination with PLA₂ to destroy membrane phospholipids.

Bee venom hyaluronidase causes changes in cell permeability by altering cell membranes and disrupts collagen, thereby allowing other venom components to penetrate into the victim's tissues; it is also called the "spreading factor."

Melittin is the major component of bee venom, representing 50% of dry venom. It acts as a detergent disrupting cell membranes and liberating biogenic amines and potassium. Melittin is a protein that hydrolyzes cell membranes, alters cellular permeability, and causes histamine release. Phospholipase A₂ and melittin act synergistically, breaking up membranes of susceptible cells and enhancing their cytotoxic effects which are responsible for intravascular hemolysis and rhabdomyolysis [15]. It is also considered the constituent chiefly responsible for local pain because of the release of lysosomal enzymes from leukocytes, serotonin from thrombocytes, and histamine from mast cells [13]. Melittin has been studied in preclinical phases for its potential therapeutic application as an antiarthritis and pain reliever agent, as well as its antimicrobial and anticancer effects on different types of tumor cells and human peripheral blood lymphocytes [16, 17].

Peptide 401 (or mast cell degranulating peptide) causes mast cells to degranulate, releasing histamine and vasoactive amines, which may contribute to the toxicity of bee venom. However, in mouse models the lethality of bee venom does not appear to require this action.

Apamin is a neurotoxin that acts on the spinal cord. When injected into mice (≥ 1 mg/kg), animals develop uncoordinated, uninterrupted movements and generalized convulsions [15]. This action has not been correlated with any clinical symptomatology observed in patients suffering Africanized bee envenomation.

Bradykinin acts as an agonist on B₂ receptors, participating in vasodilatation via the release of

prostacyclin and nitric oxide, contributing to hypotension.

Adolapin inhibits prostaglandin synthetase and has anti-inflammatory actions; it has been postulated that it may be useful in the treatment of arthritis.

Histamine represents only 0.1–0.5% of the total venom but plays an important role in the inflammatory response by increasing permeability of capillaries. The catecholamines dopamine and norepinephrine enhance venom circulation by increasing heart rate. Serotonin is an irritant and contributes to pain caused by envenomation [15].

With the complete sequencing of its genome, the honeybee is now a preferred model organism for Hymenoptera species for venom characterization. Using a proteomics approach, most previously characterized venom proteins have been confirmed, and several new proteins and peptides have been described. Some of these constituents are of immunological significance [18–22].

Pathophysiology

A mouse model of subcutaneously injected venom, melittin and PLA₂, induced several pathophysiological alterations are observed precociously, such as local swelling, slower breathing, piloerection, and local muscle spasms. Coagulation disturbance is moderately observed, with enlargement in prothrombin and partial thromboplastin times and decrease in fibrinogen levels. Biochemical parameters are elevated, such as serum ALT and AST, creatine kinase (CK), creatinine, and urea nitrogen, indicating an acute liver, red blood cells, and skeletal muscle injury. The myotoxic effect of venom, PLA₂, and melittin may be demonstrated by CK increase induced by either PLA₂ or melittin and more potently by the whole venom [23]. Systemic damaging effect of very early onset on microscopic examination of the skeletal muscle shows early extensive damage in rats envenomed by Africanized bee venom. Rhabdomyolysis associated with diffuse acute inflammatory processes and vascular congestion

and increased creatine kinase levels are observed [24].

Renal histology of animals inoculated with bee venom shows acute tubular necrosis and massive tubular deposition of myoglobin [25], indicating that vasoconstriction, direct nephrotoxicity, and rhabdomyolysis are important mechanisms in the pathophysiology of bee venom-induced acute kidney injury (AKI), potentiated by the presence of hemolysis or hypotension following anaphylaxis or low cardiac output [26]. During rhabdomyolysis, the skeletal muscle is damaged, and CK, myoglobin, LDH, and AST are released into the blood and later into urine. Myoglobin may cause AKI by toxic effects on the tubule epithelial cells or inducing intratubular cast formation. The presence of myoglobin in the tubular casts, demonstrated by immunohistochemical analysis [27], reinforces the role of rhabdomyolysis in the progression of AKI after bee envenomation. In addition, myoglobin and hemoglobin are potent inhibitors of nitric oxide bioactivity and may trigger intrarenal vasoconstriction and ischemia in patients with borderline renal hypoperfusion. Renal ischemia may also occur as a consequence of a large release of norepinephrine. This may also contribute to ischemic lesions and myocardial infarction, further affecting cardiac output and causing renal ischemia [27].

Human postmortem histopathologic analysis confirms the occurrence of acute renal tubular necrosis in patients suffering hundreds of bee-stings in whom systemic rhabdomyolysis and intravascular hemolysis were observed [28–32]. Hemoglobin and myoglobin pigments, as well as erythrocytes, were found in the tubules and collecting ducts in these decedents. Thus, renal damage may involve both direct tubulotoxicity and prerenal factors such as hypotension. Generalized rhabdomyolysis and massive myoglobinemia and myoglobinuria are evidenced by increased CK levels, predominantly the CK-MM isoenzyme. Intravascular hemolysis is also a major feature of massive envenomation. Elevated serum indirect bilirubin indicates hepatocellular necrosis attributable to ischemia [28]. A toxic effect on the myocardium has been

demonstrated by the observation of necrotic cardiac myocytes [30]. Three mechanisms may be involved in the injury of myocardial cells: (a) IgE-dependent hypersensitivity reactions to venom and the vasoconstrictive effect of mast cell mediators, (b) direct toxic effects of venom, and (c) therapeutic epinephrine injection causing a decrease in coronary perfusion [33, 34].

Clinical Presentation

Bee envenomation results in a wide spectrum of clinical abnormalities, depending on the number of stings per body weight, time elapsed between the envenomation, and medical care, age, and comorbidities of the patient.

All envenomed individuals may present with some degree of local and regional reactions as a consequence of massive bee envenomation. Local pain, pruritus, erythema, and swelling at the sting site (Fig. 4) may evolve to a larger, regional reaction, mediated by allergic mechanisms and affecting parts of the body in continuity with the sting site.

A more severe type of reaction is a systemic anaphylactic response, characterized by varying degrees of urticaria, angioedema, nausea and vomiting, diarrhea, and intestinal or uterine cramping. More severe systemic reactions may include bronchospasm, laryngeal edema with inspiratory stridor, hypotension, dyspnea, loss of consciousness, cardiac collapse, and shock. Individuals who have specific IgE antibodies to allergenic components of bee venom are more susceptible to systemic reactions occurring within a few minutes of the sting.

Cases with >50 stings may develop systemic toxic reactions [35], although most cases are described in patients stung by hundreds of bees. Within 24 h post-sting, the patient may complain of generalized aches and pains, followed by brown-colored urine, as the result of rhabdomyolysis and hemolysis [28, 36–38]. Progressive increases in enzymes released from ruptured skeletal myocytes, such as CK, are seen in more than 90% of cases [30, 39]. Enzyme concentrations



Fig. 4 Male, 64 years old, stung by >500 bees, developed rhabdomyolysis and acute renal injury, recovered after supportive treatment

typically peak within the first 48 h and may be as high as 70,000 IU/L. Concentrations of other enzymes such as AST, ALT, and LDH may also be affected.

Although hemolysis also plays a role in the physiopathology of massive bee envenomation, less than 50% of patients present with jaundice or have clinical findings compatible with hemolysis [39].

Adrenergic manifestations (tachycardia, hypertension, diaphoresis, hyperthermia) are often described [40]. Cardiac involvement causing severe effects has been described in consequence of vasospasm, platelet aggregation and thrombosis, direct toxic effect, and Kounis syndrome (anaphylactic reaction). Clinically patients present atrial flutter, atrial and ventricular fibrillation, cardiomyopathy and acute coronary syndrome, ischemic stroke, and myocardial infarction [33, 41–44].

Besides infarction, reported neurological complications include encephalomyelitis, hemichorea, optic neuritis, and posterior reversible encephalopathy syndrome [43, 45–49].

Acute Kidney Injury

Acute kidney injury is a potentially life-threatening complication of massive attack by Africanized bees, especially when the patient is inflicted by 500 stings or more [28, 40, 50–52]. In

such conditions or cases, patients with AKI are unable to adequately excrete myoglobin and hemoglobin and may develop severe nephrotoxicity.

Acute kidney injury is often observed 24–72 h after envenomation [39, 52, 53], presenting with decreased or no urine output [39, 54]. Late-onset AKI has been described as a Type III hypersensitivity reaction (“serum sickness”) due to bee venom [55]. Most cases are described in elderly patients and those with underlying compromised renal function. However, children may develop AKI after 100–200 stings [56, 57], especially with late onset [58]. The duration of AKI varies from one to several weeks and is prolonged in elderly patients and those with underlying compromised renal function.

Serum blood urea nitrogen (BUN) and creatinine measurements are elevated, but do not correlate with the number of stings [37]. Besides elevation of muscle enzyme levels, myoglobinuria, and hemoglobinuria, other laboratory findings include hyperkalemia, hypocalcemia, and hyperphosphatemia [52, 56, 59].

Typically, renal function will recover, but there may be residual kidney damage [60].

Non-allergic patients attacked by swarms of bees may die as a result of the same manifestations seen in hypersensitive victims or as a consequence of systemic envenomation. The lethality rate is estimated to approximate 16%, including allergy and envenomation [39]. The median lethal dose of

honeybee venom has been estimated at 19 stings per kg or about 500 stings for adults [9, 11].

Children are at heightened risk for the effects of massive envenomation because of the larger dose of venom per kilogram body weight they receive [61], although patients older than 60 are mostly described in the severe group with higher lethality, making older age and previous kidney injury negative prognostic factors [39, 62].

Laboratory Findings

Hematologic findings of massive bee envenomation include leukocytosis with neutrophilia, which can be related to the toxic hematological and proinflammatory effects of bee venom.

In the first 24–48 h, muscle tissue enzymes (CK, AST, ALT, and LDH) rise. Total bilirubin also increases, primarily the indirect form, free hemoglobin in plasma increases, and haptoglobin decreases. The increase may persist until approximately the fourth day post-sting, with decreases from the fifth day onward [30].

Thrombocytopenia has been described, with or without coagulation changes such as prolonged or incoagulable whole-blood clotting time, international normalized ratio, activated partial thromboplastin time, and thrombin time. Serum BUN and creatinine concentrations should be assessed to monitor kidney function.

Whole venom and venom PLA₂ concentrations in serum and urine at intervals after massive bee envenomation have been quantified by enzyme immunoassay [28]. In one case, the highest whole venom antigen concentration detected on admission to hospital (3.8 µg/mL) was used to estimate the total amount of circulating venom (27.36 mg) and to estimate the number of stings received (>1,000).

Initial Management

After immediately stabilizing the airway, ventilatory requirements and assuring adequate tissue perfusion, the number of stings, allergic status, body size, historical information regarding insect sting allergy, previous cardiovascular or pulmonary diseases, and baseline renal function should be initially evaluated.

If time permits, removal of stingers still in the skin should be done as soon as possible (Fig. 5), either using a flat surface or pinching the stinger sac. Stinger removal is important to avoid further injection of the remaining venom after the bee has pulled away, although the stinger may deliver its venom content within 60 s of the sting [11, 63]. Thus, it may not be possible to remove the stingers within the time that it takes for them to empty the contents of the venom sac.

Victims must be observed closely as anaphylaxis can cause rapid clinical deterioration without



Fig. 5 Dead bees and stingers removed from the patient

warning. Cardiac monitoring, supplemental oxygen, and invasive airway management equipment must be readily available.

More severe regional reactions, and those involving multiple stings, can be initially treated in the same manner as small local reactions. However, we recommended that patients suffering from >50 honeybee stings be hospitalized and monitored closely for new onset or progression of the envenomation syndrome. Renal failure or death may occur in the range of 150–1,000 bee stings.

Treatment

The therapeutic approach to massive bee envenomation includes measures for treatment of hypersensitivity, preferably within the first hour. In cases of severe anaphylaxis, early aggressive monitoring, treatment, stabilization, and intervention are mandatory. Death may ensue quickly if the anaphylactic reaction is not managed expeditiously and appropriately. Once diagnosed, epinephrine should be given intramuscularly or subcutaneously immediately, in adults 0.2–0.5 mg of 1:1,000 solution (1 mg/mL) and children 0.01 mg/kg or 0.01 mL/kg of 1:1,000 solution (1 mg/mL). Administration may be repeated every 5–15 min as clinically indicated. For severe anaphylaxis epinephrine must be administered intravenously, in which case it must be diluted to a concentration of 1:10,000 and 0.5–1.0 mL given in adults and 0.01 mg/kg (not exceeding 1 mg) in children.

Vigilant monitoring of heart rate, heart rhythm, and blood pressure is required. Intravenous fluids are crucial to prevent vascular collapse and shock. Volumes of crystalloid solutions must be given rapidly in anaphylaxis.

Corticosteroids may benefit victims of massive bee envenomation. We recommend prednisolone sodium succinate 10 mg/kg IV, followed by prednisolone orally at 1 mg/kg bid, then tapered over 3–5 days. Intravenous infusion of saline is indicated if hypotension is present and to ensure sufficient urine output. For severe reactions, administration of fluids and electrolytes,

correction of hypovolemia, and prevention of inadequate circulation are the cornerstone of therapy. Toxic reactions to massive envenomation from multiple stings require early aggressive stabilization and therapy with fluids and may require vigilant monitoring of hematologic, cardiac, respiratory, and renal parameters for several days. Supportive therapy may be necessary until clinical stability is present. Prazosin may be used for control of hyperadrenergic states.

Dialysis is often necessary and recovery from AKI may take several weeks. Some renal damage may remain, especially in elderly patients. Rarely, conventional hemodialysis may not effectively remove myoglobin. In these cases, plasmapheresis [64] and continuous venous-venous hemofiltration [65] have been advocated.

Therapeutic Antibodies

There is an urgent need to develop antivenom to provide an effective therapeutic tool for victims of bee envenomation. In the past, an ovine bee Fab-based antivenom was produced with positive neutralization results against PLA₂ and European bee venom lethality, tested in mice [66]. However, no additional follow-up data on this antivenom has been reported. Separately, a rabbit antivenom against PLA₂ and melittin was shown to be ineffective in neutralizing venom lethality [3].

More recently, a horse antibody F(ab')₂-based antivenom was produced at our institute (Instituto Butantan) [67]. Adult horses were immunized by intramuscular injection of a mixture of 5 mg of bee venom (provided by the apiary of the Biosciences Institute of the Universidade Estadual de São Paulo, Rio Claro, southeast Brazil) and incomplete Marcol-Montanide-Tween 20 adjuvant. The obtained plasma was fractionated by adding ammonium sulfate and digested by pepsin, according to a preestablished protocol to isolate F(ab')₂ fragments and following the recommendations of the World Health Organization [68].

The antivenom obtained was effective in neutralizing *in vitro* hemolysis, myotoxicity, and hyaluronidase activity, induced by bee venom. The hemolytic action caused by 1 mg of bee

venom was neutralized by 2.4 mL antivenom (20.8 mg protein/mL). The antivenom neutralization of myotoxicity in vivo was measured by the release of creatine kinase in mouse muscle, and the effect was evaluated by morphological analysis and by monitoring the increase of plasma creatine kinase (CK) activity. The specific antivenom was able to completely neutralize the myotoxic effects and was not harmful when injected undiluted in mice [24].

To assess antivenom efficacy, we determined the effect of the neutralization antivenom on the LD50. The lethal potency of bee venom i.v. injected was 4.2 ± 0.2 µg/g of body weight. In mice, the lethal action caused by 1 mg honey venom was neutralized by 0.9 mL antivenom meaning ED50 is 1.11 mg/mL antivenom. In a case of massive bee attack involving 1,000 stings, which is considered potentially lethal for a 70 kg adult individual, it is estimated that 90 mL (9.9 mg) of antivenom would be needed to neutralize the venom effects. Scaling up the production is ongoing so as to provide antivenom for clinical studies and to assess the potential efficacy and safety of this new antivenom.

Another approach involves the production of human monoclonal single-chain Fv(scFv) antibody fragments as an alternative to inhibit systemic effects of bee venom, although studies of the neutralizing capacity of this possible antivenom are still necessary [69, 70].

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Part XXVI

Threat Agents

R. Steven Tharratt and Timothy E. Albertson

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The events of 2001, including the terrorist bombing of the World Trade Centers and the deliberate introduction of anthrax spores into the US postal system, marked a watershed in the medical planning for and response to an incident using a chemical or biologic weapon. Although much planning has focused on the prehospital and emergency department phases of these disasters, toxicology and intensive care are among the key resources in the management of the actual uses of these weapons.

Despite the popular notion of the inevitability of the threat posed by the terrorist use of chemical and biologic agents, few systematic scientific studies of mitigation efforts appropriate for civilian use have been published in the open literature. There is a paucity of systematic investigations in these areas and the majority of evidence is observational or expert consensus (level of evidence III). An Institute of Medicine study outlined priorities for research to improve the civilian medical response to terrorist incidents [1]. (level of evidence III). More recently an international task force drafted a series of consensus statements comprehensively covering the care of the critically ill in the setting of pandemics and disasters [2]. (level of evidence III). Successful management of an incident involving these weapons requires the coordinated efforts and response of a multidisciplinary team of fire, law enforcement, and medical and public health professionals and an emergency response at the federal, state, regional, and local levels. In the medical community, expertise in toxicology, emergency

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medicine, critical care, infectious diseases, and public health is required to successfully manage the medical response to these incidents. This chapter focuses on the planning for and the medical management of the severely intoxicated victims of a chemical or biologic incident.

Framing the Problem

Terrorism has many different definitions and can manifest in many different forms and venues. The US Federal Bureau of Investigation defines terrorism as “Involv[ing] acts dangerous to human life that violate federal or state law [and] appear intended (i) to intimidate or coerce a civilian population; (ii) to influence the policy of a government by intimidation or coercion; or (iii) to affect the conduct of a government by mass destruction, assassination or kidnapping” [3]. The use of a chemical, biologic, radiologic, or nuclear (CBRN) weapon as a component of a terrorist act is an extremely rare event worldwide. The vast majority of terrorist incidents in the United States have involved conventional explosives. Because most non-scientifically trained people do not understand chemical and biologic agents, they appeal to the public’s psychological fear of destruction by a powerful, imperceptible force. This fundamental fear of destruction, coupled by the intense media attention surrounding a CBRN event, fulfills the need for attention to the cause espoused by the terrorist.

Misconceptions About Chemical, Biologic, Radiologic, or Nuclear Planning

1. Medical management of a terrorist use of a CBRN weapon is the same as the medical management of a military use of a CBRN weapon.
2. Chemical terrorism incidents are the same as biologic terrorism incidents.
3. It is impossible to plan for events of this type.
4. Intensive care unit planning is the same as emergency planning in other areas of the hospital.

CBRN, chemical, biologic, radiologic, or nuclear.

To plan appropriately for terrorist incidents, a local risk assessment must be made. Incidents involving CBRN weapons may be classified appropriately as a “low-frequency/high-consequence event.” Planning for a low-frequency/high-consequence event is more successful when these contingencies are built into the framework of existing emergency plans for more common events. CBRN medical planning focuses on the similarities of patient management to the typical management of patients in intensive care units (ICUs). Several fallacies pervade planning for CBRN events. These fallacies significantly impede appropriate ICU planning. Appropriate medical planning requires an understanding of the challenges posed by the following principles.

1. Civilian medical response is not the same as military medical response.

In 1975, the United States ratified the Biological Warfare Convention, which bans the development, production, stockpiling, acquisition, and retention of biologic agents and toxins. However, during the mid-twentieth century, the United States pursued a defensive and an offensive military chemical and biologic weapons program. During this time, potentially effective medical response measures to chemical and biologic agents were developed. Although most of the experience and scientific data concerning medical management of CBRN incidents have been conducted by or under the sponsorship of the US military, the goals and use of a CBRN weapon by a terrorist are fundamentally different from the military use of these weapons. The civilian population is a more heterogeneous population, chronologically and medically, than a military force. Additional planning needs are introduced by the unknown time and location of a terrorist use of a CBRN weapon coupled with the lack of psychological preparation of the civilian population. A large amount of military medical response is predicated on minimally affecting the readiness of the military force and rapidly returning to battle as many exposed soldiers as medically possible. These concerns generally are not appropriate in the civilian population. Military doctrine refers to

Table 1 Differences between biologic and chemical agents

Biologic agents	Chemical agents
Naturally exist	Man-made
Production difficult (scientific)	Production difficult (industrial)
None volatile	Many volatile
Among most toxic agents known	Less toxic than many biologics
Infectious agents reproduce	Do not reproduce
Cannot penetrate intact skin (most)	Can penetrate intact skin
Odorless and tasteless	Odor or taste or both when exposed (most)
Effects require incubation (days)	Effects immediate
Aerosol delivery (HEPA filters protect)	Aerosol/mist/droplet delivery (self-contained breathing apparatus and vapor-tight ensembles protect)

HEPA high-efficiency particulate air

the concept of *acceptable losses*; terrorist use of a CBRN weapon produces *unavoidable morbidity and mortality* in the civilian population. From these differences, it can be seen that despite basing medical care on the data developed by the military, medical care of civilian victims of a terrorist use of a CBRN weapon requires unique planning efforts and perhaps different treatment regimens.

Differences Between Military Use and Civilian Use of Chemical, Biologic, Radiologic, or Nuclear Weapons

Goals

Military use – efficiency degradation of opponent, denial of tactical or strategic objectives, demoralization of enemy

Terrorist use – infliction of terror or death or both, media attention to cause

Other Differences

Age and medical heterogeneity of a civilian population

Physical and psychological preparation of potential victim

Known location and time (war zone) versus use at a nonmilitary location without warning

Acceptable versus unavoidable losses

2. Chemical incidents are not the same as biologic incidents.

A common pitfall equates the planning needs and management principles for these two classes of agents. Several fundamental differences exist between chemical and biologic agents (Table 1). These differences alter the latency period and the presenting signs and symptoms of victims in events involving these agents.

Chemical agents refer to man-made chemicals designed to kill or incapacitate. Several classes of common industrial chemicals produce intoxications similar to the chemical threat agents, and patient management is similar to the management of victims exposed to these industrial chemicals. Emergency medical response and hazardous material response teams are important to the management of a chemical incident.

Biologic agents refer to living organisms or their biologic products that are intended to kill or incapacitate. A successful covert use of a weapon of this type is likely to manifest as an “unusual outbreak of an unusual disease.” This outbreak is likely to be recognized initially by an astute clinician or inferred via the public health and poison control reporting infrastructures. Use of biologic weapons heavily impacts public health resources and not directly emergency response/hazardous materials teams. Although the differentiation between a natural and man-made outbreak of disease may be difficult in the early stages of the incident, the ICU management of the patients is similar.

3. It is possible to plan for a terrorist use of a CBRN weapon.

It appears daunting to plan for a terrorist attack that may result in hundreds of victims requiring intensive care. It is possible to construct extreme scenarios that can overwhelm any response plan. However, a response plan that builds on existing daily capacity, established emergency plans, and emergency procedures to respond effectively to an incident can be developed. As a general rule, it is not a prudent use of medical resources to provide for a standby capability to manage a major CBRN

incident in most locations. It is the unusual hospital system in today's medical environment that can manage even a minor CBRN incident without relying on a regional or statewide "mutual aid" and patient disbursement capability. As was seen in the critical care of repatriated Ebola infected health care workers in 2015, small numbers of victims may be better served by transport to specialized centers for intensive care rather than receiving care in inexperienced hospitals. Certain high-risk potential targets, identified through a locally based risk assessment, may require a more extensive commitment of personnel and resources. The capabilities to provide intensive care, although scalable to a certain degree, are fixed by equipment and personnel availability. When these capabilities are exceeded by the magnitude of an incident, some combination of triage and regional/national patient transfer assistance is required. It still is possible to provide for the basic management principles as outlined subsequently as part of an intensive care plan for the medical management of victims of a terrorist use of a CBRN weapon, while additional resources are marshaled and patient disbursement occurs.

4. ICU planning is not the same as emergency planning in other areas of the hospital.

The needs and planning requirements of the ICU are different from those of other areas of the hospital. Intensive care is concerned with the *successful* use of a CBRN device. These events are significantly less frequent than the *threat* or false claim of use. In 1998–1999, more than 100 hoaxes claiming the release of anthrax occurred in cities throughout the United States. These incidents triggered a significant emergency response and resulted in a major improvement in various emergency response plans [4]. None of these hoaxes proved to involve a pathologic strain of *Bacillus anthracis*, and no victims required intensive care services. Emergency departments have to plan for decontamination of victims and triage of the nonexposed "worried well" from the truly exposed. Although these plans do affect intensive care planning, these concerns are less prominent in the ICU. ICUs are more concerned with the

procurement of pharmaceuticals, life-support equipment such as ventilators, maintenance of appropriate isolation, and staffing for a prolonged high-acuity patient population. Issues such as triage of scarce resources, provision of intensive care in nontraditional areas of the hospital, and forgoing or terminating futile therapy all assume significant planning needs for ICUs. There are key planning considerations in the development of a critical care response plan.

Key Components of Intensive Care Planning for Chemical, Biologic, Radiologic, or Nuclear Events

Provision of high-acuity-level staffing for prolonged periods

Procurement of pharmaceuticals, antidotes, antimicrobials, and equipment (e.g., ventilators)

Provision and proper use of appropriate personnel protective equipment

Indications for cohort nursing

Interface with hospital epidemiology and community public health

Disposal of large amounts of potentially biohazardous waste

Provision of critical care in nontraditional areas of the hospital

Austere critical care

Triage within the intensive care unit

Termination of futile therapy

Psychological support for caregivers

Intensive media focus and interest

Chemical Agents

The chemical threat agents of interest to ICUs include the organophosphate nerve agents, the cyanides, the vesicants, and industrial chemicals with predominantly respiratory effects, including phosgene and chlorine. Each of these chemical threat agents is clinically similar to more commonly encountered industrial chemical analogues and has similar management strategies (Table 2). The medical management of exposures to these

Table 2 Typical chemical threat agents

Threat agents	Military identification	Industrial chemical with similar nature
Nerve agents	Nerve agents	Organophosphate pesticides
Cyanide	Blood agents	Cyanides
Phosgene	Pulmonary (choking) agents	Chlorine
Vesicants	Blister agents	Acids and other corrosives

more common chemical agents is discussed in depth elsewhere in this book. Treatment recommendations for the terrorism related agents are largely composed of level III evidence [5]. This chapter focuses on the clinically significant differences in the medical management of these chemical threat agents versus their more commonly encountered industrial analogues.

Nerve Agents [6]

Nerve agents are among the most toxic of the chemical threat agents. Although they are referred to in the popular literature as *nerve gases*, all are liquid at room temperature. Although these agents were originally synthesized by the Germans during World War II in search of alternatives to the embargoed insecticide nicotine, their toxicity for mammalian nervous systems soon was appreciated. All of these agents (sometimes referred to as *G agents*) are organophosphate compounds. They differ from the more commonly encountered organophosphate pesticides in that the organic side chains are relatively short (ethyl and methyl moieties), and they differ in the electronegativity of the leaving group (usually containing fluorine or a cyano group). The volatility of these agents is slightly less than that of water. Volatility determines in part the onset of symptoms and the persistence of these agents in the environment. Another nerve agent, *O*-ethyl S-diisopropylaminomethyl methylphosphonothioate, usually referred to as VX, has a significantly lower volatility and vapor pressure, resulting in more persistence in the environment and on clothing. The nerve agents all are potent

irreversible inhibitors of acetylcholinesterase and butyrylcholinesterase in humans. Organophosphorus-containing pesticides may present similarly and are more widely available. The principles of ICU management are similar [5].

Although it is claimed that several “recipes” for the synthesis of nerve agents circulate on the “Dark” Internet, a review of these pages (accessed May 2015) show little more than reaction equations. The chemistry involved in the actual synthesis of these agents, together with knowledge of the appropriate reaction conditions, requires a significant background in synthetic chemistry. This background, the tight controls placed on the likely precursor materials, the reactivity of several of the intermediate products, the requirement for specialized reaction systems, and the need for containment of the resulting agent make the actual successful synthesis of nerve agents beyond all but the most sophisticated, well-funded terrorist groups. The production of sarin by the Aum Shinrikyo cult was estimated to cost \$30 million, involved 80 persons led by a Ph.D.-level scientist, and took at least 1 year to synthesize [7].

Clinical Effects

Exposure to nerve agents occurs usually via respiratory exposure to vapor, although skin exposure to a liquid agent may occur. The few case reports of industrial exposure to sarin vapor described significant miosis, rhinorrhea, mild respiratory distress, and wheezing in the victims [8]. These signs and symptoms also were observed in the victims of the Japan sarin incident. Victims who have continued exposure to the agent rapidly progress to unconsciousness, fine motor fasciculations, respiratory failure, and cardiovascular collapse. The timing and progression of symptoms depend on the dose delivered and the exposure circumstances. Clinical effects develop almost immediately after vapor exposure; they can be delayed several minutes if cutaneous exposure to a liquid agent occurs. Cutaneous exposure also may produce local sweating and muscle fasciculations at the site of contamination followed by nausea and vomiting.

Decontamination

Rapid scene decontamination of victims is required for any contact with a liquid nerve agent. Because of the toxicity of these agents and the time required for patients to arrive to the ICU, it is unlikely that any nerve agent remains on the skin when victims are admitted to the ICU. It is possible that an agent could be present in the hair, nail beds, and other areas where it has not been adsorbed. It is vital to confirm that adequate decontamination has occurred on arrival of the victim in the ICU. If any doubt about the adequacy of decontamination exists, careful skin cleansing with soap and water by ICU personnel clothed in personal protective equipment equivalent to universal (barrier/splash) precautions is required. Particular attention should be directed to the poorly adsorbed areas of the scalp and nail beds and other areas commonly missed in rapid scene or emergency department decontamination, including armpits, perineum, interdigital areas, and feet. Although nerve agents hydrolyze more rapidly in the presence of sodium hypochlorite, the potential toxicity of this agent on ocular tissue and mucous membranes makes the use of specialized decontamination solutions unnecessary in the ICU.

Stabilization

Stabilization of a patient exposed to a nerve agent is identical to the management of an organophosphate-exposed patient. Rapid decontamination, aggressive airway control, and respiratory support with assisted ventilation usually are accomplished in the prehospital area and emergency department. A significant difference between nerve agent and other organophosphate intoxications is the amount of atropine required to modulate the muscarinic symptoms. Atropine doses of 2–20 mg usually stabilize a victim exposed to a nerve agent [8]. This dose is significantly less than the hundreds of milligrams of atropine that may be required in some cases of pesticide intoxication [9]. The relatively lower doses of atropine required to reverse the muscarinic effects of nerve agents are not understood completely; it may be due in part to the potency of the agents compared

with industrial organophosphate agents. The clinical pharmacology of atropine use is described in detail in ► [Chap. 138, “Atropine.”](#)

Oxime Therapy

After decontamination, stabilization of the patient, and reversal of muscarinic symptoms with atropine, regeneration of the organophosphate-inhibited cholinesterase by oxime therapy is required (Level III evidence). When acetylcholinesterase is inactivated by a nerve agent, the enzyme can be reactivated either by spontaneous hydrolytic cleavage (a minor pathway with nerve agents) or by use of a nucleophilic oxime antidote. If neither occurs, the nerve agent–acetylcholinesterase complex undergoes dealkylation – a process referred to as *aging* – rendering the enzyme irreversibly inactivated. The speed of the aging process depends on the specific nerve agent. The aging half-lives range from a few minutes with soman (GD) [8] to 48 h with VX [10]. Sarin and tabun are intermediate, with aging half-lives of 3 h and 14 h, respectively [8]. Oxime therapy is most effective when administered within these half-lives. The implication is that successful oxime therapy likely requires prehospital or emergency department use of oximes to be most effective in cases of soman and sarin exposures. Some prehospital providers have access to Military Mark I kits, which contain 2 mg of atropine and 600 mg of pralidoxime chloride in autoinjectors for intramuscular injection. These providers are trained to administer the contents of three Military Mark I kits to victims exhibiting severe nerve agent poisoning.

Although other oximes have shown promise, pralidoxime chloride (Protopam Chloride) remains the only oxime approved for use in the United States. Ideally, it is infused intravenously at a dose of 15–25 mg/kg although larger doses may be required [5, 10]. Hypertensive effects of this drug are minimized by slow (over 30 min) infusion. Pralidoxime chloride is formulated in 600-mg autoinjectors for intramuscular use in the field (Military Mark I kit). These devices may be the only source of pralidoxime chloride available in the early hours after a significant incident because few hospitals that do not see

organophosphate-intoxicated patients on a regular basis stock sufficient supplies of pralidoxime chloride to treat more than one or two patients. The clinical pharmacology of oximes is covered in detail in ► [Chap. 158, “Oximes.”](#)

Care in the ICU

Patients who survive to be admitted to the ICU are at risk of developing seizures. Control of seizure activity induced by nerve agents is identical to control of other chemically induced seizures and may include benzodiazepines, barbiturates, and propofol. Diazepam is used widely by the military for seizure control; it is packaged in 10-mg autoinjectors for field intramuscular injection. There are no data to suggest, however, that diazepam is any more effective than the newer benzodiazepines [5].

Considerable anxiety and uncertainty may surround the need for isolation of critically ill victims and respiratory protection of the health care team. This anxiety is extrapolated in part from the uncertainty of the appropriate levels of protective equipment required for field health care workers and emergency department personnel. Assuming that emergency field decontamination with complete clothing removal, followed by additional skin decontamination in the emergency department, has occurred, the risk of significant contamination of the ICU is small. These agents do not off-gas from victims, so the standard barrier protective equipment available to the ICU should suffice to protect the health care team. The development of miosis or rhinorrhea in any members of the ICU team should trigger a reassessment of the adequacy of patient decontamination.

A more detailed review of these agents is found in ► [Chap. 135, “Nerve Agents.”](#)

Cyanide

The physiochemical properties of cyanide make successful mass casualty use of this chemical weapon by a terrorist difficult. Cyanides are not an effective weapon in outdoor use and are more likely to be encountered as an agent of product tampering, homicide, suicide, or assassination. Law enforcement personnel are familiar with the

use of cyanide salts in booby trap-type devices. Cyanide vapors are highly toxic in closed space encounters, prolonged vapor exposures, and ingestions. If vapor exposure is terminated immediately, recovery can be rapid, even without antidote use. The management of victims exposed to cyanide fumes is identical to the management of victims exposed industrially to cyanide and is covered in ► [Chap. 97, “Cyanide: Hydrogen Cyanide, Inorganic Cyanide Salts, and Nitriles.”](#)

Vesicants

Vesicants have the capability to produce severe cutaneous, ocular, and respiratory damage. Formation of large blisters after vesicant exposure is classic. During World War I, the vesicants resulted in the largest number of chemical casualties. Although considered a major chemical threat agent by the military and suspected of being used in regional conflicts in the Middle East, there has been little use of vesicants by terrorist groups. The principal agents in this class include mustard and lewisite. There is little evidence-based treatment recommendations (level III) available with most treatment recommendations being supportive care [5].

Mustard [11]

Chemistry and Pathophysiology. Sulfur mustard, bis-(2-chloroethyl) sulfide, distantly related to the alkylating chemotherapeutic agents, is a highly reactive electrophilic molecule that alkylates cellular DNA immediately on contact. Mechanisms involving cellular depletion of glutathione and free radical-induced cellular damage also have been proposed to explain the toxicity of mustard. Mustard exists as an oily liquid with a high vapor density and relatively low volatility. Exposure to mustard is likely through direct contact with the liquid agent or inhalation of vapor. The target organs of mustard exposure include the skin, eyes, and respiratory tract. Mustard does not produce immediate pain or symptoms, even though the cellular damage occurs within minutes after exposure. It is unique among the chemical agents in its lack of immediate symptoms of exposure. Cutaneous exposure to mustard produces

erythema approximately 4–8 h after exposure. The development of fluid-filled blisters occurs 2–18 h later. Ocular exposure initially produces a conjunctivitis that progresses in approximately 12 h to blepharospasm, corneal ulcerations, and occasionally panophthalmitis. Mustard produces dose-dependent inflammation and necrosis of the upper and lower respiratory tracts. This necrosis can result in pseudomembrane formation and obstruction of the tracheobronchial tree and secondary bacterial infection. Cough, hoarseness, and sinus tenderness may be present.

Decontamination and Treatment. Because of the speed by which mustard produces cellular damage, decontamination must occur within 1–2 min after contact to be effective. Thorough decontamination of the victim is required to protect the health care team from secondary contamination resulting from residual mustard liquid on skin or clothing. Treatment of mustard exposure is supportive and is similar to the management of other chemically induced burns. Respiratory support and bronchoscopy may be required for significant respiratory system involvement. Because of the alkylating effects of these agents, severe exposures may result in bone marrow suppression and require blood product or factor support. A detailed discussion of these agents is found in ► [Chap. 136, “Sulfur Mustard.”](#)

Lewisite

Lewisite, chlorovinyldichloroarsine, an arsenical vesicant, differs from mustard in its ability to produce immediate pain and stinging on contact. Lewisite produces clinical effects similar to those of mustard, although the onset of symptoms is much faster than with mustard. The development of immediate pain and irritation after contact with lewisite reduces the duration of ocular and respiratory exposures. Large exposures to lewisite may produce an increased capillary permeability syndrome with resultant shock. A specific antidote, British antilewisite, reduces the severity of injury when applied topically and ocularly. Preparations of British antilewisite for ocular and cutaneous use no longer are manufactured. Intramuscular British antilewisite may reduce systemic effects

for lewisite exposure, although clinical studies are lacking [5].

Chemicals with Predominantly Respiratory Effects

A wide variety of chemicals potentially available for terrorist use produce toxic vapors or gases [12]. These include the traditional chemical threat agents phosgene and chlorine, the nontraditional toxic by-products of conventional explosives, and the pyrolysis products of Teflon (perfluoroisobutylene). These chemical agents may produce toxicity via asphyxiation, direct corrosive effects on the respiratory system, or systemic toxicity. A key physiochemical property determining the location and extent of injury is the water solubility of the compound. Because the respiratory system is lined with a water-rich mucosa, chemicals with low water solubility are able to penetrate deeper into the lower respiratory system. These compounds also have poor warning properties because eye, nose, and upper airway irritation may be minimal or absent. Management of exposures to these chemicals follows standard medical approaches to industrial chemical exposures. Termination of exposure, scene decontamination, aggressive management of the airway, and respiratory support should be accomplished in the prehospital or emergency department setting. Noncardiogenic pulmonary edema or adult respiratory distress syndrome or both may supervene within 24 h. Management is identical to management of adult respiratory distress syndrome induced by other etiologies. There are little data (level III evidence) to support the prophylactic use of corticosteroids or inhaled sodium bicarbonate [5].

High-temperature pyrolysis of Teflon-containing substances produces perfluoroisobutylenes. Inhalation of this chemical produces a syndrome of fever and rapid development of pulmonary edema within 1–4 h (polymer fume fever). This edema may be worsened by significant exertion in the immediate postexposure period. Treatment is supportive. Inhalational

fevers are discussed in greater detail in ► [Chap. 100, “Irritant and Toxic Pulmonary Injuries.”](#)

Biologic Agents

Recognition

Biologic agents present more of a planning challenge to intensive care because the toxicity of these agents results in victims who potentially require prolonged critical care services and because of the geographic dispersion of victims that occurs during the incubation period. The delay from agent exposure to disease manifestation (due to the incubation period of most biologics) in the setting of worldwide rapid transportation systems makes it possible for a victim to be exposed to a biologic agent on one continent and manifest disease on another. The lack of immediate symptoms after exposure is a significant difference between chemical and biologic agents. This distinction is crucial because a successful covert use of a biologic agent is likely to manifest as an unusual outbreak of an unusual disease. The initial recognition of a terrorist event is likely to be made by an astute clinician recognizing an unusual outbreak of disease. The investigation of an outbreak of this type follows basic epidemiologic investigative principles, although there is tremendous pressure to accelerate the process. Most of the biologic threat agents exist naturally in the environment as zoonoses (e.g., anthrax and plague), represent rare intoxications (e.g., botulism), or typically present in geographically defined epizootic outbreaks (e.g., hemorrhagic fever viruses). Table 3 lists the biologic agents believed to present threat for terrorist use.

The requirements for successful use of a biologic agent arguably have been oversimplified in the popular press. Although much is written about the “ease” with which pathologic bacteria or viruses may be obtained, isolated, or genetically modified, the difficulty of producing large volumes of infective material and converting this material into a form and size suitable for delivery

Table 3 Critical biologic agents

Bacterial agents
<i>Bacillus anthracis</i> (anthrax)
<i>Yersinia pestis</i> (plague)
<i>Francisella tularensis</i> (tularemia)
Bacterial toxins
<i>Clostridium botulinum</i> toxin (botulism)
Viral agents
Variola (smallpox)
Filoviruses
Ebola hemorrhagic fever
Marburg hemorrhagic fever
Arenaviruses
Lassa fever
Argentine hemorrhagic fever

Adapted from Biological and Chemical Terrorism: Strategic Plan for Preparedness and Response: Recommendation of the CDC Strategic Planning Workgroup. MMWR Morbid Mortal Wkly Rep 49(RR-4), 2000

to victims is underestimated. The Aum Shinrikyo cult apparently tried unsuccessfully to deliver biologic agents on multiple occasions without any evidence of successful infection [14]. In 1346 in the siege of Caffa, the corpses of plague victims were hurled into the city via catapult. This vignette illustrates the importance of the delivery system in the successful use of a biologic weapon!

Because many of the threat biologic infections present with similar nonspecific early symptoms and rapidly progress to a clinical picture indistinguishable from septic shock, it is likely that the initial victims would reach the ICU without a specific diagnosis being established. Because most of these threat infections are rare and because most physicians have never seen a case of plague, inhalational anthrax, or tularemia, they often are not included in the differential diagnosis of septic shock. Multiple cases of unexplained sepsis occurring in previously healthy young individuals should trigger the suspicion of a possible biologic outbreak. Further complicating the ability to reach a specific diagnosis rapidly is that many of the threat agents are not cultured in the microbiology laboratory because they resemble contaminants that routinely are discarded or not worked up further (*Bacillus*) or because the

appropriate medium is not plated routinely (tularemia and some *Salmonella* species). Because few case series of antimicrobial therapy of these uncommon diseases have been reported, and randomized trials of treatment regimens are sparse, antibiotic recommendations are largely anecdotal, derived from in vitro sensitivities of antimicrobials to the organism or extrapolated from animal models of disease (level III evidence).

Level of Isolation

Among the earliest decisions to be made in the ICU is the appropriate level of isolation of victims. This level is determined largely by the identification of the infecting organism. Early uncertainty as to the etiologic organism or fear and emotional reaction to the terrorist event often lead to maximal isolation – “just in case.” This irrational isolation may have adverse effects on personnel and resources. Most biologic threat agents either have no person-to-person transmission potential (anthrax) or have limited transmission potential (plague and hemorrhagic viruses). This limited potential for transmission should not be equated with minimal need for rigorous biocontainment protocols. As was seen with the Ebola outbreak in 2015, nosocomial transmission of virus occurred requiring the rapid development of detailed personal proactive equipment use protocols [15]. The major exception to limited transmission likely is smallpox, which may have significant secondary transmission potential. Cohort care and quarantine procedures may be appropriate if an outbreak of smallpox is suspected. Because skin adsorption of these organisms does not occur, barrier isolation (universal precautions) with HEPA level air filtration, respirators, and masks is sufficient to care for most patients in the emergency situation of an ICU with multiple victims. Additional patient decontamination beyond the emergency field decontamination is of a lower priority with biologic agent exposure compared with chemical agents. Because of static electrical charge, most crude biologic weapons

likely constructed by a terrorist group do not resuspend back into the air or produce secondary contamination of the health care team. A thorough shower or bed bath with antiseptic soap should suffice to decontaminate ICU patients adequately.

Chemoprophylaxis and Vaccination of the Health Care Team

The need for prophylactic antibiotic and vaccine administration for members of the health care team must be considered carefully. This need must be based on the transmission potential of the agent together with the ability of prophylactic antimicrobial therapy to prevent or attenuate disease. It is not reasonable to ask health care providers to care for patients at personal risk if an appropriate prophylactic regimen is available but not used. Fear and uncertainty regarding appropriate chemoprophylaxis can lead to inappropriate self-medication. Firm recommendations for prophylactic treatment of health care team members who have *not* been exposed in the terrorist incident have not been reported. Smallpox requires vaccination of treating personnel as soon as possible with vaccinia vaccine. If possible until arrival of the vaccine, victims should be cared for by previously vaccinated caregivers, who may be afforded at least partial immunity. Anthrax, because of lack of person-to-person transmission, probably requires no prophylaxis for caregivers. Cases of plague, particularly the pneumonic form, may be appropriate for health care team prophylaxis with a fluoroquinolone or doxycycline. Effective prophylactic antivirals currently do not exist for the viral hemorrhagic fevers.

Specific Agents

Anthrax

Anthrax (*B. anthracis*) is a gram-positive, nonmotile, spore-forming bacillus that has a worldwide distribution. Because of its ability to form long-lived, environmentally resistant spores, anthrax has significant potential as a biologic threat

agent. Anthrax naturally exists primarily as a zoonotic disease of cattle that become infected by ingestion of spores. Humans become infected by contact with infected animals or their contaminated products, such as wool, meat, or hides. Virulence factors in *B. anthracis* include an antiphagocytic capsule and two exotoxins, lethal and edema. Clinical disease in humans usually manifests as cutaneous anthrax, gastrointestinal anthrax, or inhalational anthrax. Inhalation of anthrax spores produces a hemorrhagic mediastinitis after an incubation period of 1–6 days. Although this incubation period is cited widely, an epidemiologic investigation of an anthrax outbreak in Sverdlovsk, Russia, in 1979, ascribed to an airborne release of weaponized anthrax, suggested that the incubation period may be as long as 45 days [16]. The mediastinitis rapidly progresses to septic shock. Meningitis may occur and manifest as seizures. When symptoms develop, even with aggressive supportive care, mortality of inhalational anthrax is estimated at 85%. The mortality of the inhalational anthrax series in the eastern United States in 2001–2002 was 45%.

Consensus recommendations (Level III evidence) for the medical management of a terrorist use of anthrax exist [17, 18]. Anthrax infection is treated with combination antimicrobial therapy often including high-dose penicillin [19]. Tetracycline, chloramphenicol, and erythromycin have also been suggested. In vitro activity has been shown against anthrax by the fluoroquinolones, gentamicin, vancomycin, and clindamycin – although there is not as much clinical experience with these drugs. Two antitoxins, raxibacumab and anthrax immune globulin, may also have utility in treatment [18]. In the early stages of an anthrax outbreak, the scarcity of antibiotics may require use of a variety of treatment regimens until the arrival of one of the predeployed national pharmaceutical caches. These caches, controlled by the US Public Health Service, are intended to supply a medical community rapidly with sufficient pharmaceuticals to treat the victims of a chemical or biologic incident.

Prophylactic antimicrobial treatment beginning within 24 h after exposure to anthrax aerosol confers protection against the development of disease in a primate model [20]. Ciprofloxacin, doxycycline, and penicillin were the antibiotics used in conjunction with active immunization with the human anthrax vaccine. This vaccine is produced from filtrates of an attenuated *B. anthracis* and contains predominantly protective antigen. Exposed victims not manifesting signs of illness need to receive prophylaxis with antibiotics as soon as possible after exposure and continue on oral antibiotics until vaccination with anthrax vaccine can be accomplished.

Plague

The causative agent of plague, *Yersinia pestis*, a gram-negative, nonsporulating, non-lactose-fermenting bacillus, that exists worldwide. Transmitted by fleas to rodents, *Y. pestis* normally produces enzootic infection in rodents. Intermittent epizootic outbreaks in rodents, particularly in rural areas, allow for human infection, usually from bites by infected fleas. Several virulence factors of *Y. pestis* have been identified and are coded for both chromosomally and on three plasmids. Because natural outbreaks of human disease sporadically occur, distinguishing a natural epizootic infection from a deliberate act may be difficult in the early stages of the outbreak.

Plague manifests in humans in the bubonic form, a suppurative lymphadenitis in the regional nodes draining the fleabite site; a primary septicemic form, similar in clinical presentation to other gram-negative septic states; and a primary pneumonic form, contracted from inhalation of an infectious *Y. pestis* aerosol. Septicemic plague also can develop into secondary pneumonic plague by involving the respiratory system. Plague often is suspected when a patient presents with the bubonic form, but less so when patients present with primary plague septicemia. A review of naturally occurring epizootic plague cases in New Mexico revealed that the correct diagnosis was suspected in 69% of bubonic patients but only 17% of the primary septicemic patients. Diagnosis of these

septicemic patients took 1 day longer (5 days), and the overall mortality was 33% [21]. Diagnosis of plague is made by Gram stain or direct fluorescent antibody stains of aspirates from the buboes and is confirmed by culture.

Because of the potential for person-to-person transmission of plague, plague patients with pneumonia and suspected primary pneumonic plague patients need strict isolation for the first 4 days of antibiotic therapy. Consensus treatment recommendations for plague include streptomycin and doxycycline [19]. It is unlikely that large amounts of these antibiotics would be available for treatment of multiple patients early in an outbreak. Gentamicin also has been used clinically. *In vitro* activity against *Y. pestis* has been shown by cefotaxime and levofloxacin [19]. A murine model of pneumonic plague showed the efficacy of ciprofloxacin and high-dose (20 mg/kg) gentamicin [23].

Tularemia

Tularemia, a zoonotic disease with worldwide distribution, is produced by *Francisella tularensis*, a gram-negative aerobic bacterium. Its principal animal reservoir is in several species of tick. Rabbits and other small mammals maintain the infection in nature. Humans become infected either via inhalation of an infectious aerosol or via breaks in the skin. Extremely low numbers of bacteria, on the order of 10–50 organisms, are sufficient to produce disease [24]. Most patients who cutaneously contract tularemia present with ulcers on the skin or mucus membranes, together with lymphadenopathy. Inhalational infection results in a nonspecific syndrome of fever, chills, headache, and myalgias. Pulse-temperature disassociation may be present, having been described as typhoidal tularemia. Diagnosis of tularemia is made by serologic evidence of infection or culture of the organism from fluids. Streptomycin is the current antibiotic of choice for treatment [19]; however, it is unlikely that a hospital would have sufficient stores of this antibiotic to treat multiple patients. Clinical experience supports the use of gentamicin. Ciprofloxacin and

doxycycline have afforded protection in animal challenge studies [25].

Botulism

The neurotoxins produced by clostridial organisms rank among the most potent toxins known. *Clostridium botulinum*, an anaerobic, spore-forming bacterium, elaborates seven neurotoxins that are capable of producing a flaccid descending paralysis with prominent bulbar symptoms. The bacterium has a worldwide distribution and usually produces intoxication via ingestion of contaminated food products. Direct multiplication of the agent in infants results in infant botulism [26]. Intravenous drug abusers can contract botulism via injection of contaminated illicit drugs [27]; in rare cases, direct contamination of open wounds produces wound botulism. These routes of exposure constitute the “typical” cases of botulism. In addition to these routes, direct inhalation of the purified toxin is a potential terrorist route of exposure.

Bulbar symptoms, including diplopia, ptosis, dysphagia, and dysarthria, are among the earliest manifestations of botulism. Muscle weakness progresses in a descending fashion until respiratory failure supervenes. The absence of convulsions can differentiate botulism from nerve agent exposure. Botulism differs from the other biologic agents discussed in the absence of fever and a nonspecific viral-like syndrome. Because of the small amount of botulinum toxin needed to produce disease from inhalation, it is unlikely that serologic examination of blood would yield the diagnosis. Enzyme-linked immunosorbent assay identification of the toxin from samples obtained from nasal mucosa identifies inhalational botulism in primate models.

Early administration of botulinum immune globulin can attenuate symptoms; however, it is less effective after the disease manifests. In the USA with the exception of Alaska and California, which control their own supplies of immune globulin, botulinum immune globulin is controlled by the Centers for Disease Control and Prevention (CDC) [18]. A toxoid exists for preexposure

prophylactic use. Botulism is discussed in greater detail in ► Chap. 132, “Botulism.”

Smallpox

Variola virus, the causative agent of smallpox, is a member of the Poxviridae family of double-stranded DNA viruses. Because of the absence of an animal reservoir, natural smallpox was eradicated worldwide in 1977. Currently, smallpox virus exists officially in only two locations – the CDC in the United States and laboratories in Russia. Clandestine stockpiles of variola virus may exist in several other countries. The high contagion rate of smallpox together with the virtual absence of immunity to the natural disease ranks smallpox among the most dangerous of the biologic threat agents.

Smallpox is infectious by aerosol and through contact with infectious lesions. Mortality in unvaccinated victims is approximately 30%. Immunity conferred by vaccinia vaccination wanes after approximately 10 years. Persons previously vaccinated would be expected to have an attenuated form of variola with an estimated mortality of 3%.

The lesions of variola resemble other vesicular exanthems, especially varicella (chickenpox). Because most clinicians practicing today have never seen a case of variola, the possibility exists of delay in recognizing the disease. Table 4 highlights some key differences distinguishing varicella and variola lesions. Consensus recommendations for management of terrorist use of smallpox have been published [18, 28].

Even a small suspicion of smallpox infection requires immediate strict isolation. The suspected diagnosis must be reported immediately by telephone to public health personnel because this

disease has international quarantine requirements. A single case of smallpox would strongly suggest that a bioterrorism event has occurred. Treatment of smallpox is largely supportive, although the antivirals tecovirimat and cidofovir are in late stage development [18].

Viral Hemorrhagic Fevers

Several RNA viruses from diverse families share the ability to induce an acute febrile illness in humans with profound increased vascular permeability and shock. These syndromes all have high morbidity and mortality. Most of these viruses have an animal host, although some (e.g., Ebola) have not had the animal reservoir conclusively identified. Table 5 lists the hemorrhagic viral agents considered to be threats.

The development of clinical illness varies with each agent and depends on the route of exposure, viral virulence factors, and host responses to infection. The onset of a viral prodrome, with fever, malaise, conjunctival injection, and myalgias, rapidly develops into shock with generalized bleeding from the mucous membranes. The degree of hemorrhagic manifestations is variable, being less in Lassa fever and more prominent in Ebola hemorrhagic fever. Diagnosis of a hemorrhagic fever is made initially on a clinical basis with confirmation by immunologic identification of antibodies to the virus. The patient’s travel history usually is a key part of the history to suggest the particular etiologic virus. This history is not present with a terrorist use of one of these agents. Although the virus usually can be isolated from the patient, the virulence of these agents requires special containment procedures, and viral culture

Table 4 Key features for distinguishing between variola and varicella

Feature	Variola (smallpox)	Varicella (chicken pox)
Incubation	7–17 days	14–21 days
Prodrome	Fever 2–4 days before rash	None
Pock aging	Synchronous	Asynchronous
Pock spread	Centrifugal	Centripetal
Pock location	Involves palms and soles	Seldom involves palms and soles
Infectivity	From exanthem until vesicles scab	1 day before exanthem until vesicles scab

Table 5 Threat of viral hemorrhagic viruses

Disease	Virus (family)	Natural distribution
Ebola hemorrhagic fever	<i>Filovirus</i>	Africa
Marburg hemorrhagic fever	<i>Filovirus</i>	Africa
Lassa fever	<i>Arenavirus</i>	Africa
Argentine hemorrhagic fever	<i>Arenavirus</i>	South America

attempts are carried out only in highly specialized and secured laboratories.

Treatment of hemorrhagic fevers is supportive; volume replacement, correction of reversible coagulation abnormalities, and blood product support are crucial. Case reports of critical care management of ebola have been published [29]. Ribavirin has been shown to have activity against Lassa fever [30] and hemorrhagic fever with renal syndromes produced by viruses in the Hantavirus genus [31]. A loading dose of 33 mg/kg, 16 mg/kg every 6 h for 4 days, and 8 mg/kg every 8 h for 3 additional days seems effective. Barrier precautions seem to be effective for naturally occurring outbreaks of these diseases. No vaccine exists for these viruses except for yellow fever vaccine although several vaccines and antiviral therapies are under active investigation for Ebola virus.

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History of the Use of Nerve Agents

Nerve agents are organophosphate (OP) compounds, similar to OP pesticides, and are a group of potentially lethal chemical warfare agents (CWA). They are extremely potent inhibitors of the enzyme acetylcholinesterase (AChE), a key regulator of cholinergic neurotransmission. Early attempts in the synthesis of OP were made by Von Hofman, who developed methylphosphor chloride in 1873. Michaelis in 1903 introduced a compound with P – CN bond, which led to the synthesis of many OP compounds, including the nerve agent tabun. Lang and Von Kreuger synthesized compounds with P – F linkage in 1932. Schrader developed sarin and tabun in 1937; in 1944, Germans developed soman. British scientists developed VX in 1952 [1].

Exposure of nerve agents to humans was restricted to one prospective study with VX and sarin and to case reports of treatment of accidental exposure to sarin and soman [2]. The first reported use of nerve agents in a war occurred in February 1984 in Majnoon Island, by the Iraqi army against the Iranian troops. The nerve agent tabun was found in the environmental samples and in the postmortem examination of the patients who died soon after exposure. More than 300 patients died within 30 min of exposure in the field, and several thousands were poisoned by tabun [3]. Toxicologic analyses of the blood, urine, skin, and gastric juice of the chemical war gas victims revealed tabun and sulfur mustard [4]. Later in 1987 and 1988, particularly during the Halabjah massacre, another nerve agent (sarin) also was identified [5].

A presumed terrorist attack with sarin occurred in a residential area of the city of Matsumoto, Japan, on June 27, 1994. About 600 residents and rescue staff were poisoned; 58 were admitted to hospitals, and 7 died [6]. On March 20, 1995, terrorists released sarin at several points in the Tokyo subway, killing 11 and poisoning more than 5500 people [7]. United Nation has confirmed that sarin was used on 21 August 2013 in Ghouta area of Damascus, Syria [8].

Relevant Chemistry

Nerve agents are divided into two groups of G (comes from Germany) and V (abbreviated from Victory, as the British who first synthesized after the World War I victory, named it) agents. The G agents (except for tabun, which is a cyanide derivative) are fluorinated OP compounds. The V agents are sulfur-containing OP compounds. The principal G agents, GA, GB, and GD, have the common names of tabun, sarin, and soman, respectively. The other G agents and V agents do not have common names. The oldest and most common V agent is called VX. The names and chemical structures of all nerve agents are summarized in Table 1.

Although both G and V agents are commonly called nerve gases, they exist under temperate conditions as clear, colorless, viscous liquids with high boiling points. They become aerosolized when dispersed by spraying or by an explosive blast from a shell or bomb. The G agents are only moderately volatile (vapor pressure of <2 mmHg at 20 °C), but owing to their great

Table 1 Names and chemical structures of nerve agents

Short name	Common name	Synonym	Chemical name
GA	Tabun	mLe-100	Ethyl dimethylphosphoramidocyanidate
GB	Sarin	Zarin	Isopropyl methylphosphonofluoridate
GD	Soman	Zoman	Pinacolyl methylfluorophosphonate
GE	–	–	Isopropyl ethylphosphonofluoridate
GF	–	–	Cyclohexyl Methylphosphonofluoridate
VX	–	–	O-Ethyl-S-(2-diisopropylaminoethyl)methylphosphonothioate
VE	–	–	O-Ethyl-S-(2-diethylaminoethyl)ethylphosphonothioate
VG	–	–	O,O-Diethyl-S-(2-diethylaminoethyl)phosphonothioate
VM	–	–	O-Ethyl-S-(2-diethylaminoethyl)methylphosphonothioate

toxicity, the vapors pose a significant inhalational hazard. Vapor pressure of the G agents is sufficiently high for the vapor to be disseminated rapidly. GB (sarin) is mainly a vapor hazard. VX is less volatile and is normally a liquid contact hazard. Delivery systems of nerve agents include bombs, missiles, cluster spray, and spray tanks. G agents spread rapidly on surfaces such as skin and in the lungs. They are dispersed within hours and are described as *nonpersistent agents*, whereas VX spreads slowly and remains in the place for weeks or longer after exposure and is thus called a *persistent nerve agent*. Clothing releases G agents for about 30 min after contact with vapor [9]. If G agents are released into the air, they are degraded rapidly by reaction with photochemically produced hydroxyl radicals and have an estimated half-life of 10 h.

Nerve agents are four to six times more dense than air. As a result, they tend to remain close to the ground and pose a risk particularly to people in low areas and below-ground shelters. The nerve agents are soluble in water, organic solvents, and fat. After contact with water, they are hydrolyzed to products that are less toxic than the parent compounds [10].

Pathophysiology

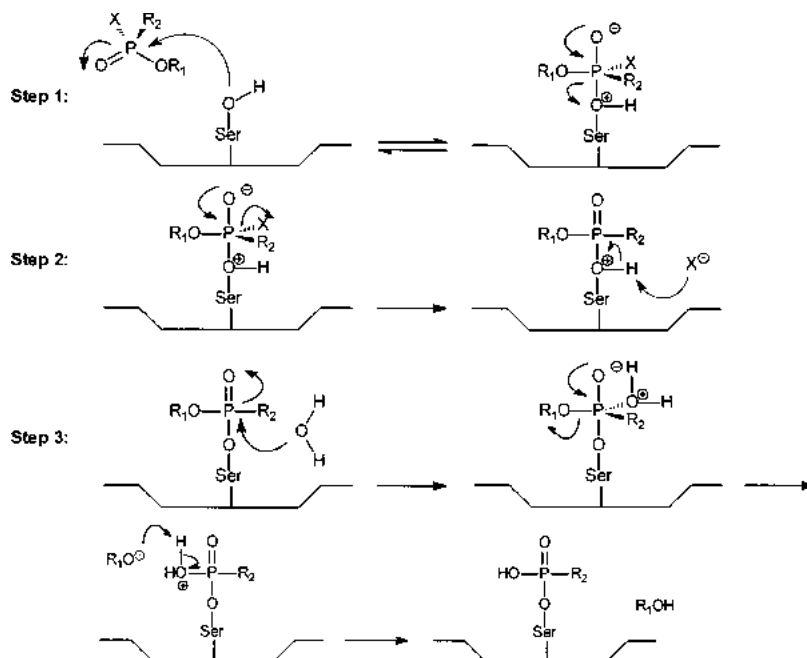
Mechanism of Action

The well-known mechanism of action of OP compounds is the inhibition of cholinesterases. Two types of cholinesterase are involved:

1. AChE is a specific enzyme useful for the diagnosis of OP poisoning; it also is called *true cholinesterase*. It usually is estimated in red blood cells and called *RBC AChE* or *erythrocyte AChE*.
2. Butyrylcholinesterase (BChE) is less specific but more sensitive than AChE for the diagnosis of OP poisoning. It also is called *pseudocholinesterase*. BChE is usually estimated in plasma and is so-called *plasma cholinesterase*.

The reaction between OP compounds and AChE occurs in three steps, as shown in Fig. 1 [10]. The toxic manifestations and lethality after nerve agent exposure seem to follow the irreversible phosphorylation of the serine-containing active site of AChE. BChE also is inhibited. People with BChE genetic variation deficiencies may

Fig. 1 Three-step reaction mechanism for the inactivation of acetylcholinesterase (AChE) by an organophosphate compound. Step 1 depicts the formation of a reversible complex between a serine residue in the AChE active site and the organophosphate. Step 2 shows the elimination of the organophosphate leaving group (X^-). In step 3, the aging of the AChE is completed, forming a phosphorylated AChE



be at risk. The clinically most important variant is atypical (D70G) BChE because people with this variation have 2 h of apnea after receiving a dose of succinylcholine that is intended to paralyze muscle for 3–5 min [11].

Different aging mechanisms are involved. Tabun and butyl-tabun seem to be accommodated similarly in the active center, as suggested by molecular modeling via kinetic studies of phosphorylation and aging with a series of HuAChE mutants (E202Q, F338A, F295A, F297A, and F295L/F297V) [12]. A variety of proteolytic enzymes (e.g., chymotrypsin, trypsin) also may be inhibited by OP nerve agents. Soman and sarin are detoxified in part via a two-step pathway involving bioactivation of the parent compound by the cytochrome P-450 system, then hydrolysis of the resulting oxygenating metabolite (oxon) by serum and liver paraoxxygenase (PON1). Serum PON1 has been shown to be polymorphic in humans [13].

Biochemical Changes

Acetylcholine accumulation is involved in the calcium flux into skeletal muscle fibers during OP poisoning [14]. Bright and coworkers (1990) [15] reported a histochemical demonstration of sarin-induced calcium influx in mouse diaphragm, which may be linked with OP-induced myopathy. Sarin may induce myonecrosis. Significant increase in alkaline phosphatase and creatine phosphokinase activity and minor changes in coagulation parameters (prothrombin time, activated partial

thromboplastin time, fibrinogen) were observed after soman poisoning in rabbits [16]. Significant increases in creatine phosphokinase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, and serum potassium, associated with damage to striated muscle and metabolic acidosis, occurred 2 days after GF poisoning in 20 male rhesus monkeys [17].

Toxicity

The vapor pressure of the three G agents (GA, GB, and GD) makes them significant inhalational hazards, especially at warmer temperatures or when droplets are created by explosion or spray. Based on information from animal studies, the lethal inhaled dose of G agents in humans may be about 1 mg. The G agents also represent a skin contact hazard, particularly when evaporation is minimized and contact is prolonged by contamination of clothing. The percutaneous absorption of G agents is much less rapid and complete, however, than the inhalational form [9].

VX does not pose a major inhalational hazard under usual circumstances, but it is well absorbed through the skin [9]. The relative lethality as determined in animal studies is VX > soman > sarin > tabun [18]. Acute toxic values of nerve agents in humans are summarized in Table 2.

The acute toxicity of nerve agents is due primarily to irreversible inactivation of AChE leading to an accumulation of toxic levels of acetylcholine. Similar to other OP compounds, these agents act by

Table 2 Summary of available acute toxic values of nerve agents in humans

Term	Unit	Route	Tabun	Sarin	Soman	VX
LD ₅₀	mg/kg	PC		28		
LD ₅₀	mg/m ³	Inhale		70		
LCLo	μg/kg	PC				86
LDLo	mg/kg	PC	23		18	
LDLo	mg/m ³	Inhale	150			70
TDLo	μg/kg	IV	14	2		1.5
TDLo	μg/kg	Oral				30
TDLo	μg/kg	SC				3.2

IV intravenous, *LCLo* lethal concentration at the lowest dose, *LD₅₀* median lethal dose, *LDLo* lethal dose at the lowest concentration, *PC* percutaneous, *SC* subcutaneous, *TDLo* toxic dose at the lowest concentration

Based on Dunn and Sidell [9]; Sidell and Borak [10]

binding to a serine residue at the active site of a cholinesterase molecule, forming a phosphorylated protein that is inactive and incapable of breaking down acetylcholine. The stable phosphoryl enzyme complex can undergo one of two possible processes:

a. Reactivation: The use of an appropriate nucleophile can trigger hydrolysis of the phosphoryl enzyme which can lead to reactivation of the enzyme [19].

b. Aging: Cleavage of the PO-C bond of the phosphorylated protein and the subsequent release of an alkyl carbenium ion is a process that is referred to as aging. In this case, the enzyme can no longer be reactivated even with the aid of a nucleophile.

In addition to the classical definition of aging of AChE described above, other definitions have also been proposed. One example involves the breakage of the P-N bond (as opposed to the PO-C bond) [12].

The reactivation of the aged AChE in many cases is not feasible, and the inhibition of the enzyme is considered irreversible. This is in part due to the negative charge at the active site of the enzyme, which makes any nucleophilic attack difficult [20].

The accumulation of toxic levels of acetylcholine at the synapse initially stimulates, then paralyzes cholinergic synaptic transmission (Fig. 2). Cholinergic synapses are found in the central nervous system, at the termination of somatic nerves, in the ganglionic synapses of autonomic nerves, and at the parasynaptic nerve endings, such as those in the sweat glands [10].

The rate of aging varies greatly among the nerve agents. The half-time of aging is within minutes after soman exposure, about 5 h after sarin exposure, and more than 40 h after exposure to tabun and VX [18].

OP compounds also bind to other esterases and cholinergic receptors. Inactivation of neurotoxin esterase by some OP pesticides can lead to delayed peripheral neuropathic effects known as organophosphate-induced delayed neuropathy (OPIDN). At many times the median lethal dose (LD_{50}), the nerve agents inhibit neurotoxin esterase to some extent, although the activity of VX is much less than that of G agents [21]. Possible involvement of neurotrophic factor (growth-related enzyme ornithine decarboxylase) during early stages of

OPIDN, particularly after diisopropylfluorophosphate, has been reported [22]. Nerve agents also bind quickly to cardiac muscarinic (M_2) receptors at higher than physiologic concentrations, but whether this contributes to cardiac toxicity is unknown [23]. They also interact with the nicotinic acetylcholine receptor-ion channel complexes, but only at tissue concentrations of 10–100 times greater than the concentrations fully inhibiting AChE. Sarin, soman, and tabun are partial agonists of these channel complexes, whereas VX acts as an antagonist [24]. There also is evidence that nerve agents affect noncholinergic mechanisms in the central nervous system at a dose approaching LD_{50} [25]. Antagonistic effects of γ -aminobutyric acid (GABA)-ergic systems may explain convulsive activity after OP poisoning. Effects of soman and tabun on the uptake and release of GABA and glutamate in the synaptosomes of guinea pig cerebral cortex did not support the previous belief that nerve agents cause convulsions by affecting the uptake or release of GABA or glutamine. Indirect evidence that soman and tabun inhibit catabolism of GABA and glutamine was obtained, however [26].

Acute exposure to tabun, sarin, or soman increases brain levels of cyclic adenosine monophosphate and decreases cyclic guanosine monophosphate as a result of stimulation of adenylyl cyclase and phosphodiesterase systems [6, 27]. VX at concentration of 10 μ M produced a significant reduction in cell metabolism within 2 min as measured by changes in the acidification rate of medium culture after 4 h of exposure. Two alkali degradation products of VX produced no cytotoxicity [28].

Toxicokinetics

As the OP nerve agents are lipophilic, they are absorbed rapidly following inhalation or ingestion. Dermal absorption is slow, but severe poisoning may still ensue if exposure is prolonged. Following absorption, OP nerve agents accumulate in fat, liver, kidneys, and salivary glands. Shih and co-workers (1994) studied toxicokinetics of GB, GD, and GF in rats. They had collected urine, blood, and lung tissue from rats dosed

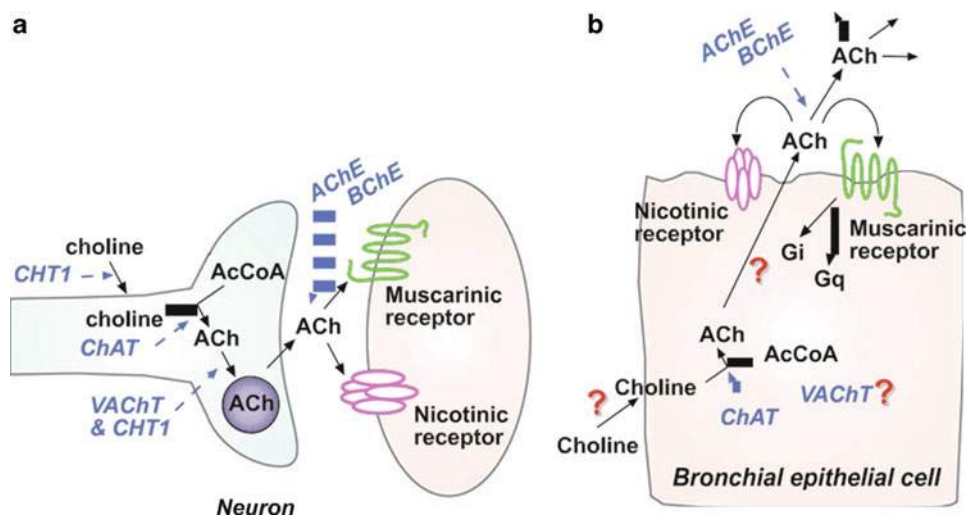


Fig. 2 Cholinergic signaling in neurons and bronchial epithelial cells. **(a)** In neurons, choline for ACh synthesis is transported by the choline high-affinity transporter (CHT1). ACh is then synthesized by the action of choline acetyltransferase (ChAT) and packaged into synaptic vesicles by the action of the vesicular acetylcholine transporter (VACHT) and CHT1. ACh is then secreted by the complex processes that control synaptic release. Released ACh then interacts with postsynaptic nAChR and mAChR as well as presynaptic receptors. Signaling is terminated by acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). Key signal transduction events lead to the generation of action potentials, opening of membrane and internal ion channels, muscle contraction, and kinase activation. **(b)** In bronchial epithelial cells (BEC), though CHT1 is present, CHT1 does not appear necessary for choline transport for

ACh synthesis. In BEC, as for neurons, ChAT is utilized for ACh synthesis, though since there are multiple isoforms of ChAT, different splicing products may be utilized in different cell types. Since CHT1 is not required, and BEC do not have synaptic vesicles, the role of VACHT and CHT1 in ACh secretion is unknown, though both are expressed in BEC. ACh released by BEC is inactivated by the same cholinesterases as expressed in neurons. A key difference is that released ACh is not limited just to synaptic communication, but can also signal multiple neighboring cells as a paracrine factor or more distal cells as a hormone (From *Muscarinic Receptors: Handbook of Experimental Pharmacology* 208, 2012. Fryer AD, Christopoulos A, and Nathanson NM, eds, Springer, with permission)

subcutaneously at $75 \mu\text{g kg}^{-1}$. Urinary excretion of the metabolite was the major elimination route for these three nerve agents. The major differences between them were primarily the extent and rate of excretion. Alkylmethylphosphonic acid is the single major metabolite formed and excreted in urine by a nonsaturable mechanism. Nearly total recoveries of the given doses for GB and GF in metabolite form were obtained from the urine. The terminal elimination half-lives in urine were 3.7 ± 0.1 and 9.9 ± 0.8 h for GB and GF, respectively. GD metabolite showed a biphasic elimination curve with terminal half-lives of 18.5 ± 2.7 and 3.6 ± 2.2 h. GD was excreted at a slower rate with a recovery of only 62%. Lung was the major organ of accumulation for this nerve agent. The toxic G agents were concentrated more in red blood cells than in plasma [29].

The metabolism of nerve agents results in the formation of inactive phosphonic acids, which are excreted via kidneys [30–32]. Experimental studies reveal that the elimination half-life of G agents was less than 1 h which is shorter than VX, which persists for several hours following intravenous administration and even longer after percutaneous exposure [33].

Oxidation and hydrolysis are principal metabolic inactivation pathways, which occur mainly by reaction with glutathione and also by glucuronidation and demethylation. Tabun causes the largest number of degradation products among the G agents. Detoxification of tabun takes place slowly, by di-isopropyl-fluorophosphatase, formerly termed tabunase. There are sparse toxicity data available for the subset of tabun degradation products. Ethyl-dimethylaminophosphoric acid is

the main product of tabun dimethylamine, which is also produced by hydrolysis of tabun. Dimethylamine causes human irritation in the respiratory tracts [34].

Isopropyl-methylphosphonic acid (IMPA) is a metabolite of sarin which subsequently hydrolyses to the high stable methylphosphonic acid (MPA) which mildly irritates rabbit skin and human skin and eyes [35].

In rats, 10 min after intravenous sarin, around 70% of the plasma was bound to large protein molecules similar to carboxylesterase [36]. The toxicity of sarin enhanced 6–8 times when the rats were pretreated with triorthocresyl phosphate, which is a weak anti-ChE OP with irreversible blocking carboxylesterase activity [37].

In a report of Little et al. (1986) who injected 80 µg/kg of sarin intravenously to mice, sarin concentration was at the highest in the kidney, liver, and plasma within one minute. Over the first minute, about half of the labeled sarin was associated with the major sarin metabolite; IMPA and the kidneys contained the highest concentration of sarin and its metabolites. Much lower hepatic concentrations after 24 h suggest a primary role of the kidneys in detoxification of sarin [38]. In another experiment of Little et al. (1988) with the same method, hypothalamus contained concentrations of both sarin and the metabolites 2–5 times greater than those in other brain areas. This finding suggests that the hypothalamus is more important with respect to central effects of nerve agents [39]. In 4 of 12 patients of Matsumoto with sarin exposure who underwent the study, the levels of IMPA and MPA correlated with clinical manifestations [40].

Pinacolyl methylphosphonic acid is the predominant hydrolytic product of soman [41].

A two-compartment model, with a biologic half-life of 1–1.5 min, described toxicokinetics of the four stereoisomers of soman in atropinized rats. The extremely toxic C(±) P(–) isomers could be followed in rat blood samples for more than 4 and 2 h at doses of 6 and 3 LD₅₀ (82 µg/kg). The toxicokinetics of P(–) isomers was described with a three-compartment model, with terminal half-lives of 40–64 min and 16–22 min at doses of 6 and 3 LD₅₀, respectively [41].

Clinical Presentation and Complications

The nerve agents cause toxic effects mainly by interfering with cholinergic synaptic function. This effect occurs at cholinergic neuroeffector functions (muscarinic effects), at the skeletal myoneural junctions and autonomic ganglia (nicotinic effects), and in the central nervous system. The signs and symptoms of nerve agent poisoning are classified according to whether they are due to overstimulation of muscarinic, nicotinic, or central nervous system receptors [42–53]. Nerve agents also cause long term and late complications [54–57].

Muscarinic effects of acetylcholine stimulation include miosis; blurred vision; eye pain; hypersecretion by salivary, sweat, lachrymal, and bronchial glands; bronchoconstriction; cough; cyanosis; pulmonary edema; nausea; vomiting; diarrhea; crampy abdominal pains; tenesmus; urinary and fecal incontinence; hypotension; and bradycardia (see ► Chap. 23, “Anticholinergic Syndrome”). Nicotinic effects include easy fatigue, weakness, muscle cramping, fasciculations, skeletal muscle twitching, convulsions, and flaccid paralysis. Nicotinic stimulation also can obscure muscarinic parasympathetic effects and produce mydriasis, tachycardia, and hypertension by stimulation of the adrenal medulla. Central nervous system effects include irritability; nervousness; giddiness; ataxia; fatigue; generalized weakness; depression of respiratory and circulatory centers with dyspnea, cyanosis, hypoventilation, and hypotension; lethargy; impairment of memory; confusion; convulsions; coma; and respiratory depression [6, 7, 10, 42, 51–53]. The main toxic effects of nerve agents at various sites in the body are summarized in Table 3.

Clinical Manifestations by Routes of Exposure

The effects of nerve agent exposure occur via inhalation, contact with skin and the eyes, and, rarely, ingestion. Most often, exposure is to vapor (inhalation) or liquid (percutaneous). After small-to-moderate doses, initial effects and their time of onset are determined by the route of exposure [47, 58–63]. In

contrast, large doses cause similar effects by all exposure routes, although the time of onset varies [10]. Gastrointestinal absorption rarely may occur through ingestion of contaminated food.

Inhalation

Exposure to low vapor concentrations may affect only the eyes, nose, and airways. Miosis, visual disturbances, rhinorrhea, and some degree of dyspnea develop within seconds to several minutes. The severity of dyspnea is dose dependent. Usually, these effects do not progress significantly when the patient is removed from contamination. After inhalation of high vapor concentrations, victims lose consciousness within 1 or 2 min, then have seizures, flaccid paralysis, and apnea. Other early effects of high vapor concentrations include miosis and copious secretions. Involuntary micturition and defecation also may occur. Unless medical assistance is immediate, victims may die within 30 min [43–46].

Skin Absorption

Percutaneous absorption of nerve agents varies according to the body site exposed and the

ambient temperature. VX was absorbed nearly eight times more rapidly from facial skin than it was from the volar forearm, and absorption increased markedly as surrounding temperature increased from 18 °C to 46 °C [27]. Initial local effects of liquid, which seldom are noticed, include muscular fasciculations and sweating at the contamination site. A large droplet also may cause gastrointestinal effects and complaints of malaise and weakness. Droplets containing near-lethal or lethal doses cause loss of consciousness, seizures, flaccid paralysis, and apnea. The onset of these effects is sudden, usually after a symptomatic interval of 10–30 min [10, 42].

Eyes

Miosis rapidly occurs after splash exposure or eye contact with vapor and later, if at all, after systemic poisoning. Unilateral miosis can occur if only one eye has been exposed. Miosis may be accompanied by deep aching eye pain, conjunctival irritation, and visual disturbances. Dim vision may be due to constricted pupils or inhalation of cholinergic fibers of the retina or central nervous system. The miotic pupil may improve vision (the pinhole effect),

Table 3 Main Toxic Effects and Clinical Manifestations of Nerve Agent Poisoning

Receptor	Target organ	Symptoms and signs
Muscarinic	Glands	
	Nasal mucosa	Rhinorrhea, nasal hyperemia
	Bronchial mucosa	Bronchorrhea
	Sweat	Sweating
	Lacrimal	Lacrimation
	Salivary	Salivation
	Smooth muscle	
	Iris	Miosis, blurred vision, decreased eye field
	Ciliary muscle	Failure of accommodation, eye pain
	Bronchial tree	Breathing difficulties, tightness of breath, bronchospasm (wheezing)
	Stomach	Nausea and vomiting
	Gut	Abdominal cramp, diarrhea
	Bladder	Frequency, involuntary micturition
	Heart	Bradycardia, hypotension
Nicotinic	Autonomic ganglia	Sympathetic effects, pallor, tachycardia, hypertension, mydriasis
	Skeletal muscle	Weakness, fasciculation, muscle twitching, convulsions, muscle paralysis, flaccid paralysis
Central	Central nervous system	Giddiness, anxiety, restlessness, headache, tremor, confusion, failure to concentrate, convulsions, respiratory depression, cyanosis, coma, apnea, death

although complaints of blurred vision are common [58]. Direct installation of diluted nerve agent into the eyes does not produce tissue damage [10].

Life-Threatening Complications

The most life-threatening complication is respiratory failure, which is due mainly to the effect of the nerve agents on the central nervous system [59, 60], although in one animal experiment with sarin, respiratory paralysis could be purely central, peripheral, or both, depending on the doses of sarin and atropine antidote employed [61]. Hypoxia also is a major problem in the nerve agent poisoning, as it may cause cerebral edema and convulsions and may induce histopathologic brain damage.

Cardiovascular complications sometimes are severe and life-threatening [47, 62] (See Figs. 3 and 4). The nerve agents tabun, sarin, soman, or VX at 5–10 times the LD₅₀ administered to guinea pigs induced circulatory arrest a few minutes after apnea in nontreated animals. Antidote treatment by atropine (10 mg/kg) and HI-6 or HLo-7 (30 mg/kg) 2 min later rapidly restored heart rate and arterial pressure and respiratory function to various degrees. The nerve agent injection caused marked sinus bradycardia and a subsequent complete atrioventricular block within 1–2 min. In guinea pigs with depressed respiratory function (<50%), intermittent ST-T wave alterations and second-degree atrioventricular heart block were observed [47]. Other reported electrocardiogram abnormalities in animal experiments and in humans exposed to nerve agents include torsades de pointes, atria fibrillation, idioventricular dysrhythmias, complete heart block, and ventricular fibrillation [6, 10, 47, 62]. Histopathologic changes compatible with toxic myocarditis were observed after sarin and soman in animal experiments [47], but myocarditis has not been reported in humans.

Intermediate Syndrome

The intermediate syndrome consists of marked weakness of the proximal skeletal musculature

(including the muscles of respiration) and cranial nerve palsies that occurs 1–4 days after acute poisoning. This syndrome, which was observed after certain OP pesticides poisoning [63], has not been reported yet after OP nerve agent poisoning. Intermediate syndrome may be a consequence of cholinergic overactivity at the neuromuscular junction, and a connection has been made between the intermediate syndrome and OP-induced myopathy or undertreatment. Myopathy has been observed histologically in experimental animals with the nerve agents tabun, soman, and sarin [14, 15]. It can be anticipated that the intermediate syndrome occurs in some cases of nerve agent poisoning (Fig. 5).

Delayed Neuropathy

Organophosphorus pesticides-induced delayed neuropathy is a symmetric sensorimotor axonopathy, tending to be most severe in long axons and occurring 7–14 days after exposure. In severe cases, it is an extremely disabling condition [64]. Inhibition of neuropathy target esterase seems to be necessary for OPIDN to develop. Other mechanisms may be involved, however. The trophic factor ornithine decarboxylase, a growth-related enzyme, was decreased in the spinal cord after the neuropathic agent diisopropyl-fluorophosphate [22]. Although OPIDN was not observed after nerve agent poisoning in experimental studies [65, 66] and in accidental nerve agent poisoning, a case of sensory polyneuropathy 7 months after sarin poisoning has been reported [67].

Temporary psychological effects, such as depression, fatigue, insomnia, irritability, nervousness, and impairment of memory, have been described after nerve agent exposure [57]. Electroencephalography in a person who was severely intoxicated with sarin showed marked slowing with bursts of high-voltage waves at a rate of five per second [42]. Epileptic-type changes of the electroencephalography were observed after sarin poisoning 11 months after exposure [6].

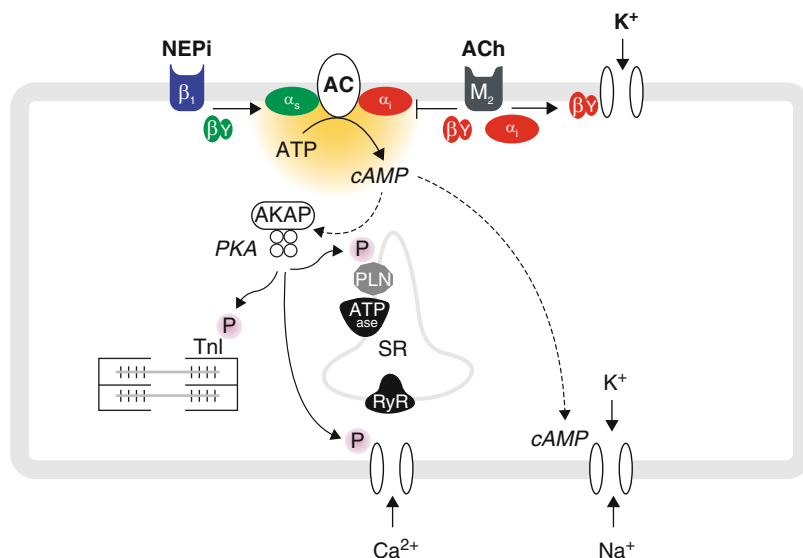


Fig. 3 Muscarinic signaling pathways in supraventricular (sinoatrial, atrial, and atrioventricular) myocytes. Acetylcholine (ACh) acts through M2 receptors to regulate ACh-activated K channels via a membrane-delimited mechanism involving direct activation by the $\beta\gamma$ subunits of the inhibitory G protein G_i . ACh also acts through M2 receptors to inhibit adenylyl cyclase (AC) activity via the α_i subunit of G_i , resulting in a decrease in cAMP production. This may occur in the absence or presence of agonists that stimulate cAMP production. Norepinephrine (NEPi) acts through β_1 -adrenergic receptors to stimulate cAMP

synthesis by directly activating all isoforms of adenylyl cyclase (AC) via the α_s subunit of the stimulatory G protein G_s . Changes in cAMP affect targets of protein kinase A (PKA)-dependent phosphorylation such as troponin I (TnI), phospholamban (PLN), and the L-type Ca^{2+} channel. Changes in cAMP also directly regulate pacemaker channels, which are permeable to both Na and K (From Muscarinic Receptors: Handbook of Experimental Pharmacology 208, 2012. Fryer AD, Christopoulos A, and Nathanson NM, eds, Springer, with permission)

Course and Prognosis

Victims with heavy exposure to nerve agents may die within a few minutes in the field. Persons with physical and chemical protection (pyridostigmine) who remain in a heavily contaminated area may become intoxicated after 30 min. A patient with moderate-to-severe intoxication who receives first aid and emergency medical treatment may survive for a few days to a few weeks, according to the severity of intoxication and type of treatment [44]. Death, however, is common.

Hypoxia, coma, convulsions, and respiratory failure are signs of a poor prognosis. Patients who remain severely hypoxic and cyanotic may develop cardiac arrhythmias and die quickly. Patients who develop apnea and do not receive assisted ventilation immediately may incur brain damage and either die or become vegetative. It is

unlikely that nerve agents possess the potential to give rise to OPIDN [45].

Soldiers who are caught unaware and who are exposed to large amounts of nerve agent before donning respirators and other protective clothing and who rapidly develop severe symptoms and signs are unlikely to survive. Soldiers who rapidly develop respiratory failure and who become incapable of self-administering their own autoinjector devices also have a poor prognosis, unless emergency medical treatment is provided rapidly [44]

Late Complications

The nerve agents are less likely to cause chronic diseases in comparison with sulfur mustard poisoning. However, hypoxic encephalopathy is reported as one of the most remarkable long-term neurologic toxic effects of the nerve agents [46]. Cardiomyopathy has been reported in soman

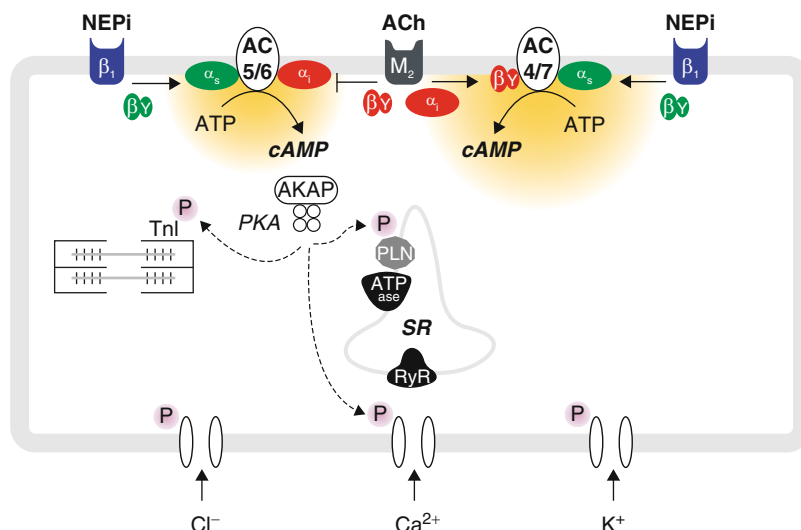


Fig. 4 Muscarinic signaling pathways in ventricular myocytes. Responses to M2 receptor activation are only observed in the presence of agonists that stimulate cAMP production. Norepinephrine (NEPi) acts through β₁-adrenergic receptors to stimulate cAMP synthesis by directly activating all isoforms of adenylyl cyclase (AC) via the α subunit (α_s) of the stimulatory G protein G_s. Acetylcholine (ACh) acts through M2 receptors to inhibit AC5/6 activity via the α subunit (α_i) of the

inhibitory G protein G_i. ACh acting through M2 receptors can also stimulate AC4/7 activity via the βγ subunits of G_i. Changes in cAMP affect targets of protein kinase A (PKA)-dependent phosphorylation such as troponin I (TnI), phospholamban (PLN), as well as L-type Ca²⁺, delayed rectifier K⁺, and CFTR Cl⁻ channels (From Muscarinic Receptors: Handbook of Experimental Pharmacology 208, 2012. Fryer AD, Christopoulos A, and Nathanson NM, eds, Springer, with permission)

and sarin intoxicated rats, which may be a cause of death; however, it is not reported in human cases yet [47]. Neurological assessment of 43 Iranian veterans 22–27 years post exposure revealed fatigue, paraesthesia, and headache as the most common symptoms and sensory nerve impairments as the most common observed clinical complication in the Iranian veterans with the nerve agents of tabun and sarin. Sensory nerve dysfunction is more prevalent than motor nerves, which predominantly was a distal sensory deficit [48].

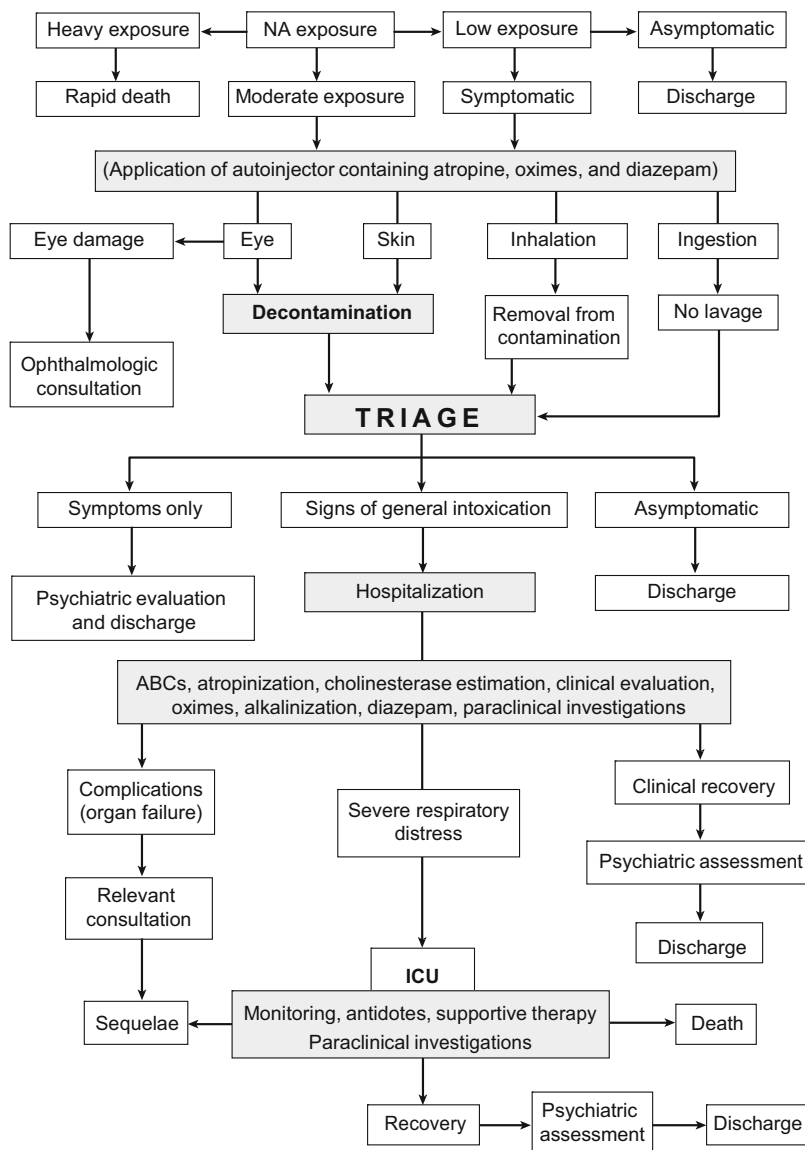
Engel et al. (2004) reported fatigue, depression, and chronic pain as the common clinical presentations of “Gulf war syndrome” [49]. Electroencephalogram (EEG) studies on sarin patients showed significant slowing with bursts of high voltage waves at a rate of five per second on EEG, 11 months after the exposure [50, 51]. Asthenia, insomnia, fatigue, blurred vision, narrowing of the visual field, shoulder stiffness, slight fever, and asthenia were observed in patients who exposed to sarin 1 and 3 years after Tokyo subway explosion

[52]. Fullerton and co-authors (1990) on a review of article mentioned temporary psychological effects such as depression, insomnia, fatigue, nervousness, irritability, and memory impairment as long-term complication of exposure to NAs [53]. Page (2003) on a telephone survey of 4,022 sarin exposed patients 28 years post exposure reported poor concentration abilities and sleep disturbances in comparison with the controls [54]. Grauer et al. (2008) have studied late neuronal and behavioral deficit after sarin exposure in rats. The data showed long lasting impairment of brain function after single sarin exposure that developed with time [55]. There is no real evidence on carcinogenicity, mutagenicity, and teratogenicity of NAs [56, 57].

Diagnostic Considerations

Initial diagnosis of nerve agent poisoning can be made based on the exposure history (accidental, terrorism, chemical warfare attack) and clinical

Fig. 5 Management of nerve agent (NA) poisoning. *ABCs* airway, breathing, circulation, *ICU* intensive care unit



manifestations. In low-level exposure, the route of absorption may affect the clinical features, but in high-level exposure, severe intoxication occurs. Absorption is faster through inhalation than by skin contact. Estimation of AChE in erythrocytes is required to confirm the anticholinesterase diagnosis and to estimate the severity of intoxication. BChE estimation also may help, although it is not specific and may be low due to genetic variations [11].

Diagnostic certainty of nerve agent exposure requires toxicologic analyses of the environment,

blood sampling, or both. A biosensor, which is a potentiometer enzyme electrode for direct determination of OP nerve agent, has been developed [68].

A fiberoptic enzyme biosensor for the direct measurement of OP nerve agents has been developed. Concentrations of 2 μM can be measured in less than 2 min using the kinetic response. When stored in buffer at 4 $^{\circ}\text{C}$, the biosensor shows long-term stability [69]. A new method for retrospective detection of exposure to OP

nerve agents was applied to estimate serum sarin concentrations of the Matsumoto incident. The concentrations ranged from 0.2 to 4.1 ng/mL in serum [70]. Definitive evidence for the acute sarin poisoning of the Tokyo subway was obtained by detecting sarin-hydrolyzed products from erythrocytes of four victims in postmortem examinations [71].

Intravenous administration of atropine can be used as a diagnostic test for anticholinesterase poisoning, whereas oximes are used only for treatment [72]. Cholinesterase activity in postmortem blood as a screening test for OP nerve agent exposure was performed in 53 nonpreserved postmortem whole-blood specimens. There was a negligible loss of cholinesterase activity by the 7th day of the study. Cholinesterase activity could be applied as the screening test for anticholinesterase nerve agents [73].

Diagnosis of the delayed neurotoxin effects can be made by estimation of neuropathy target esterase, although it is unlikely to occur after nerve agent poisoning. Marked reduction of neurotrophic factor (ornithine decarboxylase) during the early stages of neurotoxicity also may be helpful when it is possible to perform it [22]. Measurement of nerve conduction velocity and electromyography may be useful for the diagnosis of the delayed neuropathy of OP nerve agents [74].

Toxicologic Analyses

Cholinesterases and Neuropathy Target Esterase Determination

Estimation of BChE in plasma is widely available and should be performed as soon as possible. Erythrocyte AChE is more specific, however, and has more quantitative value than BChE, although both enzymes usually are measured spectrophotometrically. Inhibition of greater than 50% activity of either enzyme confirms the diagnosis of an anticholinesterase poisoning. Reactivation of BChE is relatively more rapid, depending on the agent, severity of intoxication, and use of oximes, taking 1–4 weeks. In contrast, reactivation of AChE may take up to 3 months [6]. Neuropathy

target esterase shall also be estimated when there are clinical features of delayed neuropathy.

Nerve Agent Detection

Detection and estimation of nerve agents are easier in environmental samples than in blood and urine samples of patients. By using new technology, such as biosensors and fiberoptic bioenzyme, and new methods for detection and determination of nerve agents (e.g., sarin) in the serum and erythrocytes, identification and estimation of common nerve agents are possible [68–72, 75].

Oxime Estimation

Estimation of pralidoxime concentration in blood may be required, although it is not necessary for the routine management of the patient. To achieve a maximal therapeutic effect, however, a blood pralidoxime concentration of 4 mg/L should be reached. An obidoxime plasma level in the range of 10–20 μ M was estimated as appropriate. This was achieved in 34 severely OP-poisoned patients using regimen of 250 mg i.v. as bolus, followed by 750 mg/24 h and was maintained as long as reactivation was possible. The result confirmed using this definite regimen for adults [75].

Biochemical and Hematologic Analyses

Acid–base and electrolyte disturbances are common during severe nerve agent poisoning. Arterial blood gas analysis, estimation of serum electrolytes, liver and kidney function tests, amylase, creatine phosphokinase, and lactate dehydrogenase may be required for patient management. Hypokalemia and hyperglycemia are common and should be considered and corrected. Elevation of serum amylase may reveal acute pancreatitis. Transient elevation of liver enzymes, hematuria, leukocyturia, and proteinuria may be observed during nerve agent poisoning. Blood cell count and other hematologic tests may be performed as clinically indicated. Transient leukocytosis, particularly in polymorphonuclear neutrophils, may

be observed during severe nerve agent poisoning [45].

Other Investigations

Chest x-ray, electrocardiogram, electroencephalogram, electromyogram, nerve conduction velocity, spirometry, computed tomography, magnetic resonance imaging, and other investigations may be performed in nerve agent poisoning as clinically indicated [44].

Severity Grading of Intoxication

Severity grading of nerve agent poisoning can be done based on clinical manifestations, cholinesterase activity, and initial atropine dose required for atropinization.

Clinical Symptoms and Signs

Patients with OP nerve agent poisoning can be divided into four groups – mild, moderate, severe, and fatal – according to symptoms and signs of poisoning (Table 4).

Inhibition of Cholinesterases

Patients with nerve agent poisoning may be divided into three groups according to cholinesterase activities (Table 5).

Atropine Dose

Patients with OP nerve agent poisoning can be divided into three groups according to the initial atropine dose required for atropinization:

1. Mild: less than 2 mg
2. Moderate: 2–10 mg
3. Severe: greater than 10 mg [45]

Causes of Death

Death after nerve agent exposure is mainly due to respiratory failure resulting from depression of the respiratory center, paralysis of respiratory muscles, and obstruction caused by bronchospasm and bronchial secretions. Some animal studies suggest that lack of central drive is the major factor [59, 60]. Cardiomyopathy in soman-intoxicated and sarin-intoxicated rats has been reported [34] and may be a contributory cause of death.

Table 4 Symptoms and signs of organophosphate nerve agent poisoning

Grade	Symptoms	Signs
1 – Mild	Dizziness, anxiety, headache, nausea, weakness, tightness of breath	Failure of accommodation, rhinorrhea, sweating, salivation, coughing, lacrimation
2 – Moderate (worsening of the above features plus the following)	Restlessness, confusion, dyspnea, disorientation, abdominal pain, diarrhea	Pallor, miosis, failure of concentration, tachycardia, hypertension, muscle twitching, fasciculation, respiratory depression, bronchorrhea, loss of consciousness, bronchospasm
3 – Severe (worsening of the above features plus the following)	–	Convulsions, respiratory failure, pulmonary edema, flaccid paralysis, involuntary micturition/defecation, cyanosis, deep coma
4 – Fatal	–	Coma, convulsions, miosis, hypersecretions, apnea within a few minutes after exposure

Table 5 Cholinesterase Activities^a

Grade	Butyrylcholinesterase activity (%)	Acetylcholinesterase activity (%)
1 – Mild	40–50	50–90
2 – Moderate	10–40	10–50
3 – Severe	<10	<10

^aButyrylcholinesterase activity has less quantitative value than acetylcholinesterase activity

Status epilepticus occurred in animals after high doses of sarin, soman, or VX despite early treatment with atropine and pralidoxime. Prolonged seizures may cause anoxia and morphologic brain damage, which induces more morbidity and mortality [65, 66].

Treatment

Priorities

The first rule for managing chemical casualties is that the emergency responders must protect themselves from contamination, resulting from contact with casualties and the environment (Fig. 2). This can be done by wearing personal protective equipment or by thoroughly decontaminating the patient. At minimum, rescuers should wear a protective mask (or mask containing a charcoal filter for a self-contained breathing apparatus device, not a surgical or similar mask) and heavy rubber gloves (surgical gloves offer negligible protection) and avoid skin contact with victims until decontamination has been carried out [9, 76].

As soon as possible, victims should be removed from the contaminated place and decontamination must be initiated. Antidotes should be given at the onset of effects as appropriate (e.g., autoinjector containing atropine, obidoxime, and diazepam). For unconscious or severely intoxicated patients, priorities must follow the ABCs (airway, breathing, and circulation) of resuscitation. Oxygen administration and assisted ventilation should be undertaken as soon as possible in patients with respiratory distress. Because atropine reverses bronchoconstriction within minutes, one could hesitate to intubate a dyspneic, conscious patient who is likely to improve quickly. In a severely poisoned, unconscious, apneic patient, however, endotracheal intubation with assisted ventilation should be undertaken as quickly as possible.

Airway resistance may be high initially, causing some mechanical ventilators to malfunction, but this should return to normal after atropine administration. Frequent airway suctioning may be required for copious bronchial secretions.

Supplemental oxygen through an endotracheal tube with positive end-expiratory pressure is indicated for severely hypoxic patients. It is important to improve tissue oxygenation before atropine administration to minimize the risk of ventricular fibrillation. Advanced life support, including intravenous line placement, should be provided to all victims with evidence of respiratory compromise or other signs of severe exposure [10, 44].

Decontamination

Decontamination must be carried out at the earliest opportunity to limit skin absorption of the agent and prevent contamination of the rescuers. Thorough decontamination is essential before casualties enter an emergency department or other site of medical care to avoid contamination of staff and other patients.

Indications for ICU Admission in Nerve Agent Poisoning

1. Patients with severe nerve agent intoxication (see section on “[Severity Grading of Intoxication](#)”), particularly patients with respiratory failure who need mechanical ventilation, should be admitted to the intensive care unit.
2. Although intermediate syndrome has not clearly been reported in nerve agent poisoning, it may occur in some cases. Patients with moderate-to-severe intoxication even without assisted ventilation should be monitored, preferably in the intensive care unit, for treatment of possible sudden respiratory arrest due to muscle paralysis.

If the eyes have been exposed, they should be irrigated as soon as possible with running water or saline. Skin should be decontaminated by pouring on large amounts of a chlorine-liberated solution, such as 5% hypochlorite solution (household bleach), followed by copious water rinsing. If bleach is not available, the skin should be blotted gently (without rubbing) with generous amounts of alkaline soap and water followed by a water

rinse. Generous amounts of water alone can be used if nothing else is available. Water dilutes and physically washes away the nerve agents, but it does not hydrolyze them. Contaminated clothing and jewelry should be removed, and the underlying skin should be decontaminated thoroughly. Care should be taken to clear under the nails, the intertriginous areas, the axillae, the groin, and the hair [10, 45].

Experimental Antidotes

Fetal bovine serum AChE protected mice from multiple LD₅₀ doses of OP nerve agents [77]. BChE purified from human plasma also was effective in vitro and in vivo in mice and rats as a single prophylactic antidote against the lethal effects of nerve agents [78]. Addition of the oxime HI-6 to fetal bovine serum and AChE as a pretreatment drug amplified the efficacy of enzyme as a scavenger of nerve agents [79].

Recombinant DNA-derived AChEs showed a great improvement over wild-type AChEs as bioscavengers; they can be used to develop effective methods for the safe disposal and storage of OP nerve agents and are potential candidates for preexposure or postexposure treatment for OP toxicity [80]. By the use of cell immobilization technology, immobilized *Escherichia coli* with surface-expressed organophosphorus hydrolase was made to detoxify nerve agents [81]. By protein engineering techniques, one BChE mutant, G117H, was made to hydrolyze V and G agents, but it reacted much too slowly [82].

OP acid hydrolyses from two species of *Alteromonas* were cloned and sequenced to detoxify G agents, which was effective [83]. Cholinesterases that are covalently linked to a polyurethane matrix can be used effectively to remove nerve agents from and decontaminate surface biologic areas (skin or wounds) or other areas (clothing or medical equipments) or the environment. These cholinesterases could protect medical personnel from secondary contamination while attending chemical casualties and civilians exposed to highly toxic nerve agents [84].

A reactive skin decontamination lotion active against classic nerve agents and sulfur mustard was developed. The inactivation process was time and agent dependent and related to the ratio of OP to reactive skin decontamination lotion [85].

Pretreatment

In animal studies, pretreatment with reversible carbamate AChE inhibitors, such as pyridostigmine and physostigmine, enhances the efficacy of postexposure treatment of soman exposure or soman poisoning with atropine and pralidoxime chloride and permits survival at higher agent challenges [86]. His protection apparently is due to the fact that the more lethal nerve agents cannot attack AChE molecules bound by carbamates. Carbamylation of 20–40% of the erythrocyte AChE is associated with antidotal enhancement. Carbamate pretreatment does not reduce the effects of the agents and by themselves carbamates provide no benefit. Pretreatment is not effective against sarin and VX challenge and should not be considered a panacea for all nerve agents. It is of value for soman intoxication when agent challenge is followed by atropine and an oxime. Pretreatment is ineffective unless standard therapy is administered after the exposure.

Because physostigmine is toxic at the amounts required, pyridostigmine is the drug of choice for pretreatment (Grade III recommendation). The standard dosage is 30 mg orally every 8 h for impending nerve agent attack. Because pyridostigmine does not cross the blood–brain barrier, it causes no central nervous system toxicity of nerve agents. Carbamates must never be used after nerve agent exposure; in that setting, carbamate administration worsens, rather than protects from toxicity. Excessive doses cause many of the same toxic effects as do the nerve agents, and the recommended amounts caused annoying side effects in more than half of the population in a war zone. Eptastigmine treatment given intravenously protected mice better than physostigmine against soman exposure [87].

Pretreatment with a drug mixture (pyridostigmine, benactyzine, and trihexypenidyl) and antidotal treatment (HI-6 and benactyzine) were investigated in rats. This cholinergic-anticholinergic pretreatment in restoring respiratory and circulatory changes induced by soman is important [88].

Antidotes

Available antidotes (atropine, oximes) do not prevent respiratory failure or incapacitation [89]. Early aggressive medical therapy with antidotes and intensive care management are the keys, however, to prevention of morbidity and mortality associated with nerve agent poisoning.

Atropine

Atropine should be titrated with the goal of drying secretions and resolving bronchoconstriction and bradycardia [90]. There is no actual dose for atropine. The dose (2 mg) of atropine available in an autoinjector is not adequate for moderate-to-severe exposure to nerve agents. Atropine should be given intravenously in doses to produce mild-to-moderate atropinization (dryness of tongue, oropharyngeal and bronchial tree, tachycardia, mydriasis, and flushing) as soon as possible. At least the same amount as the initial atropinization dose should be infused in 500 mL of dextrose 5% constantly to sustain the atropinization and should be repeated as needed until the patient becomes asymptomatic. Continuous infusion of atropine effectively antagonizes the muscarinic effects and some of the central nervous system effects of nerve agent poisoning, but it has no effect on skeletal muscle weakness, seizures, unconsciousness, or respiratory failure [10, 44]. Large doses of atropine require higher concentrations of atropine preparation (e.g., 100 mg/10 mL made in Germany) or at least a vast amount of atropine (10–100 mg) in dextrose 5% solution, ready-made for intravenous infusion in severely nerve agent-intoxicated patients. Much lower atropine doses are required for nerve agents than for the severe OP pesticides poisoning.

Atropine should not be given intravenously to a hypoxic patient. (Grade III recommendation) Hypoxia occurs as a result of hypersecretion in the respiratory tracts. The secretion must be suctioned and oxygen given to overcome hypoxia before inducing atropinization. If the patient is hypotensive, atropine can be given through an endotracheal tube or intratracheally for more rapid absorption through the peribronchial vessels [45]. Aerosolized atropine has also been used and can be administered quickly by inhalation. Studies suggest that in addition to the local effects in the lungs, it is absorbed systemically [91].

Oximes

Oximes are mainly pyridinium compounds, which are divided into mono-pyridium and bis-pyridium oximes. Common oximes used in the treatment of nerve agent poisoning are presented in Table 6. Although oximes have been designed to reactivate the inhibited AChE, clinical experience has indicated that they are not always effective as reactivators, and at this time, none of them can be regarded as a broad-spectrum antidote [92]. The choice of oximes based on the data presently available also may depend on factors other than protection against lethality, such as cost and availability of the oxime and its side effects. Obidoxime (Toxogonin, Merck, Germany) is likely to cause more toxic effects (hepatitis after high doses) than pralidoxime and HI-6 [93]. HI-6 is the least toxic, but it is less stable in solution and is not commercially available in many parts of the world.

Pralidoxime, HI-6, and HGG-12 were used in dogs with soman and tabun poisoning. Pralidoxime (in conjunction with atropine and diazepam) showed the best protective effects in soman-poisoned dogs: The protective indices were 9 for pralidoxime, 6.3 for HI-6, and 3.5 for HGG-12. None of these agents was effective against tabun poisoning [94]. Efficacy of two other oximes, HLo-7 and pyrimidoxime (an analog of trimedoxime), in three times the LD₅₀ of sarin, soman, and GF and two times the LD₅₀ of tabun, was tested in mice. HLo-7 produced significant ($P < 0.05$) reactivation of

phosphorylated AChE, resulting in 47%, 38%, 27%, and 10% reactivation of sarin-inhibited, GF-inhibited, soman-inhibited, and tabun-inhibited mouse diaphragm AChE, respectively [95]. In a comprehensive study, the order of effectiveness against soman was HI-6, HLo-7, and pyrimidoxime. HLo-7 was extremely effective against tabun poisoning, whereas HI-6 and pyrimidoxime were of moderate value. Against GF, HI-6 and HLo-7 were extremely effective, obidoxime was moderately effective, and pralidoxime and pyrimidoxime were least effective [96]. In soman-intoxicated guinea pigs, HI-6 was therapeutically slightly more effective than HLo-7; HLo-7 was more effective than HI-6 against tabun intoxication [97].

Pharmacokinetics and effects of HI-6 in blood and brain of soman-intoxicated rats were studied. High doses of HI-6 can reach the brain in sufficient amounts to reactivate inhibited brain AChE. Signs of soman poisoning correlated positively to AChE inhibition and negatively to the concentration of inbound HI-6 in the brain, and soman intoxication significantly decreased uptake of HI-6 into the brain [98]. Reactivating potency of obidoxime, pralidoxime, HI-6, and HLo-7 in human erythrocyte AChE inhibited by soman, sarin, cyclosarin, and VX was studied in vitro. After soman, sarin, cyclosarin, and VX inhibition, the reactivating potency decreased in the following order: HLo-7 > HI-6 > obidoxime > pralidoxime [99]. Dose–response effects of atropine and HI-6 treatment in soman and tabun poisonings were studied in guinea pigs. Atropine had a large effect on the efficacy of HI-6 against both the nerve agents. They also were more effective

against soman than against tabun. Adjunctive treatment with diazepam enhanced the efficacy of HI-6 and atropine against soman [100]. The effects of common oximes in different nerve agent poisonings are summarized in Table 7.

Despite many oximes tested in animal experiments, the human experience in war or terrorism is limited to pralidoxime and obidoxime. Pralidoxime should be administered intravenously at a dose of 30 mg/kg initially over 30 min followed by a constant infusion of 8 mg/kg/h in dextrose 5%. Pralidoxime can be continued until full recovery or until atropine is required. Obidoxime was hepatotoxic at high recommended doses of 8 mg/kg initially and 3 mg/kg/h [5]. It may be given at a dose of not more than 500 mg initially and 750 mg/day. Liver function tests should be checked regularly during obidoxime therapy [45].

Diazepam

Behavioral efficacy of diazepam against nerve agents in rhesus monkeys was studied. The results showed that diazepam would be an excellent adjunct to traditional nerve agent therapy to facilitate behavioral recovery from nerve agent intoxication that might be encountered by medical military personnel on the battlefield [101]. Diazepam was the drug of choice for treatment of convulsions in nerve agents poisoning. (Grade III recommendation) The initial IV doses of 0.2–0.5 mg/kg in children and 5–10 mg in adults are recommended and may be repeated as required [102, 103].

Table 6 Common oximes used in the treatment of organophosphate nerve agent poisoning

Type of oxime	Generic name	Trade name	SUPPLIER/COUNTRY
Monopyridinium	Pralidoxime chloride (2-PAM)	Protopam	Ayerst/U.S./Canada
	Pralidoxime methylsulfate	Contrathion	SERB/France
	Pralidoxime methanesulfonate	P2S	U.K. government
Bispyridinium	Trimedoxime	TMB-4	
	Obidoxime	Toxogonin	Merck/Germany
	HI-6		
	HLo-7		
	HGG-12		

Table 7 Relative effects of oximes in organophosphate nerve agent poisoning

Oximes	GA (Sarin)	GB (Soman)	GD (Tabun)	GF	VX
Pralidoxime ^a	+++ ^b	++	+	+	+++
Pyrimidoxime	++	++	++	+	++
Obidoxime	++	+++	++	++	+++
HI-6	+++	++++	++	++++	+++
Hlo-7	++++	+++	++++	++++	++
HGG-12	NA	+++	+	NA	NA

^aproPAM, the tertiary amine analog of pralidoxime, penetrates the central nervous system more readily than pralidoxime. Consequently, proPAM would be expected to have greater beneficial effect in nerve agent poisoning than pralidoxime. This expectation has not in general been realized in experimental studies

^bKey: + = least effective; ++ = partially effective; +++ = moderately effective; ++++ = most effective
NA no data available

Diazepam has not only symptomatic anticonvulsant effect but also has more specific effect on cholinergic and GABAergic systems [104]. In severe cases of nerve agents poisoning, convulsion starts within seconds after losing consciousness. It may persist for several minutes until the victim becomes flaccid and apneic. In these cases, diazepam must be administered promptly [103].

Other anticonvulsant benzodiazepines, such as lorazepam and midazolam, are effective in stopping seizures in acute nerve agents poisoning [105–108]. (Grade III evidence) Midazolam, however, is more potent and more rapid than diazepam in treatment of seizure in nerve agents poisoning. It is thus recommended that midazolam replace diazepam as an urgent anticonvulsant treatment for the nerve agents-induced seizures. (Grade III recommendation) Barbiturates, phenytoin, and other anticonvulsants are not effective against seizure in nerve agents poisoning [102]. Fast acting barbiturates may be effective, but they have more CNS depressive than the benzodiazepines. Propofol may be used in OP-induced grand mal convulsions if the response to benzodiazepines was not satisfactory.

Gacyclidine

Gacyclidine is an antiglutaminergic compound that was studied as a complement to the available emergency therapy in OP poisoning. It was used in conjunction with atropine, pralidoxime, and diazepam in nerve agent poisoning in primates.

Gacyclidine prevents the mortality observed after early administration of the aforementioned classic emergency medications. (Grade III recommendation) Electroencephalogram recordings and clinical observations revealed that gacyclidine prevented soman-induced seizures and motor convulsions. It also markedly accelerated clinical recovery of soman-challenged primates. Gacyclidine prevented the neuropathology observed 3 weeks after soman exposure in animals [72]. In a case of severe nerve agent poisoning, gacyclidine represented a promising adjuvant therapy to the currently available polymedication to ensure optimal management of OP nerve agent poisoning in humans. Administration of gacyclidine at zero to 30 min after intoxication obtains optimal neuropathological protection [109].

Serum Alkalinization

Effects of sodium bicarbonate in OP pesticide poisoning were investigated in patients with moderate-to-severe intoxication. The goal of the investigation was to make an alkalization to reach and sustain the arterial blood pH between 7.45 and 7.55. Sodium bicarbonate was administered intravenously first to correct the metabolic acidosis, then as a constant infusion of 3–5 mg/kg/24 h until recovery or until atropine was required. Arterial blood gas analysis was performed at certain intervals to adjust the dosing [104, 105, 110, 111]. Esteratic portion of OP molecules are hydrolyzed in alkaline solution. Increasing one unit of

pH is accompanied by a 10-fold increase in OP nerve agent hydrolysis. The arterial pH of >7.50 makes the OP hydrolysis faster particularly the nerve agents and their metabolites that are weak acids [112, 113]. However, it should be administered carefully to avoid severe metabolic alkalosis. Administration of sodium bicarbonate helps to control the cardiotoxicity as judged by electrocardiogram [114] (Grade III evidence).

Magnesium Sulfate

IV administration of magnesium sulfate (4 g) in the first day after admission would decrease the hospitalization period and improve outcomes in patients with OP pesticides poisoning [115] (Grade II-3 evidence). Magnesium sulfate may reduce ACh release by blocking calcium channels [116]. It also reduces CNS overstimulation and reversed the neuroelectrophysiological defects from OP toxicity [117]. Additionally, magnesium sulfate has a bronchodilating effect in mild to severe asthmatic patients, and it may relieve bronchoconstriction in a dose-dependent manner [118]. Magnesium sulfate has recently been administered up to 16 g per day in OP pesticides poisoning in the Mashhad Toxicology center without serious side effects. However, applying magnesium sulfate in nerve agents poisoning needs further study.

Drug Interactions

Drugs reported as contraindicated in severe OP nerve agent poisoning are morphine and its derivatives, aminophylline, theophylline, and chlorpromazine. Morphine derivatives and chlorpromazine potentiate the drowsiness and coma. Aminophylline and theophylline may potentiate nicotinic syndrome. Drugs known to be hydrolyzed by the enzyme cholinesterase, such as suxamethonium (succinylcholine) and procaine, may have sustained effects [104].

Hemoperfusion

Effects of hemoperfusion through coated resin adsorbent synachrome E-5 were studied in five

anesthetized dogs after intoxication by two to six times the LD_{50} of VX and another four dogs after intoxication by two to three times the LD_{50} of sarin. Hemoperfusion therapy prevented the development of serious signs of intoxication, provided that the dose of both nerve agents was only two times the LD_{50} . It was concluded that hemoperfusion therapy in poisoning by the nerve agents sarin and VX is only partially successful [45].

Yokoyama et al. (1995) reported a 45-year-old woman who was severely intoxicated by sarin during Tokyo subway attack. She had been treated with atropine, 2-PAM, and respiratory support, while she received hemofiltration and hemoperfusion because of an insufficient response to treatment. When she regained consciousness, her pupils were dilated, cholinesterase activity had increased, and the patient survived [119].

Based on the first author's clinical experience, charcoal hemoperfusion may be used in severely intoxicated OP nerve agent patients, as the OPs and some of their metabolites are lipid-soluble organic compounds and can be absorbed by charcoal.

Intravenous Lipid Emulsion

Following the introduction of intravenous lipid emulsion in the treatment of human poisoning with lipophilic drugs [120], some authors express a hypothesis that the combination of intravenous lipid emulsions can apply to treating severe OP poisoning [121]. However, in a study on mice, it showed no significant effect of intravenous lipid emulsion against OP toxicity [122]. Whether lipid emulsion is beneficial is unknown. For a severely poisoned patient *in extremis*, it may be potentially beneficial.

Special Populations

Pediatric Patients

Children are more susceptible to OP nerve agents, as was seen during the Sardasht and Halabjah massacres. Mortality was higher in children than in adults. Children have lesser mass and more surface/volume ratio, more immature respiratory

system, and stratum corneum in the skin that facilitates dermal absorption. Besides, their neurotransmitter systems are immature that makes them more susceptible to an epileptogenic stimulus [105, 123].

Children are more sensitive to atropine and oximes [123]. Atropine administration should include the monitoring of vital signs, especially the pulse rate. Atropine must be adjusted based on heart rate between 140 and 160 beat/min [104, 123] (Grade III recommendation). Loading dose of pralidoxime in children should be at 25 mg/kg, which is infused over 15–30 min. It may continue by 10–20 mg/kg/h to achieve a plasma concentration of >4 mg/L [110, 124]. Half-life of pralidoxime in children is about twice that of adults [105].

The Program for Pediatric Preparedness of the National Center for Disaster Preparedness (NCDP) issued the first recommendations and treatment guidelines of pediatric disaster and terrorism awareness that is nationally accepted [125]. They recommended that the Mark 1 Auto-injector kits should be applied as first treatment of children with severe and critical nerve agents poisoning, especially when intravenous therapy is impossible or unavailable [123, 125]. In a recent experimental study, perinatal (postnatal day [PND] 7, 14 and 21) and adult (PND 70) rats were more susceptible than pubertal (PND 28 and 42) rats to the lethal effects associated with exposure to tabun, sarin, soman, and cyclosarin [126].

Pregnant Patients

OP nerve agents may cross the placenta and induce fetal intoxication. The fetus is more sensitive to OP nerve agents than the mother and more sensitive to atropine than the mother. Fetal intoxication may occur because OP nerve agents cross the placenta. The sensitivity of fetus to OP compounds and atropine is higher than their mothers [110]. Clinical experience on pregnant women in Sardasht and Halabjah who were exposed to sarin in the Iran-Iraq war discovered that mortality rate is higher in fetus than in the

mothers [104, 110]. Fetus of survived sarin poisoned pregnant women died within a few hours to a few days [104]. However, some pregnant women in the second and third trimesters of pregnancy intoxicated with commercial OP compounds have been successfully treated with atropine and 2-PAM and have delivered healthy newborns [127].

In pregnant women, administration of atropine should be with caution and at lower doses. Pralidoxime has potential teratogenic properties in animal studies, but has not been shown in humans and therefore should be used as clinically required [128]. Obstetric consultation may be necessary. Removing of a dead fetus should be performed immediately after improving the mother's clinical condition [110].

OP nerve agents may be excreted in the mother's milk. It would be advisable to stop breast feeding at least for a few days after exposure [44].

Elderly Patients

Elderly people also are more susceptible to OP nerve agents. Experience with sarin poisoning during the Iran-Iraq War in Sardasht and Halabjah revealed that morbidity and mortality were higher among the elderly. Multiple organ failure and complications were more common among the elderly than other adult age groups. Atropine, oxime, diazepam, and any other medication should be administered with caution. Depending on the age and clinical condition of the patient, critical care therapy should be initiated more rapidly. Elderly patients with OP nerve agent poisoning should be treated in the same priority group as children [104].

Rescue Staff and Hospital Personnel

Rescue staff and hospital personnel who are in contact with victims of OP nerve agent poisoning may become intoxicated due to secondary exposure. Among 59 rescuers and duty physicians, 8 had mild symptoms of sarin poisoning during the Matsumoto incident. All the rescue activities

had taken place without gas masks or decontamination procedures [108].

Secondary contamination of house staff that treated victims occurred during the sarin Tokyo subway incident. More than 20% of the house staff had symptoms, including ocular pain, headache, sore throat, dyspnea, nausea, dizziness, and nasal pain, but none were seriously affected [7]. Rescue staff and medical personnel in the field, during transportation, and in the hospital should protect themselves by proper gas masks, clothing, and thick gloves (not surgical gloves) [104].

Experience in War and Terrorism

Observations during the nerve gas attack of the Iraqi army against the Iranian troops in Majnoon Island revealed that the heavily exposed people died within 30 min after onset of coma, convulsions, hypersecretion, respiratory failure, and apnea. Although the medical facilities were not adequate in Majnoon Island, first-aid treatment and decontamination were performed. The victims with moderate-to-severe intoxication were transferred from the field hospital to medical centers in big cities for further management [45].

Recorded clinical manifestations include miosis, hypersecretions, hypotension, nausea, vomiting, abdominal cramps, diarrhea, loss of consciousness, respiratory depression, cyanosis, pulmonary edema, muscle twitching, and convulsions. Bradycardia and hypotension were observed more before treatment with atropine, whereas tachycardia, normal hypertension, mydriasis, and dryness of the tongue were recorded more after atropinization. Morbidity and mortality were higher in patients with severe respiratory distress and cyanosis who received large doses of atropine. It is vital to correct the severe hypoxemia and cyanosis before atropinization (see section on “[Treatment](#)”). Suctioning of naso-oropharyngeal and bronchial secretions (clear airway) and establishing adequate ventilation are the first priority. Intermediate

syndrome, which was described after OP pesticide poisoning [63], has not been observed with nerve agent poisoning [44, 45].

Sulfur mustard was the most common chemical warfare agent that was used by the Iraqi army. Mixed poisoning by tabun and sulfur mustard also was common. No exact quantitative records of the nerve agent exposure are available. It has been estimated that greater than 2000 patients with nerve agent (later on diagnosed as tabun) poisoning were treated in March 1984. Another massive nerve agent poisoning occurred during the Halabjah massacre. It also was diagnosed as sarin and mixed with sulfur mustard [68, 69].

Two main terrorist attacks with sarin occurred in Japan. The first one occurred on June 27, 1994, in Matsumoto with about 600 casualties and 7 deaths [6]. The second attack occurred on March 20, 1995, in the Tokyo subway system, killing 11 and injuring more than 5500 people [7]. Diagnosis of sarin on both occasions was made based on the chemical analysis of environmental samples similar to the diagnosis of tabun in Majnoon Island and sarin in Halabjah [4]. Confirmative tests of serum sarin concentrations of the Halabjah massacre, Matsumoto incident, and Tokyo subway incident [70] and detection of sarin hydrolysis products from erythrocytes of four victims of the Tokyo subway incident [71] were performed after the incidents.

Preparation for a chemical incident resulting from an accident, war, or terrorism is important in every community. Because the rescue staff and medical personnel usually are from different departments, coordination between them is required. Guidelines and treatment protocols [129] should be available to all personnel. It should be updated at certain intervals to use the results of new research. For instance, recent clinical studies have confirmed that midazolam is effective when given at the onset of seizures caused by nerve agents. However, midazolam and the other benzodiazepines are less effective at terminating seizures when given 30 min or later after OP nerve agents seizure onset, likely because of internalization or

downregulation of synapses, which can lead to diminished potency and seizure recurrence [130].

Teaching the staff and performing a simulation exercise at certain intervals is necessary. Public awareness through the mass media and even written instructions to the public are valuable and may prevent chaos during the chemical incident [45].

Key Points in the Diagnosis and Management of Nerve Agents

1. Although plasma cholinesterase activity is given as percentages or U/mL, it should be valued qualitatively rather than quantitatively. Because of genetic variation in plasma cholinesterase, lower activity may be observed in 5–20% of normal individuals. However, treatment is based on clinical manifestations.
2. Hypokalemia and metabolic acidosis, which occur during organophosphate nerve agent poisoning, should be corrected near to the upper limit of normal range.
3. Administration of atropine in single repeated doses is mentioned in other textbooks. Mild-to-moderate atropinization must be produced and sustained until the patient's recovery.
4. Mydriatic eye drops are not needed; mydriasis will be induced by intravenous atropine.
5. Aminophylline and theophylline should not be administered for bronchospasm during organophosphate nerve agent poisoning. Anticholinergic bronchodilators and β_2 -agonists (salbutamol, terbutaline) should be administered instead.
6. Although pulmonary edema is less common in organophosphate nerve agent poisoning than in pesticide organophosphate poisoning, it should be treated only by atropine and not by morphine, aminophylline, furosemide, or digoxin. Morphine and aminophylline are contraindicated in organophosphate poisoning; furosemide might induce dehydration and electrolyte imbalance.

Conclusion

Nerve agents are the deadliest CWA that need immediate interventions. The Iraqi army used nerve agents against the Iranian troops and innocent civilians in the cities of Sardasht and Halabjah during the 1980s. Sarin was also used in terrorist actions in Matsomoto and Tokyo Metro in 1994 and 1995, respectively. It was used in Syria civil war as well in August 2013. In spite of the chemical weapons convention and the active role of the Organization for Prohibition of Chemical Weapons, nerve agents may be used again as CWAs in a war or terrorist attack. Therefore, health professionals should be familiar with the medical aspects of the nerve agents and prepare for appropriate action as required.

The nerve agents are OP compounds, similar to OP pesticides, but are more toxic than the pesticides. Applying first aid kits, for example, MARK1 is important to reduce toxicity. However, atropine and oximes are the well-known antidotes for the treatment of OP nerve agents. There are several adjuvant and additional therapies including magnesium sulfate, sodium bicarbonate, gacyclidine, benactyzine, tezampanel, hemoperfusion, and bioscavengers that have recently been used for OP nerve agents and pesticide poisoning with promising effects.

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The exact date of the first sulfur mustard synthesis is uncertain [1]. There are several reports on the formation of a chemical compound formed by the reaction of sulfur dichloride and ethylene in the early nineteenth century by the Belgian-French chemist César-Mansuète Despretz [2–5]. However, it is unclear whether Despretz realized the irritating or toxic properties of his newly discovered product [2]. The German chemist Albert Niemann reported in 1860 during experiments with ethylene and sulfur dichloride the formation of an oily liquid, “Even traces brought into contact with the skin, while painless at first, result in a reddening of the skin after several hours, and in the following days produce blisters which fester, heal slowly and with great difficulty, and leave behind significant scarring” [2, 6, 7]. Niemann likely suffered from sulfur mustard-induced pulmonary late effects that resulted in an early death. Almost in parallel, the British chemist Frederick Guthrie reported the same reaction [8, 9]. In 1886, the German chemist Viktor Meyer established the first reliable synthesis of pure sulfur mustard based on the chlorination of thiodiglycol, produced from chloroethanol and potassium sulfide, with phosphorus trichloride [10, 11]. This process is recognized as the “Meyer method” and has to be considered an important step toward the large-scale production of sulfur mustard [12]. The Levinstein process involved the reaction of ethylene and sulfur chloride and resulted in less pure products [3, 5, 13]. These impurities are responsible for the characteristic odor (garlic-, horseradish-, mustard-like) of non-distilled sulfur mustard [3, 5, 14, 15].

The use of chemicals for warfare can be dated to World War I. At the beginning of World War I, there was a widespread belief that the conflict would be short or, at least, would last for a few months only [16]. However, as the battle turned into a trench war, combating parties progressively ran out of conventional ammunition. Thus, other means of warfare were considered. A well-developed chemical industry, especially in Germany, resulted in an unfortunate coalition of politics and science [11, 16]. From 1914 attempts were made in a number of countries to convert harmless chemical compounds into chemical

weapons [11]. Sulfur mustard found its way onto the battlefield. Fritz Haber, director of the Kaiser Wilhelm Institute for Physical Chemistry and Electrochemistry in Berlin, was the driving force for its use. Wilhelm Lommel, an employee of the Bayer company in Leverkusen and Wilhelm Steinkopf, head of the chemical weapons research unit of Haber’s institute, investigated the toxicochemical properties of sulfur mustard in 1916. They developed a method for its mass production and prepared the agent for use in the war [16, 17]. This circumstance is the reason for the acronym “S-Lost,” representing “S” for “Schwefel” (sulfur) and the initials of *L*ommel and *S*teinkopf.

On July 12, 1917, the German artillery delivered approximately 50,000 sulfur mustard containing shells near Ypres, Belgium [18]. More than 20,000 casualties resulted from this first use of sulfur mustard as a chemical warfare agent [19]. Although sulfur mustard was introduced later in the war, it became known as the “King of Battle Gases” because it eventually caused more chemical casualties than all the other agents combined, including chlorine, phosgene, and cyanogen [19]. In summary, the use of chemical weapons such as chlorine, phosgene, and mustard gas had resulted in more than 1.3 million casualties and approximately 90,000 deaths and entitled World War I as “the chemists war” [2, 5, 19].

After the initial use of sulfur mustard in World War I, further use was reported including the Rif War in Morocco (1921–1926), the Italian–Ethiopian War (1935–1936), the Japan–China War (1939–1945), and the Egypt–Yemen War (1963–1967) [4, 11]. Fortunately, chemical weapons were not deployed in World War II, although their use was almost put into practice: Germany stockpiled nerve agents and about 25,000 t of sulfur mustard, while the USA stockpiled a total of about 135,000 t of chemical agents in 1945 [20]. As the USA did not possess nerve agents at that time, thus it has to be assumed that the majority of the US stockpiles may have been alkylating agents and lung agents. Moreover, the US Liberty ship “SS John Harvey” carried approximately 100 t of sulfur mustard and was bombed by the German Air Force during the air raid on Bari,

December 2, 1943. The destruction of the John Harvey caused the release of sulfur mustard. Eight hundred men were hospitalized, of whom 617 suffered from sulfur mustard exposure [21]. In 1981, Iraq invaded Iran (Gulf War I, 1981–1988). During that conflict, Iraq repeatedly used sulfur mustard, even against civilians [1]. Probably the most severe attack took place in 1987, when the Iraqi army delivered 1 t of sulfur mustard on Sardasht, a Kurdish town in northern Iran [22]. Today, it is estimated that about 45,000 Iranians still suffer from severe long-term health effects from these attacks [4]. Now, chemical weapons are banned by the Chemical Weapons Convention (CWC) which came into force in 1997 and has been signed by 192 member states ([23, 24] accessed on 22.02.2016). One major goal of the CWC is the destruction of all existing chemical weapons under international verification by the Organisation for the Prohibition of Chemical Weapons. Although substantial progress in the destruction of old chemical munitions, including sulfur mustard stockpiles, has occurred, there is strong evidence that terrorist groups used sulfur


mustard against Kurdish Peshmerga forces in Iraq [25]. Whether sulfur mustard was acquired from old ammunition or has been synthesized de novo is a matter of debate. However, the chemical synthesis of sulfur mustard can be achieved by simple means. Moreover, accidental exposures during the destruction and neutralization of sulfur mustard have been reported [26].

Relevant Chemistry

Sulfur Mustard

Sulfur mustard (bis(2-chloroethyl)sulfide, CAS Number 505-60-2) – also referred to as Yperit(e) with regard to its first use on the battlefield near Ypres, “Senfgas” which is the German translation of mustard gas, “yellow cross” as German sulfur mustard shells were marked with a yellow cross, H and HS (“Hun Stuff”) or HD (“Hun Stuff distilled which is also the official NATO code”) – is an oily liquid at room temperature (Table 1) [3, 27,

Table 1 Important physicochemical properties of sulfur mustard [3–5, 14, 15, 21, 27–29]

Chemical name	bis(2-chloroethyl)sulfide
Common names	Sulfur mustard
	Mustard gas
	Yperit(e)
	Senfgas
	H, HS, HD
CAS Number	505-60-2
Chemical formula	$C_4H_8Cl_2S$
Chemical structure	
Molecular weight	159.08 g/mol
Density	Solid 1.34 mg/cm ³
	Liquid 1.27 mg/cm ³
Appearance at 20 °C	Oily liquid
	Colorless to pale yellow to dark brown
Melting point	13–14.5 °C
Boiling point	217.5 °C
Solubility	Poor in water (920 mg/L at 22 °C)
	Good in organic solvents (e.g., alcohol, ether)
	Soluble in fat
Vapor pressure	0.08 mmHg at 22 °C
	0.11 mmHg at 25 °C
	0.23 mmHg at 30 °C

28]. Thus, the term mustard “gas” is imprecise although it is commonly used in general linguistics. Pure sulfur mustard is colorless. When produced in “industrial” large scale and allotted to chemical warfare, the agent is pale yellow to black brown [14, 28, 29]. Weapons-grade sulfur mustard may contain stabilizers, starting materials, or by-products formed during manufacturing and products formed from slow reactions during storage [28]. These impurities are responsible for the characteristic odor (garlic-, horseradish-, mustard-like) and color (Fig. 1) [3, 5, 14, 15]. The vapor pressure of sulfur mustard is moderate (0.11 mm Hg at 25 °C), but is high enough for it to be in air in the immediate vicinity of liquid droplets [28, 29]. At 25 °C, sulfur mustard deposited on surface soil will evaporate within 30–50 h [28]. Weather conditions (i.e., temperature and wind) will greatly affect the persistence of sulfur mustard on soil. Warm temperatures and stronger winds decrease the persistence of sulfur mustard [28]. In winter, sulfur mustard can still be detected after as long as 2 weeks [28]. Sufficient levels of chlorine in the water (e.g., salt water) will inhibit sulfur mustard hydrolysis. Moreover, stable sulfonium polymers may be formed at the outer surface of a sulfur mustard droplet in salt water. These polymers are able to accumulate, thus creating a thick boundary

layer, which prevents hydrolysis of sulfur mustard within the inner part of the droplet. Thus, sulfur mustard may persist over decades.

Nitrogen Mustards

Nitrogen mustards (HN) (Table 2) are also alkylating agents similar to mustard gas. Although HN1, HN2, and HN3 were developed for use in chemical warfare, they never found their way onto the battlefield [31]. However, during their development in World War II, scientists and physicians noted their antitumor potential, especially with regard to hematologic malignancies [32, 33]. Soon, clinical trials were started and these heralded the new age of chemotherapy [34, 35]. Other nitrogen mustards including cyclophosphamide, chlorambucil, uramustine, ifosfamide, melphalan, and bendamustine were developed and are still in use for chemotherapy [36]. Some of these substances require conversion into active substances in vivo (e.g., cyclophosphamide). Exposure to nitrogen mustards may cause a comparable clinical picture compared to sulfur mustard [3].

Pathophysiology

Although medical research for many decades has proposed several hypotheses of sulfur mustard-induced pathological effects, none of these hypotheses is considered all encompassing. It is likely that the plethora of proposed mechanisms identified so far runs in parallel and results in a complex pathophysiology, which is not completely understood [37–39].

Alkylation

Alkylating properties of sulfur mustard are well established. One of the chlorine atoms can be cleaved resulting in a carbenium ion [5, 21, 37]. This highly reactive carbenium ion is capable to cause covalent modification of various biomacromolecules including RNA, DNA, and proteins, thus altering their biological function

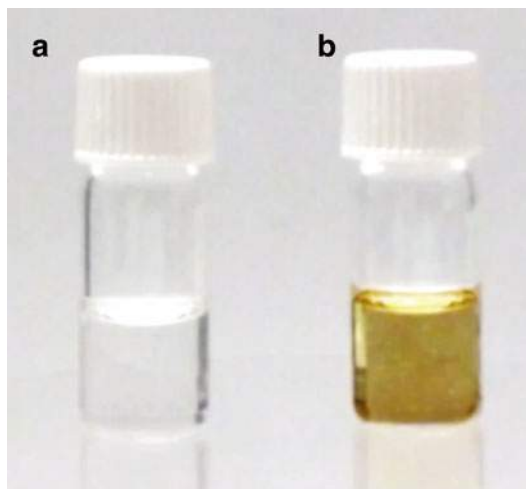
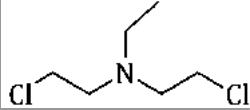
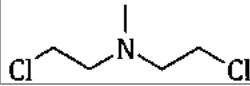
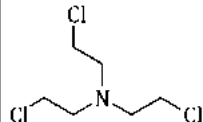


Fig. 1 Sulfur mustard from different sources. NMR spectroscopy revealed a purity of >99.9% (a) and 98.5% (b). Copyright [30]

Table 2 Overview of selected nitrogen mustards [3]

HN1	
Chemical name	bis(2-chloroethyl)ethylamine
Common names	n.a.
CAS Number	538-07-8
Chemical formula	$C_6H_{13}Cl_2N$
Chemical structure	
HN2	
Chemical name	2,2'-dichloro- <i>N</i> -methyldiethylamine
Commons names	Chlormethine Mechlorethamine Mustine Mustargen
CAS Number	51-75-2
Chemical formula	$C_5H_{11}Cl_2N$
Chemical structure	
HN3	
Chemical name	2,2',2''-trichlorotriethylamine
Commons names	n.a.
CAS Number	555-77-1
Chemical formula	$C_6H_{12}Cl_3N$
Chemical structure	

[21, 37, 38, 40, 41]. Well documented and comprehensively analyzed are covalent alkylations of nucleic acids [3, 5, 37, 42–44].

Experiments conducted by Brookes and Lawley demonstrating covalent binding of sulfur mustard to bacterial DNA represent the pioneering work in that field [43]. Later on, it was found that the reaction of DNA and sulfur mustard in vitro led to the alkylation of guanine bases at the N7-position, resulting in the formation of N7-(2-((2-hydroxyethyl)thio)-ethyl)guanine (“N7-HETEG”) as the most abundant adduct (Fig. 2) [42]. Other adducts were found at the N3-position of adenine bases resulting in N3(2-((2-hydroxyethyl)thio)-ethyl)adenine (“N3-HETEA”) [42]. Sulfur mustard possesses two side chains which are both highly reactive. Thus, the formation of bifunctional adducts between DNA resulting in bis(2-

(guanineethyl)sulfide) (“Bis-G”) is frequently observed [42]. A less abundant but biologically highly relevant adduct is the alkylation product of guanine at the O6-residue resulting in the formation of O6-[2-[(2-hydroxyethyl)thio]ethyl]guanine (O6-HETEG). This adduct was found to account only for some 0.1% of all adducts, but apparently this lesion is lacking repair via DNA alkyltransferases and thus has to be considered mutagenic [45]. The frequency of occurrence of these sulfur mustard–DNA adducts may vary to some extent. Investigations using high-resolution mass spectrometry techniques revealed a considerably higher rate of bifunctional adducts after sulfur mustard exposure, both in vitro and in vivo [46]. N7-HETEG occurred in 64–81%, Bis-G in 18–42%, N3-HETEA in 1.3–4.6%, and O6-HETEG in 0.04–0.62% of all DNA adducts

et al. in 1979 who demonstrated that UV light-provoked DNA lesions induced the formation of poly(ADP-ribose) and facilitated DNA repair [68]. The role of poly(ADP-ribosylation) ("PARylation") in DNA repair is complex and not fully understood. In general, PARylation is a posttranslational modification mediated by poly(ADP-ribose) polymerases ("PARPs") in response to various stimuli [54]. Two members of the PARP-family (PARP-1 and PARP-2) are activated by DNA strand breaks [54]. Most probably, PARylation represents a sensor and marker of DNA lesions and inducer of DNA repair [54, 69]. Thus, PARPs might orchestrate the delicate balance between survival and death signaling [70]. The role of PARylation in sulfur mustard cell damage has been extensively investigated [54, 71–73]. PARylation is dependent on the availability of cofactors (NAD) and energy equivalents (ATP) [68]. Thus, excessive PARylation may cause severe depletion of these indispensable cofactors with the consequence of rapid, uncontrolled cell death (necrosis) (Fig. 3). Based on that fact, Berger formulated his well-known "suicide hypothesis" which correlates cell death to the depletion of cofactors (i.e., NAD) during PARylation of DNA strand breaks [68]. With regard to sulfur mustard-induced DNA lesions, Papirmeister and colleagues postulated the occurrence of DNA strand breaks as repair intermediates triggering PARP-1 activation and subsequent loss of NAD and ATP, which resulted in cell death (Papirmeister theory) [74]. As a corollary, PARP inhibitors were tested as potential antidotes against sulfur mustard toxicity. Although PARP inhibitors were able to maintain NAD levels in sulfur mustard-exposed cell, the overall cell survival was not improved, but a shift from necrosis to apoptosis was evident [61, 75–77].

Apoptosis and Necrosis

Cell death is a key event after sulfur mustard injury. Both apoptosis and necrosis can be observed [37, 61, 62, 71, 78, 79]. At high-dose exposures, sulfur mustard predominantly provokes cell death through necrosis caused by

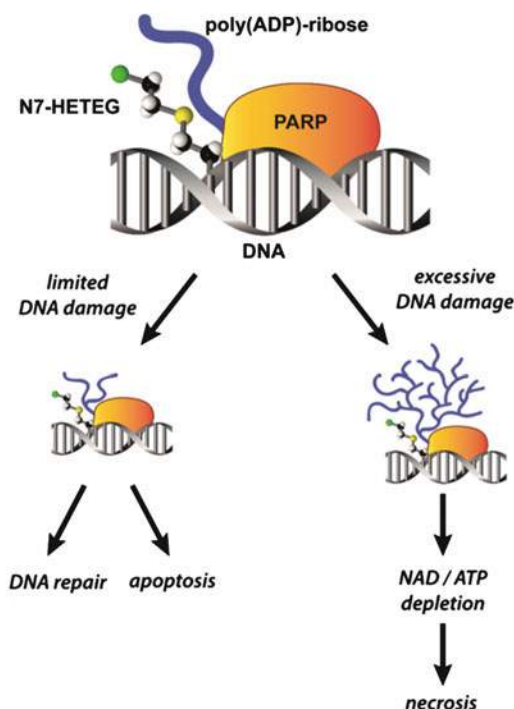


Fig. 3 Role of PARP during sulfur mustard-induced cytotoxicity ([37] modified). Sulfur mustard-induced DNA lesions are recognized by PARP. DNA repair or controlled cell death mechanisms are initiated when there is limited DNA damage. Excessive DNA damage results in cofactor depletion and necrosis

PARP activation and cofactor depletion. Even though recent findings also describe necrosis as an orchestrated process [80], it has to be considered as a "worst case" scenario which is barely controllable. In contrast, apoptosis is a highly controlled and regulated mode of cell death. The apoptotic machinery is driven by the activation of proteases known as caspases (cysteine-dependent, aspartate specific proteases) [81, 82]. In short, the activation of effector caspase-3, caspase-6, or caspase-7 results in cleavage of a plethora of cellular proteins. The breakdown products are embedded into membrane-surrounded apoptotic bodies, which are released into the extracellular space. These remnants are cleared by efferocytosis. In contrast to necrosis, there is no significant contact of cytoplasmic content with the environment thus preventing an inflammatory response frequently observed during necrosis. There are numerous studies demonstrating

apoptosis after sulfur exposure both in vitro [83–85] and in vivo [86, 87].

Death receptor-mediated apoptosis (also called “extrinsic apoptosis”) is initiated by binding of specific ligands (e.g., Fas ligand) to their designated receptors (e.g., Fas receptor) initiating apoptosis. This process has also been demonstrated for sulfur mustard [88–90]. Both Fas ligand and receptor were upregulated in sulfur mustard-exposed human keratinocytes, and keratinocytes lacking the Fas-associated death domain were less sensitive than wild-type cells [88]. In vivo findings underline the relevance of Fas-mediated apoptosis in sulfur mustard pathophysiology because an increase of Fas ligand was detected in the bronchoalveolar lavage fluid of sulfur mustard-exposed rats [90].

In contrast to extrinsic, death receptor-mediated apoptosis, intracellular events may also initiate apoptosis (so-called intrinsic apoptosis). Proteins of the Bcl-2 family, which regulate the mitochondrial outer membrane permeabilization (MOMP) and the release of proapoptotic mitochondrial proteins (e.g., apoptosis-inducing factor) into the cytosol can trigger apoptosis and finally lead to activation of effector caspase-3. [91] Sulfur mustard impacts the Bcl-2 family of proteins and MOMP [92].

Inflammation

A common characteristic of sulfur mustard injury is inflammation. In vitro and in vivo studies document an increase of pro-inflammatory cytokines after sulfur mustard exposure [83, 93–100]. IL1(α/β), IL6, IL8, and TNF α are key players in the pro-inflammatory response and are released shortly after sulfur mustard exposure [37, 101–103]. The number of inflammatory leukocytes (e.g., neutrophils, macrophages) increased in mouse skin after exposure to nitrogen mustard, underlining the relevance of the in vitro findings [104].

NF- κ B and mitogen-activated protein kinase pathways have been reported to be substantially involved in the regulation of pro-inflammatory gene expression after sulfur mustard injury [105, 106]. Remarkably, Nf κ B pathways were found upregulated in sulfur mustard-exposed patients [107]. Moreover, sulfur mustard increased the

expression of other pro-inflammatory proteins, e.g., cyclooxygenase (COX)-2, inducible nitric oxide synthase, or myeloperoxidase [98, 108].

Reactive Oxygen and Nitrogen Species

Superoxide ($O_2^{\bullet -}$) and hydroxyl radicals (OH^{\bullet}) represent the two major oxygen-derived radicals (reactive oxygen species (ROS)). Radical nitrogen species (RNS) contain the nitric oxide radical (NO^{\bullet}). In a biological context, both ROS and RNS are formed in normal metabolism and have important roles in cell signaling and homeostasis [109, 110]. Reactive oxygen species and RNS are generated by tightly regulated enzymes, such as NO synthase (NOS) and NAD(P)H oxidase isoforms, respectively. Depending on the micro-environment, nitric oxide (NO) can be converted to various other RNS such as nitrosonium cation (NO^+), nitroxyl anion (NO^-), or peroxynitrite ($ONOO^-$), which represents the reaction product of $O_2^{\bullet -}$ and NO^{\bullet} [110]. Thus, levels of ROS and RNS will influence each other. Moreover, catalytic or stoichiometric scavengers like GSH may intercept ROS and/or RNS and thus attenuate ROS- or RNS-induced cell damage. Reactive oxygen species and RNS have been proposed as key mediators of sulfur mustard-induced cytotoxicity [108, 111–113]. Indeed, glutathione (GSH) depletion due to sulfur mustard exposure was demonstrated both in vitro and in vivo [114, 115]. First direct evidence that radicals are involved in sulfur mustard toxicity was provided by electron paramagnetic resonance spectroscopy showing that free radical and lipid peroxidation occurred in vivo after pulmonary exposure to sulfur mustard vapors [116]. In addition, sulfur mustard-induced formation of carbon-based radicals with subsequent formation of superoxide, peroxy, and hydroxyl radicals has been shown [117]. Further, superoxide radicals derived from catalytic uncoupled endothelial NO synthase have been implicated in contributing to sulfur mustard cytotoxicity [108]. Moreover, the conjugation of GSH with sulfur mustard has been demonstrated [118, 119] and may be conducive to enhanced ROS levels.

To make matters worse, sulfur mustard decreases antioxidant enzyme activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase in vivo [120], thereby aggravating ROS-induced cell damage. There are numerous reports that demonstrate the involvement of NO/NOSs in sulfur mustard toxicity [121–124]. Recent work has demonstrated mitochondrial dysfunction and mitochondrial-derived ROS as an important event in sulfur mustard pathophysiology [125–128].

Toxicokinetics

Sulfur mustard can enter the body through different routes. Absorption of the agent after skin contact and vapor absorption through the respiratory system are the two major routes of uptake [4, 40, 129]. Uptake of sulfur mustard through the gastrointestinal system or eye contact is theoretically feasible, but of minor relevance with regard to toxicokinetics. Nevertheless, local health effects would be severe [40].

Skin Absorption

The penetration rate of liquid sulfur mustard was determined ex vivo with 71–294 $\mu\text{g}/\text{cm}^2/\text{h}$ using a Franz-type glass diffusion cell [130]. Absorption through human skin was estimated with 60–240 $\mu\text{g}/\text{cm}^2/\text{h}$ [130]. There are some relevant parameters like skin thickness, hair density, and moistness that may have an impact on the absorption rate. Early reports have postulated that under nonocclusive conditions, about 80% of topically applied sulfur mustard will evaporate and only 20% will be absorbed [131]. From this fraction, 10–20% is likely to react with biomacromolecules and 80–90% reach the blood circulation [130, 131]. A depot of sulfur mustard within the lipid-rich stratum corneum is likely to exist [131]. After a 12 min application of ^{14}C -labeled sulfur mustard vapors, 90% of total radioactivity was located in the exposure skin area [132]. Occlusion of the skin after contact to sulfur mustard may result in a dramatic increase (up to 100-fold) of absorption [133].

Respiratory Absorption

The absorption of sulfur mustard through the respiratory system is a highly relevant route of entry when the agent is used in armed conflicts or in terrorist attacks. Sulfur mustard is readily absorbed in the upper respiratory tract [4, 40]. However, some studies postulate that sulfur mustard does transit the distal upper airways to promote lower airway injury [134]. Toxic lung injury of the lower airway system with alveolar epithelial injury and detachment of cells from basement membranes following exposure to mustards is frequently observed [135]. In vivo experiments in rats revealed that after a 10 min exposure toward 250 mg/m^3 ^{14}C sulfur mustard vapor, a total of 18.1 μg sulfur mustard was absorbed [132].

Distribution

In deceased victims it was found that highly lipophilic sulfur mustard accumulates in fatty tissues (Table 3) [136, 137]. The distribution of sulfur mustard can be described by using a two-compartment model with an initial α -halftime of 5.56 min and a terminal β -halftime of 3.59 h with a steady-state distribution volume of 74.4 l/kg [138].

Biotransformation

Sulfur mustard is rapidly hydrolyzed in physiological environment, resulting in the major biotransformation product thiodiglycol (TDG) [40, 139]. Thiodiglycol may further be oxidized to TDG sulfoxide which is then conjugated to glutathione forming 1,1'-sulfonylbis[2-S-(*N*-acetylcysteinyl)ethane]. Following the β -lyase pathway, the 1,1-sulfonylbis[2-(methylsulfinyl)ethane] (SBMSE) and 1-methylsulfinyl-2-[2-(methylthio)ethylsulfonyl] (MSMTESE) ethane can be formed [40]. In addition, sulfur mustard is able to react with free cysteines of various proteins [40]. Sulfur mustard adducts have been identified especially in albumin and hemoglobin [55, 140, 141] but also in other proteins e.g., cytokeratins or actin [48].

Table 3 Sulfur mustard tissue concentration in a deceased victim [136]

Tissue/Organ	Concentration (mg/kg)
Fat	15.1
Skin, including subcutaneous fat tissue	11.8
Brain	10.7
Skin	8.4
Kidney	5.6
Liver	2.4
Muscle	3.9
Cerebrospinal fluid	1.9
Spleen	1.5
Blood	1.1
Lung	0.8
Urine	Not detected
Blister fluid	Not detected

Elimination

Sulfur mustard metabolites are eliminated mainly through the renal route [132, 138, 142–144]. Eighty percent of radioactivity from ^{14}C -labeled sulfur mustard was found in urine, whereas only 3% were excreted with feces [138]. It is important to realize that distinct background levels of TDG and TDG sulfoxide can be found in the urine of healthy, unexposed persons, whereas the β -lyase pathway products were exclusively found in the urine of exposed individuals. The total clearance of sulfur mustard was calculated at 21 l/kg/h [138].

Clinical Presentation

Sulfur mustard is classified as a vesicant or blister agent. However, the agent can affect other organs or tissues. Skin, respiratory tract, eyes, and internal organs (bone marrow) are all targets of sulfur mustard toxicity. A malicious characteristic of sulfur mustard injury is the fact that contact with the agent does not immediately cause any clinical symptoms [1, 12, 20, 26]. Depending on exposure dosage and time, the onset of clinical symptoms may occur within

a few hours to up to 24 h [1, 12]. The maximum intensity of symptoms can be reached after days [12]. Sulfur mustard can cause acute, chronic, and delayed health effects.

Acute Health Effects

Skin

Sulfur mustard penetrates rapidly through normal clothing and predominantly affects moist and thin skin areas, e.g., the genital or axillae region [4, 26]. Physical stress with increased blood circulation and sweating as well as local mechanical shear stress (e.g., from a backpack) may enhance sulfur mustard-induced skin effects. The onset of cutaneous symptoms depends on the concentration of sulfur mustard vapor and exposure time (concentration * time). At higher doses symptoms occur within a few hours [4, 12, 26]. For dermal exposures, sulfur mustard vapor concentrations between 100–300 $\text{mg} \cdot \text{min} / \text{m}^3$ and liquid amounts between 10–20 $\mu\text{g} / \text{cm}^2$ have been postulated as threshold doses [12]. Beyond these concentrations, clinical symptoms will start with itching and erythema some 4–8 h after exposure (Fig. 4, Table 4). At higher doses (vapor, 1000–2000 $\text{mg} \cdot \text{min} / \text{m}^3$; liquid, 40–100 $\mu\text{g} / \text{cm}^2$), blister formation starts with the formation of small vesicles which may flow together to form large bullae [12]. Typical sulfur mustard-induced blisters are thin walled and filled with a yellowish liquid, which do not contain any agent [12]. Sulfur mustard targets rapidly proliferating keratinocytes of the basal layer in the first line. Blister formation occurs between the epidermis and dermis [145, 146]. The Nikolsky signs – which are associated with toxic epidermal necrolysis – are positive [12]. Sulfur mustard-induced blisters disrupt if they are large enough and may proceed to deep ulcerations, which are associated with wound-healing disorders [147–149]. Inflammation of affected skin areas is frequently observed [4, 12, 20, 145]. Moreover, hyperpigmentation that can last for years is also common [4, 26].



Fig. 4 Clinical presentation of an accidental sulfur mustard exposure on day 7 after exposure. Three exposure sites (thorax, middle abdomen, lower abdomen) are distinguishable. A distinct erythema and deep ulcerations at all sites are evident [150]

Table 4 Acute dermal symptoms after sulfur mustard exposure ([12] modified)

Severity	Clinical presentation
Mild	Erythema
	Itching
Moderate	Severe erythema
	Blister formation
Severe	Rapid development of erythema and blisters
	Ulceration of dermal structures

Lungs

The respiratory tract is more sensitive to sulfur mustard than the skin. Sulfur mustard vapor concentrations in the range of 12–70 mg*min/m³ are able to induce clinical symptoms within a few hours [147]. The onset of symptoms correlates inversely with the dose of sulfur mustard. Acute human lung exposures to sulfur mustard can be lethal in a short period (the mortality of sulfur

mustard is stated with 2–3% [5] and is mainly attributed to acute lung injury [151]). On the other hand, exposure may also lead to chronic devastating airway or pulmonary disorders [152]. Effects of sulfur mustard on the respiratory tract from the nasal mucosa to the terminal bronchioles are dose dependent [4]. After a symptom-free period irritation of nasal mucosa, hoarseness, sneezing, and coughing are the first clinical signs of respiratory tract damage (Table 5) [12, 153]. Moderate exposure results in lacrimation, rhinorrhea, loss of smell and taste, and discharge of mucus from nose and throat [4, 12, 151]. Although sulfur mustard predominantly affects the upper respiratory tract, with increasing dose, the terminal airways may also be affected causing severe cough, dyspnea, and hemorrhage into the alveoli and lung edema [154]. A critical event is the detachment of pulmonary epithelium which mixes with mucus and edema fluid resulting in the formation of “pseudomembranes,” resembling those characteristic of diphtheria infection, which can slough and obstruct the airway with fatal consequences [151]. Severe forms of lower airway disease can be expressed as the acute respiratory distress syndrome (ARDS), with a high mortality rate [153]. Pulmonary inflammation usually develops within a few days after sulfur mustard exposure. In severe cases, bacterial superinfection and lung gangrene may occur [153].

Eyes

The eyes are the most sensitive organ with regard to sulfur mustard exposure. Clinical symptoms develop generally faster (i.e., within 1–2 h) compared to other effects, such as skin lesions [12]. Acute intoxication presents with conjunctivitis, blepharospasm, lacrimation, miosis, photophobia, eyelid edema, and severe eye pain (Table 6) [12, 147, 151]. Sulfur mustard vapor doses beyond 400 mg*min/m³ result in severe full-thickness corneal damage with ulcerations and occlusion of conjunctival blood vessels due to endothelial damage [12]. Corneal vascularization starts a few weeks later leading to pannus formation [12]. Iranian victims reported a burning sensation and pain in the eyes and throat shortly

Table 5 Acute pulmonary symptoms after sulfur mustard exposure ([12] modified)

Severity	Clinical presentation
Mild	Irritation of nasal mucosa
	Hoarseness
	Sneezing
	Coughing
Moderate	Lacrimation
	Rhinorrhea
	Loss of smell and taste
	Hacking cough
	Tracheobronchitis
	Pseudomembranes
Severe	Edema in upper and lower airways
	Ulcerations

(within minutes) after an attack with the agent [12]. Severe blepharospasm may prevent lifting the eyelid which may be perceived as “blindness” [129]. However, recovery from conjunctivitis after mild ocular exposure (dose range of 12–70 mg*min/m³) can usually be observed within a few days [151]. Additional reports from Iranian casualties revealed that 75% of the patients presented severe (purulent) conjunctivitis [129]. Conjunctivitis (18%), opacity of the cornea (27%), and erosions and opacity of the cornea (50%) were the most severe eye complications, and only 36% of the patients showed a full recovery at discharge [129].

Systemic Toxicity

The effects of systemic sulfur mustard poisoning are very similar to those caused by radio- or chemotherapy. This is not surprising, as described earlier, alkylating chemotherapeutic agents which are still frequently used in clinical cancer therapy, originated from the alkylating sulfur mustard [4]. Low-dose exposure may result in headache, nausea, vomiting, and loss of appetite (Table 7). High-dose exposure may damage the gastrointestinal tract and the bone marrow more severely. After initial leukocytosis [155], a significant reduction of white blood cell count was reported in mustard gas intoxication by all routes of exposure [156]. This may result in severe immunosuppression due to the bone marrow

Table 6 Acute ocular symptoms after sulfur mustard exposure ([12] modified)

Severity	Clinical presentation
Mild	Conjunctivitis
	Grittiness under the eyelid
	Tearing
	Pain
Moderate	Corneal edema
	Photophobia
	Severe blepharospasm
	Moderate to severe pain
Severe	Severe corneal damage
	Ulceration
	Perforation

suppression reported in patients exposed to high doses of sulfur mustard [4, 12, 151, 155, 156]. Hemorrhage, anemia, and other hematological complications are other bone marrow-related consequences [12]. Bone marrow and blood count examination of Iranian casualties revealed a toxic-infectious picture similar to the side effects of cytostatic treatment. Specifically, erythropoiesis was altered and showed signs of hyperplasia (78%) or dyschromia (44%). Granulopoiesis was suppressed (22%) or showed a left shift (33%). Megakaryopoiesis was increased in 22% of the investigated patients [129].

Chronic Health Effects

Skin

Chronic skin injury usually arises in veterans who developed blister formation and skin necrosis after sulfur mustard exposure [157]. Hyper- and hypopigmentation (poikiloderma) and dermal scarring are also frequently observed [4, 26]. Hyperpigmentation (20–55% incidence) seems to occur more often than hypopigmentation (5–25% incidence) [158]. Moreover, skin dryness is observed in formerly affected skin areas [12, 26, 151]. Persistent pruritus, burning sensations, and desquamation may occur [4, 12, 157]. Lesions characterized by erythema and edema only, without vesication and ulceration, usually do not result in chronic dermal effects [159]. Malformations of the vasculature in

Table 7 Acute systemic symptoms after sulfur mustard exposure ([12] modified)

Severity	Clinical presentation
Mild	Nausea and vomiting
	Loss of appetite
Severe	Immune suppression
	Leucopenia
	Diarrhea
	Cachexia

the form of cherry-like hemangiomas and telangiectasia have been observed in some patients [160]. Others may complain about paresthesias in formerly affected skin regions [160].

Lungs

Sulfur mustard-induced acute pulmonary lesions may directly progress to long-lasting chronic health effects [12, 151]. However, delayed onset of chronic lung injury can also be observed. It is assumed that up to 43% of Iranian veterans are still suffering from sulfur mustard-induced lung injury [161]. Remarkably, death that was related to a sulfur mustard exposure is believed to be caused by pulmonary lesions or pulmonary dysfunctions primarily [162]. Common clinical findings are chronic cough, dyspnea, and sputum production [163, 164]. Late pulmonary effects after sulfur mustard injury include obstructive and restrictive lung diseases that have been referred to as “Mustard Lung” [163–165]. The clinical picture of Mustard Lung resembles common signs and symptoms of chronic obstructive pulmonary disease (COPD). Sputum production, shortness of breath, and a productive cough occur in patients with Mustard Lung. Additionally, a reduced ratio between forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) supports the diagnosis, especially in patients with previous blister formation [164]. Bronchiectasis, air trapping in expiration, and mosaic parenchymal attenuation are indicative of a diagnosis of bronchiolitis obliterans (BO) in sulfur mustard-exposed patients [166, 167]. However, the exact mechanisms leading to Mustard Lung have not been unraveled. Some distinct pathophysiological differences have been described, e.g., although inflammation is known as one of the main

pathogeneses involved in COPD, there is some debate whether inflammatory processes have significant contributions to the pathogenesis of Mustard Lung [165]. Chronic persistent bronchitis was reported in 59% of patients with a single severe sulfur mustard exposure. These individuals suffer from a severe morbidity [162, 168]. Pulmonary involvement has been considered the major determinant of long-term mortality and morbidity in sulfur mustard-affected individuals [169]. 20 years after sulfur mustard exposure, BO has been identified as the most prominent delayed respiratory effect [169, 170]. On the other hand, pulmonary fibrosis was also found in sulfur mustard-exposed Iranian soldiers [171]. Fibrotic remodeling of the lung may also result in significant scars and narrowing of the bronchial system, thus aggravating chronic lung injury.

Eyes

Ocular damage was diagnosed in 39.3% of sulfur mustard-exposed Iranian casualties, in particular after high-dose exposures [161]. In the chronic phase, the patients may complain of itching, burning sensation, photophobia, tearing, decreased vision, dry eye, red eye, ophthalmic pain, and foreign body sensation [151]. Chronic sulfur mustard-induced eye injury is known as “mustard gas keratopathy” (MGK) and is characterized by persistent epithelial lesions, corneal neovascularization, progressive corneal degeneration, chronic blepharitis, meibomian gland dysfunction, dry eye, perilimbal conjunctival ischemia, stem cell deficiency, epithelial irregularity, recurrent or persistent epithelial defects, corneal neovascularization, tortuous blood vessels, stromal scarring, and secondary degenerative changes including lipid and amyloid deposition [4, 172–174]. Remarkably, MGK can develop between 15 and 20 years after exposure [175, 176]. The pathophysiology of these changes is not clear. Limbal stem cell deficiency is proposed [172, 177].

In some cases, an ocular phenomenon known as delayed-type ulcerative keratitis, characterized by corneal thinning, corneal opacification and neovascularization, and corneal epithelial deficiency, may occur after a symptom-free period [151]. Delayed-type ulcerative keratitis may lead

to late-onset blindness and may even persist after corneal transplantation [151].

Cancer

The DNA-alkylating compound sulfur mustard is classified as a Group I carcinogen (definite human carcinogen) by the International Agency for Research on Cancer (IARC) [178]. There are numerous *in vitro* studies that have demonstrated mutagenic properties of sulfur mustard using phages, bacteria, fungi, protozoa, plants, or insects [4, 179]. *In vivo* experiments investigating carcinogenicity in rats and mice after sulfur mustard exposure through different routes (oral, skin, inhalation, subcutaneous or intramuscular administration) resulted in a significant increase of tumor incidence [4, 178–182]. Also *in vivo*, sulfur mustard induced micronuclei formation in mouse bone marrow cells [183]. In summary, it is established that sulfur mustard has mutagenic and carcinogenic potency in animals.

However, despite the IARC assessment, evidence for carcinogenicity of sulfur mustard in humans is mixed. Definitive evidence of the carcinogenic properties of sulfur mustard was provided by occupational exposures of individuals working in chemical warfare agent plants [182]. Studies revealed an increased incidence of different cancers, especially of the respiratory tract, in workers of Japanese, German, or British chemical agent factories [182, 184]. Workers responsible for the deconstruction of the “Heeresmunitionsanstalt St. Georgen” in Germany after WWII were inadequately equipped with protective measures [12]. Here, an increase of multiple skin tumors, such as basal cell carcinoma, Bowen’s disease, Bowen’s carcinoma, and spinocellular carcinoma, was detectable [12].

Experience from World War I revealed a positive association between a single-dose exposure and cancer development, however, with a low overall risk [182]. In an American 20-year follow-up study on World War I veterans, death rate by cancer was found at 2.5% in comparison to 1.9% in the control group. The risk of death from lung cancer among exposed men was estimated as 1.3, with 95% confidence limits of 0.9–1.9 when compared to unexposed controls [185].

A long-term follow-up cohort study on Iranian veterans revealed a significantly increased cancer incidence after exposure to sulfur mustard [186]. The incidence rate ratio of cancer was 1.81 (95% CI 1.27–2.56) and the hazard ratio of cancer was determined with 2.02 (95% CI 1.41–2.88) compared to the control group [186]. Despite the fact that the overall risk for cancer development was elevated, a statistically significant difference for specific types of cancer was not apparent between control and exposure group [186]. The described study exhibits some significant limitations: (i) the group of unexposed veterans was not matched for age, (ii) the unexposed population was not recruited on the basis of similar risk behaviors as the sulfur mustard exposure group, and (iii) data did not allow a correlation to the frequency of sulfur mustard exposure (“mostly acute and one-time exposures”) [186]. Thus, the overall results have to be interpreted with care and might underestimate sulfur mustard-induced carcinogenic effects. Remarkably, after chemotherapy with nitrogen mustard, an increased incidence of leukemia was reported [187]. A higher rate of chronic myeloid leukemia was also detected in Iranian mustard gas victims [188].

However, studies of cancer incidence in survivor populations with single, high-dose sulfur mustard exposure have thus far failed to demonstrate a strong correlation between exposure and disease occurrence [182, 189]. Nevertheless, there are hints that a single exposure to mustard agent may trigger cancer development [189].

Epigenetic perturbations may be involved in sulfur mustard-caused long-term health effects [190–193]. Recent *in vitro* and human data reveal that sulfur mustard causes epigenetic modifications (e.g., DNA hypermethylation) in skin samples of an accidental, single human exposure even 1 year after the event [192]. Epigenetic modification, in particular, aberrant promoter hypermethylation that is associated with inappropriate gene silencing, is linked with carcinogenesis [194–196].

In conclusion, it is well documented that sulfur mustard may cause cancer after long-term, chronic exposures. Some data allow the assumption that cancer might develop upon exposure toward a high single dose of sulfur mustard,

although the evidence is not very strong and definitive [182]. Nevertheless, epigenetic data derived from in vitro experiments and human exposure cases give reason to assume that single sulfur mustard may cause epigenetic perturbations comparable to those found in carcinogenesis.

Treatment

First, neither an antidote nor a specific therapy against sulfur mustard injury exists. Thus, wearing suitable protective equipment to avoid contact to sulfur mustard is important, whenever possible. If exposure is not preventable, early and thorough decontamination is critical. Decontamination of liquid skin exposures is the first-line treatment. Reactive Skin Decontamination Lotion (RSDL) and Fuller's earth or sodium hypochlorite are suitable substances for that purpose. However, although these substances are efficient for agent binding or hydrolysis, skin compatibility may be compromised. In particular, a decontaminant for wounds is not available. All suggested solutions affect wound healing to various degrees. Thus, for wounded, exposed individuals, the only method available is extensive showering with pure water at medium temperatures. High water temperatures should be avoided because vasodilatation with increase skin blood flow may facilitate absorption of sulfur mustard.

After decontamination, therapy generally is performed according to clinical signs and symptoms. As mentioned above, no specific treatment is available, but various promising symptomatic approaches have been described and are the subject of current research.

Sulfur Mustard Scavengers

The highly reactive sulfur mustard can covalently bind to cysteine residues within various sources resulting in stable alkylated products. Thus, after both reactive side chains have undergone alkylation reactions, sulfur mustard is no longer reactive or toxic. The well-tolerated GSH-precursor drug *N*-acetylcysteine may be used to provide cysteine

equivalents. *N*-acetylcysteine may either function directly as a sulfur mustard scavenger or indirectly by supporting production of GSH that in turn may scavenge the highly reactive agent [197–203]. Prophylactic administration may also be beneficial for scavenging sulfur mustard in the circulation, e.g., after redistribution from lipid depots. Other nucleophilic scavengers like 2,6-dithiopurines reveal promising effects in in vivo experiments [204].

N-acetylcysteine is well tolerated and is the antidote of choice in acetaminophen poisoning [205]. Although it does not have a regulatory approval with regard to sulfur mustard poisoning, the available experimental data may favor an off-label use with dosages equivalent to those used in acetaminophen poisoning [205]. Therefore, the routine use of NAC in sulfur mustard poisoning – especially with regard to high-dose exposure cases – is recommended. After intravenous administration of a loading dose (150 mg/kg) within 15 min, treatment should be continued with 50 mg/kg i.v. over 4 h, followed by oral administration of 70 mg/kg every 4 h for additional 72 h (Grade III recommendation). If oral administration is not feasible, intravenous administration is an alternative.

Anti-inflammatory Compounds

Inflammation is frequently observed in sulfur mustard injury, in particular after dermal exposure. Anti-inflammatory compounds like COX inhibitors or corticosteroids show beneficial effects both in vitro and in vivo [206–209]. With regard to COX inhibitors, indomethacin shows pronounced effectiveness in mitigating sulfur mustard-induced inflammation [206]. Some prodrugs of nonsteroidal anti-inflammatory drugs (NSAIDs) were also tested for their effectiveness in vivo. Inflammation and edema caused by the monofunctional sulfur mustard analogue CEES (2-chloroethyl ethyl sulfide) were significantly reduced after treatment with prodrugs of diclofenac, indomethacin, and naproxen; however, notably ibuprofen amplified the inflammation [210]. These findings were confirmed in other studies showing that a diclofenac prodrug reduced mouse ear edema after sulfur mustard exposure, whereas ibuprofen did not [211]. Our own results

also identified diclofenac as a potent pharmaceutical against sulfur mustard-induced inflammation, whereas ibuprofen aggravated cytotoxicity. In conclusion, comparatively little is known about the efficacy of anti-inflammatory drugs after sulfur mustard exposure in humans, despite the fact that these compounds are likely to be used whenever medical personnel will be confronted with sulfur mustard and the inevitable inflammation. Although the available experimental *in vitro* and *in vivo* data are limited, the use of COX inhibitors or NSAIDs for counteracting inflammation and edema in sulfur mustard poisoning appears reasonable. Whether diclofenac is the compound of first choice or other pharmaceuticals may be more effective needs clarification in further studies. At this stage, administration of extended-release tablets containing 75 mg twice a day for at least 1 week is recommended (Grade III recommendation). The use of a proton pump inhibitor should be considered to prevent diclofenac-induced mucosal ulcerations.

The use of corticosteroids in sulfur mustard poisoning is discussed controversially. In general, positive effects with regard to inflammation and edema have been described [207, 212]. However, corticosteroids may have negative impacts on wound healing and thus should be considered with caution in cases of severe sulfur mustard-induced ulcerations. The topical use in mild affected areas, limited to erythema without blister formation, is reasonable [213] (Grade III recommendation).

With regard to pulmonary sulfur mustard lesions, inhalation of glucocorticoids is often performed [214]. However, the overall benefit is debatable. There is general agreement that long-term oral administration of corticosteroids should be omitted [214].

At present, a reliable recommendation for the use of corticosteroids in acute sulfur mustard poisoning is difficult. Results obtained from different animal models implicate that postexposure treatment with corticosteroids in combination with NSAIDs results in significant protective effects *in vivo* [207, 209, 215]. The treatment, however, did not completely prevent the ensuing cytotoxic processes in the epithelial layer [207].

In conclusion, the use of corticosteroids in sulfur mustard-induced acute lung injury demonstrates beneficial effects with regard to lung edema and

inflammation in animal *in vivo* experiments [212, 216]. In addition, protective effects with regard to long-term immune activation and lung fibrosis through the early inhibition of pro-inflammatory mediators are seen in animal experiments [212]. However, whether corticosteroids may have comparable effects in humans with regard to acute sulfur mustard-induced toxic lung injury has not been investigated. Based on the current knowledge, inhalative application of corticosteroids after pulmonary sulfur mustard exposure is recommended (Grade III recommendation). Intravenous or oral administration is not method of choice.

Analgesia and Pruritus Therapy

Sulfur mustard-exposed patients usually complain about itching sensations shortly after exposure. The pathophysiology of pruritus in sulfur mustard poisoning is complex and still needs to be determined. Inflammation accompanied with the release of histamine and other cytokines is a well-established trigger. Indeed, H1-receptor antagonists demonstrate some relief with regard to itching and burning sensations after sulfur mustard exposure. Some studies show the activation of membrane-bound cation channels (i.e., transient receptor potential cation channel A1, TRPA1) [217]. TRP-channel activation is thought to be involved in the mediation of histamine-independent pruritus. Profound analgesia using COX inhibitors (see earlier discussion of anti-inflammatory compounds) is recommended as these will also counteract sulfur mustard-induced inflammation (Grade III recommendation). In some cases, more potent analgesics (e.g., metamizole, opioids) may be necessary and should be applied (Grade III recommendation).

Surgical Management of Sulfur Mustard-Induced Skin Ulcerations

In general, sulfur mustard-induced skin lesions should be handled according to treatment protocols of skin burns. Surgical intervention is usually not necessary for mild cases manifested by erythema

only. We recommend that in an aseptic environment (e.g., hospital), blister roofs be removed in order to evaluate the underlying wound to be aware of evolving infections that would be an indication for antibiotics. In the case of non-aseptic environments, blister roofs should be left intact to avoid infections. Deep ulcerations frequently exhibit delayed wound healing, often requiring surgical interventions. As laser ablation of sulfur mustard-induced skin wounds has resulted in a faster wound closure compared to non-treated ulcerations in *in vivo* animal experiments, such a strategy might be an alternative (Grade III evidence) [218–220]. In conclusion, in the case of sulfur mustard-induced nonhealing skin defects, a plastic-surgical intervention should be considered. In any case, dressings should be daily changed and wound healing should be carefully examined. We also recommend skin care with moisturizing lotions several times a day during wound healing. This may be necessary for several weeks.

Management of Sulfur Mustard-Induced Eye Affections

Patients with ocular symptoms after sulfur mustard exposure have to be treated immediately. Contact lenses have to be removed and eyes must be extensively rinsed with water or saline solutions. Corrosive decontamination solutions such as bleach must not be applied. In mild cases without keratopathy, the application of soothing eye drops is sufficient (Grade III evidence). Vaseline dressings may prevent adherence of the lids. Mydriatics should be applied to prevent synechiae (adherence of the iris to the cornea or the lens) (Grade III evidence). An ophthalmologist should be consulted.

Management of Sulfur Mustard-Induced Lung Toxicity

Toxic lung injury is a common phenomenon after sulfur mustard inhalation for which there is no specific therapy. These effects may be aggravated by bacterial infections. Life-threatening laryngeal edema and bronchospasm can occur. These require the use of bronchodilators [3]. Pseudomembrane

formation in the upper and lower airways that may block the lumen is a major problem in severe cases. Here, bronchoscopy and extensive lavage should be performed to remove the debris. Close pulmonary function monitoring is indicated. In the case of ARDS, standard therapy including positive end-expiratory pressure ventilation may be necessary (see ► [Chap. 16, “Treatment of Acute Respiratory Distress Syndrome in the Poisoned Patient”](#)).

Follow-Up Care

Sulfur mustard is responsible for a plethora of chronic health disorders including those of the respiratory system, skin, and eyes and development of cancer. Thus, patients should be monitored frequently at specialized hospital centers. A weekly follow-up for the first 4 weeks, followed by a monthly frequency for the next 6 months, and then a half-year interval for the next 2 years is recommended [26]. Thereafter, the follow-up interval should then be set individually in agreement with the patient.

Detection of Sulfur Mustard Exposure in Biological Samples

In principle, there are three strategies for the verification of sulfur mustard exposure: (i) detection of intact sulfur mustard, (ii) detection of sulfur mustard biotransformation products, or (iii) detection of sulfur mustard adducts with biomacromolecules. Procedures that meet litigable and forensic requirements demand highly specialized laboratories with regard to the analytical methods. Reliable in-field detection systems do not exist for that purpose. However, there are some indicative methods and test systems that allow a presumptive rapid in-field detection of sulfur mustard [38, 221, 222].

Detection of Intact Sulfur Mustard

The detection of intact sulfur mustard in biological matrices (i.e., urine, blood, or plasma) is challenging because of the quick hydrolysis of sulfur

mustard in aqueous environments. Therefore, sampling after a potential exposure should be conducted as soon as possible. Sodium chloride should be added to the sample to prevent the remaining sulfur mustard from further hydrolysis [40, 223]. Samples should be frozen at -20°C or below. Gas chromatography–mass spectrometry (GC-MS) methods for the detection of sulfur mustard in biological samples (i.e., urine) are available [139]. Two-dimensional electrospray ionization–mass spectrometry in single ion monitoring mode allows a reliable detection of 10 pg/mL blood or 10 pg/g tissue [224]. Liquid chromatography–mass spectrometry (LC-MS)-based methods were successfully applied to detect intact sulfur mustard in blood [225]. In general, reports on the successful analysis of non-hydrolyzed sulfur mustard in biological samples are rare, which is most probably due to the limited stability of the highly reactive agent in biological matrices. Thus, techniques addressing sulfur mustard biotransformation products, which exhibit stability for up to 1 week, have been predominantly used [57].

Detection of Sulfur Mustard Biotransformation Products

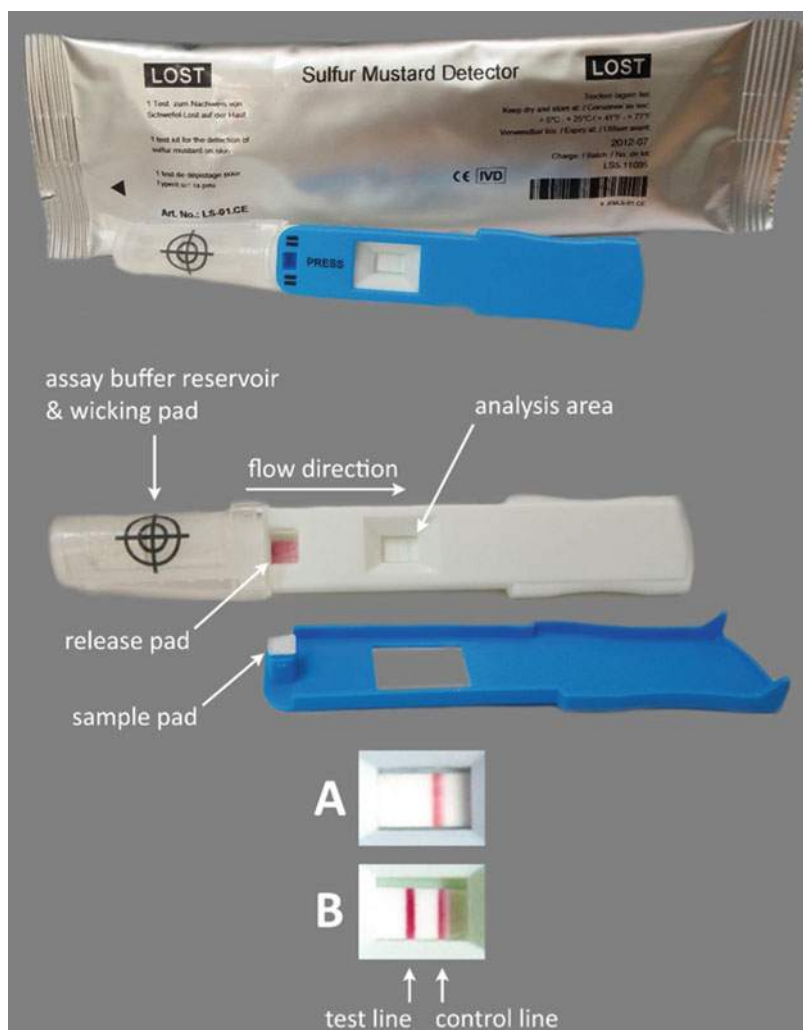
Sulfur mustard biotransformation products are eliminated via renal filtration. Thus, their detection in urine can easily be achieved [57]. The main hydrolysis product of sulfur mustard is thiodiglycol (TDG). TDG is a highly polar compound which requires derivatization into more suitable compounds before GC-MS analysis [223]. Total TDG can be determined by acidic or enzymatic hydrolysis from glucuronidated TDG. Moreover, TDG bound to proteins can be measured after release by alkaline hydrolysis [226, 227]. Oxidation of the sulfur containing biotransformation intermediates to sulfoxide or sulfone is frequently observed [228]. Thiodiglycol sulfoxide (TDGO) is best analyzed after reduction to TDG using GC-MS techniques. However, TDG can be occasionally detected at low levels in unexposed humans [229]. Therefore, the determination of TDG only is inappropriate for verification purposes. Metabolic biotransformation through β -lyase

leads to the formation of specific β -lyase biotransformation products (1-methylsulfinyl-2-[2-(methylthio)ethylsulfonyl]ethane (MSMTESE, 1,1'-sulfonylbis [2-(methylsulfinyl) ethane] (SBMSE, 1,1'-sulfonylbis[2-(methylthio) ethane] (SBMTE) and 1,1'-sulfonylbis[2-(ethylthio)ethane] (SBETE)) that are considered as unequivocal biomarkers proving sulfur mustard exposure [223, 230]. Again, GC-MS-based techniques are available to detect these β -lyase products [231, 232]. Due to the extended stability of the β -lyase products, a positive detection may be possible within 2 weeks after exposure [233]. A successful analysis of β -lyase products of sulfur mustard-exposed individuals using either GC- or LC-MS/MS-based methods in diverse biological samples (urine, blood, and blister fluid) was reported [57, 142]. Recently, the simultaneous detection of seven sulfur mustard biomarkers (bis- β -chloroethyl sulfoxide (SMO), TDG, TDGO, 1,1'-sulfonylbis-[2-S-(*N*-acetylcysteinyl)ethane (SBSNAE), SBMSE, SBMTE, and MSMTESE) in rat plasma using UPLC-MS/MS was described [234].

Detection of Sulfur Mustard Adducts with Biomacromolecules

Sulfur mustard can bond covalently to biomacromolecules like proteins and DNA [235]. Several methods for detection of sulfur mustard adducts with cysteine, valine, histidine, and aspartate/glutamic acid residues have been reported and successfully applied to verify human exposures [26, 40, 49, 228, 236]. The detection of the sulfur mustard adducts at the only accessible cysteine residue in human albumin requires enzymatic digestion of the protein, e.g., by pronase. The resulting alkylated tripeptide (Cys-Pro-Phe) has been used for detection by LC-MS/MS methods [236, 237]. However, recent reports revealed that albumin cleavage by the current available pronase result predominantly in the formation of a dipeptide (Cys-Pro) instead of the expected tripeptide [41]. Therefore, a new LC-ESI MS/MS method was established for the simultaneous detection of di-, tri-, and also tetra-peptide [41]. Sulfur mustard-induced covalent albumin modifications

Fig. 5 “Sulfur Mustard Detector” for the on-site detection of reactive sulfur mustard. (a) Negative test for sulfur mustard. (b) Positive test after sampling of sulfur mustard after application of 5 μ l with 1 mmol/L. Both tests were run accurately as indicated by the control lines



were successfully monitored in four individuals after an accidental exposure up to 90 days after the event [57]. Sensitive GC-MS/MS methods are also available to detect sulfur mustard adducts with hemoglobin after applying a modified Edman degradation releasing the alkylated N-terminal valine [56]. Additional adducts of sulfur mustard with other proteins including keratins and actin have been found by matrix-assisted laser desorption ionization coupled to time-of-flight (MALDI-TOF) techniques [48, 238]. However, analysis of these parameters for routine verification purposes is not yet established.

As described above, sulfur mustard reacts with DNA bases resulting in the formation of

four sulfur mustard–DNA adducts. The most abundant adduct, N7-(2-hydroxy-ethylthioethyl) guanine (N7-HETEG), can be detected and quantified using LC-MS techniques [42]. Comprehensive LC-MS-based methods that allow a simultaneous quantification of all DNA adducts in urine or blood have been reported [46, 57, 239]. Alkylated bases were detected from day 3 to month 1 after sulfur mustard exposure, with a maximum peak within the first week [57]. In addition to analytical techniques allowing a litigable verification of sulfur mustard exposure, methods based on antibody detection of sulfur mustard–DNA adducts have been developed (Fig. 5) [38, 222, 240–242]. A

handheld device ("Sulfur Mustard Detector," Securetec Detektions-Systeme AG, Neubiberg, Germany) for the identification of intact sulfur mustard based on an immunohistochemical method was also developed and is now commercially available [221]. Such test strip systems have several advantages, most notably the easy on-site use, the small size of the detector, and the rapid test results [221]. The developed test strip integrates into a plastic cassette containing different membranes. All materials are in capillary contact in order to allow chromatographic flow from one to the other end (lateral flow technique) [38, 221, 222]. The sampling pad contains guanine-rich oligonucleotides that are able to react with sulfur mustard resulting in the formation of N7-HETEG. After moistening of the sample pad and sampling any liquid or vapor for 30 s, the upper and lower parts of the device are reassembled. The test is started by crushing the ampule containing the assay buffer. In the presence of sulfur mustard, N7-HETEG is recognized by a gold-conjugated specific antibody. The resulting positive test line can be recognized with the naked eye. An additional control line indicates an accurate test run. This test system is able to detect sulfur mustard vapor released from a 20 $\mu\text{mol/L}$ solution and from pig skin exposed to 2 $\mu\text{mol/L}$ sulfur mustard diluted in phosphate-buffered saline. Thus, the concentrations detected were one to two orders of magnitude below vesicating concentrations. The sulfur mustard detector can provide an early warning, prompting countermeasures such as the use of protective equipment or decontamination, significantly reducing exposure, and preserving health and operational capability [222].

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Part XXVII

Antidotes

Bruno Mégarbane

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Digitalis poisoning is rare but may be responsible for life-threatening complications [1–3]. Intoxication may result from suicidal or unintentional ingestion of a single large dose (acute poisoning) or from accumulation during long-term dosing (chronic poisoning). Anti-digoxin-specific Fab fragments are now considered as the first-line treatment of digitalis poisoning [4–6]. However, several concerns remain including the indications, the minimal efficient dose, and the optimal mode of administration. Despite being an expensive therapy, anti-digoxin Fab fragments were considered beneficial in a cost-effectiveness analysis [7]. This antidote was shown useful not only in digoxin poisoning but also in poisonings with digitoxin, lanatoside C, and various cardiac glycosides contained in plants such as oleander, foxglove, and lily of the valley or venoms from toads and coconut crabs (*Birgus latro* L.) [8–12]. To date, different marketed safe and effective digitalis antitoxins are available including DigiFab (40 mg).

History

Assessment of anti-digoxin Fab fragments for the treatment of cardiac glycoside toxicity began with the development of specific antibodies for immunoassay. Subsequent investigations allowed determination of the fundamental mechanisms of

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immunotoxicotherapy. Butler and Chen [13] first suggested that purified anti-digoxin antibodies with high affinity and specificity should be developed to treat human digoxin poisonings. Digoxin, with a molecular weight of 781 d, was too small to be immunogenic; so it was necessary to link it to serum bovine albumin to generate antibodies in immunized sheep. Highly purified antibodies were obtained by separation techniques, and in vitro and animal studies were employed to assess their ability to bind cardiac glycosides avidly [13–18]. Intact IgG anti-digoxin antibodies reversed digoxin toxicity in dogs, but excretion of the digoxin/IgG complexes was delayed, and risks of hypersensitivity reactions or secondary digoxin release were postulated. Fab fragments of 50 kd were obtained by treating these IgG anti-digoxin antibodies with papain, yielding a safer and more effective therapy [15].

In 1976, Smith and colleagues [19] described the first clinical use of digoxin-specific Fab fragments in a human. Thereafter, clinical studies dealing with large numbers of poisoned patients allowed the assessment of their safety. Since 1976, large series of cardiac glycoside poisonings treated with anti-digoxin Fab fragments have been published, including 5004 cases by Hauptman and colleagues [20], 717 cases by Hickey and colleagues [21], 278 cases by Nordt and colleagues [22], 166 cases by Chhabra and colleagues [23], 150 cases by Antman and associates [24], 67 cases by Lapostolle and colleagues [3, 6], 36 cases by Chan and coworkers [25], 34 cases by Smolarz and coworkers [26], and 28 cases by Taboulet and coworkers [27, 28]. In the observational surveillance study of 717 cases, 50% of the poisoned patients exhibited full resolution of all symptoms of digitalis toxicity, 24% exhibited a partial response, and 12% exhibited no response [21]. Lack of response was explained by an insufficient dose of Fab fragments, the presence of a moribund state, or a diagnosis other than digitalis poisoning. None of the patients without heart disease who ingested a single overdose was a nonresponder. In this study, 54% of the 56 patients who had had a cardiac arrest survived, compared with 100% mortality before

the advent of Fab. No clear relationship was established, however, between the initial dose and the response to treatment, rendering it difficult to establish an effective dose. After this report, recrudescence toxicity (atrioventricular block, ventricular arrhythmias, or asystole) was reported, with rates varying from 2.8% in the series of 717 cases [21] to 11% in the series of 28 cases (which included many digitoxin poisonings) [27–29]. Therefore, earlier use of Fab therapy, before cardiac pacing or treatment with antiarrhythmic agents, has been advocated [3–6].

Properties

Anti-digoxin Fab fragments are derived by papain cleavage (Fig. 1) of all the heterologous IgG sheep-derived digoxin-specific antibodies, leading to the removal of the F_c fragment and a substantial reduction in the molecular weight (50 kd) and the risk of hypersensitivity. As shown by radioimmunoassay of digoxin levels, anti-digoxin Fab showed high affinity for digoxin and sufficient cross-reactivity with digitoxin to be clinically useful [8]. A 40-mg vial of digoxin Fab (DigiFab) binds 0.5 mg digoxin. Because of structural similarities among all cardiac glycosides (cardenolides), anti-digoxin Fab can neutralize lanatoside C, proscillaridin, scilliroside toxins, and other glycosides found in *Nerium oleander*, toad, and crab venoms. [9–12] However, higher doses may be needed in these other glycoside poisonings due to the lower-affinity binding of Fab to these toxins.

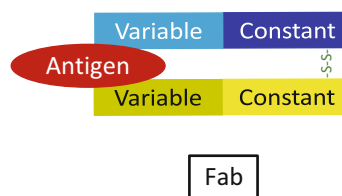


Fig. 1 Chemical structure of anti-digoxin-specific Fab fragment

Pharmacodynamics

Immunotoxicotherapy is a toxicokinetic treatment inducing redistribution of the cardiac glycoside to the extracellular compartment [4, 5, 30]. Affinity of digoxin for Fab ($10^9 10^{11} \text{ M}^{-1}$) is greater than its affinity for the membrane-bound Na^+, K^+ -ATPase receptors. The redistribution is so rapid and complete that symptoms usually resolve within a few minutes.

Cardiac glycosides inhibit Na^+, K^+ -ATPases located on the external membrane of myocardial cells. In patients with chronic exposures, compared with patients with acute overdoses, less digoxin is necessary for the development of symptoms. [31] Reversibility of the binding of these glycosides to this molecular target has been shown with Fab fragments. Clinical studies have shown that the onset of Fab action is rapid when the Fab fragments are infused over ~20–30 min. Reversal of the toxic effects of digitalis occurs within 30–45 min after administration [5]. Most patients who responded had clinically evident improvement by 1 h after termination of infusion and had a complete response, including the resolution of hyperkalemia, by 4 h [24]. Anti-digoxin Fab fragments also quickly improved digitalis intoxication-related gastrointestinal disturbances, including ischemic colitis [32].

Pharmacokinetics

Pharmacokinetics of Digoxin-Specific Fab Fragments

Apparent volume of distribution: ~0.4 L/kg (25–54 L)

Distribution: biphasic or triphasic

Elimination half-life: ~19–30 h in patients with normal renal function, tenfold in patients with renal failure (>100 h)

Total body clearance: 24.5 mL/min

Renal clearance: 13.6 mL/min

Anti-digoxin Fab fragments are effective in digitalis poisoning by causing (1) induction of an extracellular redistribution of the toxin, (2) its

sequestration in extracellular spaces, and (3) the renal elimination of the antibody/toxin complex [4, 5, 30, 33]. Administered intravenously, these fragments bind immediately to circulating free digitalis molecules, forming complexes unable to bind to tissue digitalis receptors. After infusion of a dose containing equimolar binding sites, total serum digitalis concentration increases 5–20 times whereas unbound serum digitalis decreases to 0 within minutes. By mass action resulting from the concentration gradient from their target tissue to the interstitial and intravascular spaces, free intracellular digitalis and receptor-bound digitalis are displaced, and reactivation of membrane ATPases ensues. Ultimately, bound toxin/Fab elimination depends on renal function [34].

Serum Fab fragment concentrations exhibit a biphasic or triphasic decline, reflecting their distribution into different compartments and their excretion and nonrenal elimination. The elimination half-life of Fab/digoxin complexes is about ~19–30 h in patients with normal renal function, compared with spontaneous half-lives of 39 h for digoxin and 160 h for digitoxin. The elimination half-life of Fab/digoxin complexes is prolonged tenfold in the case of renal failure, with no changes in the volume of distribution [34]. Schaumann and colleagues [35] calculated a volume of distribution ranging from 25.4 to 54 L for anti-digoxin Fab fragments. The total body clearance of Fab fragments was estimated at 24.5 mL/min, of which 13.6 mL/min was renal clearance.

The advantages of anti-digoxin Fab fragments compared with the whole IgG antibody are a threefold increase in volume of distribution, more rapid onset of action, smaller risk of adverse immunologic effects, and more rapid elimination [36]. More recent data, based on comparisons of the volume of distribution of immunoglobulins and Fab fragments, suggested that Fab fragments might enter cells despite their molecular weight. The apparent volume of distribution of Fab fragments is greater than the volume of extracellular water [35].

After massive ingestion, serum digoxin concentration does not correlate with the myocardial concentrations, and tissue distribution occurs with

a delay of ~4–6 h. After anti-digoxin Fab fragment administration, standard serum digoxin concentration determinations measure unbound and bound digoxin. Methods using ultrafiltration make free digoxin measurements possible. After infusion of sufficient doses of Fab fragments, the unbound digoxin concentration decreases to an undetectable level, with a reappearance 5–24 h later, depending on the dose, the infusion technique, and the patient's renal function. All studies with pharmacokinetic data showed that free digoxin concentration fell to almost zero within a few minutes following the administration of anti-digoxin Fab fragments [5]. There is no evidence of dissociation of the Fab/digoxin complex over time. The rebound in free digoxin concentrations is secondary to Fab's leaving the vascular space, digoxin's effluxing from the tissues, and possibly continued gastrointestinal absorption.

The institution of a maintenance infusion after the loading dose reduces the early reappearance of free digoxin. The loading dose immediately binds digoxin present in the vascular space and the digoxin that is redistributed rapidly to the vascular space. The maintenance dose provides enough Fab fragments to capture digoxin redistributed from the tissues into the serum. The risk of too rapid an infusion is that elimination of Fab occurs before redistribution of digoxin from its binding sites. In this case, the total amount of Fab fragments effectively bound to digoxin is less than that predicted [35].

Special Populations

Neonatal and Pediatric Patients

Pediatric patients with no underlying heart disease generally tolerate higher doses of digoxin than do adults. The administration of anti-digoxin Fab fragments is indicated in infants and young children with ingested digoxin doses of greater than or equal to 0.3 mg/kg, underlying heart disease, serum digoxin concentration greater than or equal to 6.4 nmol/L (≥ 5 ng/mL), life-threatening arrhythmia, hemodynamic instability, hyperkalemia (≥ 6 mmol/L), or

rapidly progressive toxicity [37–41]. Pediatric patients with chronic exposure may be treated successfully with small doses of Fab because of their small body burden of digoxin, whereas acute overdose requires quantities similar to those in adults.

Elderly Patients

The elderly are at relatively greater risk for severe digitalis intoxication [20, 42]. Age 55 years and older has been shown to be associated with an increase in mortality rate [31]. Anti-digoxin Fab fragments are also useful for digoxin-induced acute psychosis (digitalis delirium), characterized by severe agitation, delusional thinking, and assaultive behavior. Recent insights from a national hospital database clearly showed the necessity to improve digoxin poisoning diagnosis and management in this population [20]. Predictors of anti-digoxin Fab fragment use were emergent admission, hyperkalemia, arrhythmia associated with digoxin toxicity, acute renal failure, or suicidal intent. The majority (78%) of anti-digoxin Fab fragments were administered on days 1 and 2 of the hospitalization, while 10% of the patients received the treatment after day 7. Surprisingly, digoxin was reused after anti-digoxin Fab fragment administration in 14% of cases.

Pregnant and Breastfeeding Patients

Although digitalis passes through the placenta, few data are available on embryonic or fetal toxicity. Fab transplacental passage is poorly understood. Pregnant patients with acute digitalis overdose should be treated similarly to nonpregnant patients. In case of in utero exposure, the efficacy and safety of anti-digoxin Fab fragments for the fetus are not documented. Fetal cardiac rhythm should be monitored, and, if necessary, the fetus can be delivered and Fab administered to the neonate, as indicated by clinical signs and blood levels. Digitalis compounds are excreted in breast milk.

Renal Insufficiency Patients

Patients with renal failure on dialysis respond to Fab treatment in a manner similar to that in patients with normal renal function [24]. A theoretical possibility exists, however, that digoxin could be released with recurrence of toxicity because of decreased clearance of anti-digoxin Fab fragments. In the case of anephric patients, anti-digoxin Fab fragments are effective, although symptoms may recur 7–14 days later, indicating the need for an additional dose. Among 18 patients with a pretreatment serum creatinine of ≥ 4 mg/dL, including five patients on dialysis, recurrence of toxicity was observed only in one dialyzed patient. A multivariate analysis performed on the series of 717 cases did not show an increased risk of recrudescence toxicity in patients with renal failure [21]. The rebound in digoxin concentration is delayed in patients with renal dysfunction, presumably secondary to a prolonged distribution phase, and serum anti-digoxin Fab fragment concentrations remain detectable for 2–3 weeks, with a parallel decline in total digoxin serum concentration [34].

Recently, the international EXTRIP work group published a systematic review and recommendations on the extracorporeal treatment for digoxin poisoning [43]. Based on data from 84 patients including six fatalities, they concluded that digoxin is slightly dialyzable (level of evidence = B, using their system) and that ECTR is unlikely to improve the outcome of digoxin-toxic patients whether or not anti-digoxin Fab fragments are administered. Despite the lack of robust clinical evidence, they recommended against the use of ECTR in cases of severe digoxin poisoning when Fab fragments were available (1D) and also suggested against the use of ECTR when Fab fragments were unavailable (2D).

Contraindications

There are no known contraindications, apart from allergy to sheep immunoglobulin. No interactions with other medications have been reported.

Precautions

Considering the risk of allergy, particularly in cases of repeated administration, manufacturers recommended intracutaneous or conjunctival allergy tests before Fab fragment administration. Most toxicologists believe that the risk of sensitization to sheep Fab fragments is low and that such testing is unnecessary. After infusion, patients require close monitoring because a second dose may be necessary if toxicity recurs or fails to resolve. In non-digoxin digitalis poisoning, required doses of Fab fragments may be higher, as reported in the case of a child poisoned after ingesting yew berries, which contain taxine, a cardiac glycoside [16]. Recurrence of toxicity is infrequent, and its exact mechanism still is not understood fully. There is no evidence to support a dissociation of the Fab/digoxin complexes over extended periods [44, 45]. Recrudescence toxicity seems to be related to redistribution of free digoxin into the serum. Compatible clinical signs are not always accompanied by an increase in unbound digoxin concentrations, however.

Adverse Effects

Safety of a single low dose of anti-digoxin Fab fragments was assessed in multiple case series involving more than 7000 patients, with rare adverse effects [3, 4, 20–28]. Mild hypersensitivity reactions, including pruritic rash, facial swelling and flushing, urticaria, thrombocytopenia, shaking, and chills, rarely (~0.8%) occurred in the treated patients. Because anti-digoxin Fab fragments are obtained from bovine serum, there is a theoretical possibility of sensitization [46]. The likelihood of allergic reaction was greater in patients with allergy or asthma history [21]. Results of skin testing before Fab treatment were reported in 94 patients and were uniformly negative except for one patient who developed erythema without wheal or induration [24]. One patient received Fab three separate times over the course of 1 year as treatment for attempted suicide by digitalis ingestion, with no evidence of adverse effects [47]. No cross-

reactivity was noted with endogenous steroids that have structural similarities to digoxin.

Adverse reactions caused by rapid reversal of the effects of digitalis, such as accelerated ventricular rate in atrial fibrillation, worsened left ventricular function, or hypokalemia, were noted in 7% of 717 treated patients [21]. In a several-hour-old neonate, hypokalemia, worsening of congestive heart failure, and transient apnea were reported [24].

Administration

The efficacy of anti-digoxin Fab fragments in decreasing the mortality rate of digitalis intoxication has not been proved by randomized controlled trials. Only one randomized controlled trial was published regarding the treatment of yellow oleander poisoning, demonstrating an early improvement in cardiac rhythm and hyperkalemia from anti-digoxin Fab fragments and thus prompting its early termination [48] (Level 1 evidence). Otherwise, data on anti-digoxin Fab fragments in digitalis poisoning are limited to observational data, so the efficacy and indications for anti-digoxin Fab are uncertain [4, 11] (Grade II-2 evidence). Recent observational data supported an effect in acute digoxin poisoning, but a clinically meaningful effect in chronic digoxin poisoning was questioned [5]. The mortality rate ranged from 4.6% to 41% before availability of Fab fragments [1, 2] and remained between 6% and 29% after their availability [6, 24, 26]. These results raised questions regarding the accuracy of diagnosis, the selection of patients to treat with the antidote, and the amount and dosage regimen of Fab administration. Recently, in a case series of 147 patients in a center without access to anti-digoxin Fab fragments, of whom 70% had nausea/vomiting, 52% had ECG changes, and 43% had indications for anti-digoxin Fab, mortality was low at 1.4%, questioning the antidote usefulness, although the reported mean digoxin concentration of 4.3 ng/mL (5.5 nmol/L) in this series was much lower than expected from the reported dose [49]. Consistently, in a national hospital database including 88% >65-year-old patients admitted with digoxin overdose, there was no difference for in-hospital mortality or length

of stay among patients who received anti-digoxin Fab fragments within 2 days of admission and those who did not [20].

Fab administration initially was restricted to patients exhibiting actual or potentially life-threatening cardiac rhythm disturbances or hyperkalemia caused by digitalis intoxication when these conditions were refractory to treatment with conventional therapeutic modalities. The notion of administering conventional therapy, which resulted in delays in Fab fragment administration, was called into question [27, 28]. Delaying the administration of Fab fragments by waiting for the appearance of life-threatening symptoms may preclude their benefit. Therefore, current accepted indications of anti-digoxin administration include patients who have life-threatening tachy-/bradyarrhythmias, hyperkalemia (>6 mmol/L), or hemodynamic instability with an elevated digoxin concentration (>2 ng/mL or 2.6 nmol/L) [5]. However, the decision to administer digoxin Fab fragments should take into account their known safety versus the persistently high mortality of digitalis poisoning and possibly treat more patients at risk. Because many adult overdoses are polypharmaceutical, it is important to consider other toxicants in patients not responding to this antidote.

Dose

The lowest effective digoxin Fab dosing regimen has not been established [5]. The dose of Fab fragments is usually calculated on a molar basis to be equal to the amount of digoxin or digitoxin in the body (see table) [24]. The body burden of cardiac glycoside may be calculated using either the supposed ingested dose or the serum digitalis concentration. Experimental data showed the efficiency of Fab doses in full stoichiometric equivalence. However, the accuracy of these calculations is questionable for many reasons. The ingested dose frequently is not known with accuracy. Calculation of the number of vials from the ingested amount also may overestimate the dose of needed Fab because loss of digitalis may result from vomiting and gastrointestinal decontamination. The measured

plasma concentration of digoxin accurately reflects the body load, but only after equilibration, which requires at least 6 h after the last dose. The volume of distribution of digoxin also may be smaller in certain diseases (e.g., kidney injuries, hypothyroidism). It is unclear whether the theoretical equimolar dose is attained or exceeded. The necessity of administering an equimolar dose of Fab to obtain an initial beneficial response is not supported by the literature [2, 3, 21]. Initial response to therapy generally is favorable, with doses below the equimolar ratio, whereas the risk of recrudescence toxicity is more frequent if less than 50% of the estimated full neutralizing dose was administered. If initial administration of Fab fragments fails to reduce digitalis-induced arrhythmias, another dose should be administered.

Recently, dosing regimens based on much lower initial doses have been proposed, with 40 mg (one vial) for chronic poisoning and 80 mg (two vials) for acute poisoning, to be repeated after 60 min if inadequate response or recurrence or earlier if there is a clinical deterioration [5]. Larger initial doses, including that which will achieve full neutralization, were recommended only in peri-arrest patients. Consistently, the recent prospective observational DORA study demonstrated the effectiveness of only 1–2 vials of anti-digoxin Fab fragments to bind all free digoxin in chronic digoxin poisonings [25] (Grade II-2 evidence). However, moderate improvement in heart rate and potassium following the antidote administration was frequently observed, suggesting that bradyarrhythmia and hyperkalemia in the chronically poisoned patients could be related to other comorbidities including chronic renal failure, heart diseases, and medications like β -adrenoceptor blockers and calcium antagonists. In France, a strategy based on the early administration of a half-molar dose of digoxin Fab rather than that of the equimolar dose, usually recommended in life-threatening poisoning, was shown efficient to reduce mortality in digitalis poisoning by preventing further worsening of toxicity in patients with poor prognosis, even if they were initially not or only mildly symptomatic [6, 50]. Poor prognosis is defined by the presence of at least three of the following criteria in the absence

of any life-threatening toxicity: (1) male gender; (2) age of greater than 55 years; (3) underlying heart disease; (4) bradycardia with second- or third-degree atrioventricular block; (5) heart rate between 40 and 60/min refractory to administration of 1 mg of atropine, regardless of the conduction disturbances; and (6) hyperkalemia of greater than 4.5 mmol/L. These prognosticators, determined in the early 1980s when the ratio of acute digitoxin versus digoxin poisonings was 10/1 [51], are also currently used in chronic poisoning; however, prophylaxis is usually indicated if at least one of the final three criteria is present.

In contrast, in yellow oleander poisoning, dosing is higher because of the inability in contrast to digoxin to quantify adequately the body burden based on blood tests and perhaps lower cross-reactivity. A dose-response study recommended a dosage of 1200 mg [48]; however, subsequent data suggested that 800 mg may be effective [52, 53].

Calculation of Dosage of Fab Fragments from Body Load of Glycoside

From the ingested amount, if the amount and type of digitalis are known:

$$Q = IA \cdot A$$

Q = Body load of glycoside (mg)

IA = Ingested amount of glycoside (mg)

A = Digoxin bioavailability (0.6) or digitoxin bioavailability (1)

From the serum glycoside concentration, if the steady-state serum concentration is known:

$$Q = SGC \cdot Vd \cdot Wt \cdot 10^{-3}$$

Q = Body load of glycoside (mg)

SGC = Serum glycoside concentration (ng/mL)

Vd = Distribution volume: 5.61 L/kg (digoxin) or 0.56 L/kg (digitoxin)

Wt = Patient weight (kg)

Conversion factors:

$SGC \text{ (nmol/L)} \times 0.781 = SGC \text{ (ng/mL) for digoxin}$

$SGC \text{ (nmol/L)} \times 0.765 = SGC \text{ (ng/mL) for digitoxin}$

(continued)

Determination of the number of 40-mg vials needed*: $Q/0.5$

Empirical dosing recommendations with 40-mg vials (according to the authors):

Acute ingestion (adult): 2–4 up to 10–20 vials

Chronic ingestion (adult): 1–2 up to 3–6 vials

Note: For some authors, low dosage at least as starter should be sufficient; calculated full neutralizing doses of digoxin Fab are expensive and may not be required.

*Fab fragment dose (mg) = [molecular weight Fab (50 kd)/molecular weight digoxin (781 d)] × body load (mg). Using this calculation, 0.5 mg of digoxin is neutralized by each 40-mg vial of Fab fragments.

Route of Administration

Antidigitalis Fab fragments should be diluted in sterile isotonic saline solution and administered intravenously in a monitored setting. When reconstituted, the preparation should be used immediately or, if refrigerated, within 4 h. The dosage regimen initially proposed included the administration of the dose of Fab fragments over 15–30 min. However, increasing the duration of Fab infusion was recommended to optimize the binding of digoxin to anti-digoxin Fab fragments [35, 48]. Schaumann and colleagues [35] recommended a loading dose of four to six vials, followed by 0.5 mg/min for 8 h. The optimal dosage regimen using the minimal effective dose remains to be determined. More recently, based on pharmacokinetic modeling [5], it was suggested to administer (1), *in acute poisoning*, a small bolus of 80 mg (2 vials) digoxin Fab fragments, repeated if necessary and titrated against clinical effects and (2), *in chronic poisoning*, a small bolus of 40 mg (1 vial) digoxin Fab fragments at a time and repeated after 60 min if there is no response.

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Atropine (*D,L-hyoscyamine*) is a naturally occurring racemic mixture of an alkaloid obtained from solanaceous plants, such as *Atropa belladonna* (deadly nightshade) and *Datura stramonium* (jimson weed). Pharmacologic preparations are also a racemic mixture, with the *l*-isomer possessing the characteristic antimuscarinic action. Preparations of plant extracts containing atropine have been used for centuries, both medicinally and as poisons [1]. As an antidote, atropine is the cornerstone for treating organophosphate (OP) and carbamate insecticide poisoning and OP military nerve agent poisoning. In addition, atropine is a therapeutic cycloplegic, antispasmodic, inhibitor of secretions in the respiratory and alimentary tracts, and vagolytic, leading to the use of this drug to treat symptomatic bradycardia.

Pharmacodynamics

Muscarinic acetylcholine receptors are located throughout the central nervous system (CNS), primarily in the brain, at end organs innervated by the parasympathetic division of the autonomic nervous system, and in the skin at postganglionic sympathetically innervated sweat glands. The normal, physiological endogenous agonist at all muscarinic receptors is acetylcholine. The quaternary

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nitrogen in acetylcholine binds to the aspartate residue in all five muscarinic acetylcholine receptor (mAChR) subtypes (M_1 – M_5) to produce mAChR activation, which is described in the next paragraph. This ability to induce a change in the resting physiology of a living organism is referred to as *physiological efficacy*. The acetylcholine-binding site is a ligand-binding pocket formed by a series of seven trans-membrane helices [2]. The five mAChR subtypes (M_1 – M_5) are believed to have similar binding sites.

Upon activation by acetylcholine binding, muscarinic receptors couple to heterotrimeric guanine nucleotide-binding proteins (G proteins) to regulate second messengers and ion channel activities [3]. All known mAChRs are prototypical members of this superfamily of G protein-coupled receptors. The odd-numbered subtypes (M_1 , M_3 , and M_5) are linked primarily to G proteins of the Gq/11 class that mobilize phosphoinositides to generate inositol 1,4,5-trisphosphate and 1,2-diacylglycerol, by activating phosphoinositide-specific phospholipase C β , thereby increasing intracellular calcium. The even-numbered subtypes (M_2 and M_4) are linked primarily to G proteins of the Gi/o class that inhibit elevated adenylate cyclase activity and prolong the opening of potassium channels, nonselective cation channels, and transient receptor potential (TRP) channels [3–5]. In addition, mAChRs are capable of activating other signaling pathways depending on the cell type. M_1 , M_3 , and M_5 receptors can stimulate pathways involving phospholipase A2, phospholipase D, and tyrosine kinase, as well as calcium channels. M_2 and M_4 receptors can also use phospholipase A2 as a second messenger [6, 7].

Atropine is a competitive mAChR antagonist at all five mAChR subtypes. Because atropine is a competitive antagonist, it has no *physiological efficacy* at mAChR; however, atropine can antagonize acetylcholine binding with therapeutic, *pharmacological efficacy*. As this antagonism is competitive, it can be

overcome by larger concentrations of acetylcholine; the therapeutic implication is that atropine dosing must be titrated to the desired therapeutic effect.

In typical therapeutic doses, atropine's CNS effects are minimal; however, larger doses can cause excitation, delirium, and hallucinations. Low, subtherapeutic (<0.01 mg/kg or ≤ 0.5 mg in the average adult) doses of atropine can, paradoxically, cause decreased heart rate due to antagonism at presynaptic M1 receptors in the sinoatrial node. This inhibits negative feedback of acetylcholine, causing paradoxical release of acetylcholine that decreases heart rate [1, 8, 9]. This slowing is usually moderate, approximately four to eight beats per minute, and does not usually cause clinically significant decreases in cardiac output or blood pressure [1]. In therapeutic doses (0.5–2.0 mg in an average adult), atropine has the more expected effect of tachycardia due to blockade of the M2 receptors on the myocardial sinoatrial nodal pacemaker cells, antagonizing parasympathetic tone to the heart.

Respiratory effects of atropine include bronchodilation, drying of mucous membranes, and inhibition of secretions in the nose, mouth, pharynx, and bronchi. Other effects can include mydriasis, urinary retention, slowed GI motility, and decreased sweating [1].

Antagonism of clinically significant bronchospasm and bronchorrhea is the usual therapeutic end points to allow adequate ventilation and oxygenation of patients with severe OP or carbamate poisoning. Antagonism of OP- and carbamate-induced bronchospasm and bronchorrhea is critical because resistance to flow of a gas through a tube is proportional to $1/r^4$ and flow of a gas through a tube is proportional to r^4 , where r represents the radius. In other words, small changes in bronchiolar radius due to bronchospasm or bronchorrhea may have large effects on ventilation and oxygenation.

Pharmacokinetics

Elimination (β) $T_{1/2}$	Children < 2years	6.9 \pm 3.3 h [10, 11]
	Children \geq 2 years	2.5 \pm 1.2 h [11]
	Adults	3.0 \pm 0.9 h [11]
	Age \geq 65	10.0 \pm 7.3 h [10, 11]
Vd	Children < 2years	3.2 \pm 1.5 L/Kg [11]
	Children \geq 2 years	1.3 \pm 0.5 L/Kg [11]
	Adults	1.6 \pm 0.4 L/Kg [11]
	Age \geq 65	1.8 \pm 1.2 L/Kg [11]
Tmax	Intravenous (IV)	Almost immediate
	Intramuscular (IM), by auto-injector	11–30 min (12, 13) ^a
	IM, not by auto-injector	30–42 min [11, 14] ^b
	Subcutaneous	34 \pm 23 min [11] ^c
	Inhalation	15–114 min [12, 13] ^d
	Intraocular	8 min [15] ^e
Hepatic plasma clearance		519 \pm 147 mL/min [16]
Renal plasma clearance		656 \pm 118 mL/min [16]

^aTmax was 0.19 \pm 2.3 h, after 2 mg IM injection of atropine sulfate with AtroPen[®] auto-injector [12]. Tmax was 0.5 h after 1.67 mg IM injection of atropine free base with AtroPen[®] auto-injector; however, the first samples were collected at 0.5 h [13]

^bTmax was 41.7 \pm 19.1 min after IM injection of 0.02 mg/kg of atropine sulfate [11]. Tmax was seen 30 min after IM injection of 1 mg atropine sulfate [14]

^cTmax was 34 \pm 23 min after subcutaneous injection of 0.02 mg/kg of atropine sulfate [11]

^dTmax was 0.25 \pm 0.47 h after a 1.95 mg inhaled dose from an atropine dry powder inhaler [12]. Tmax was 0.6 \pm 0.2 h after a 5.2 mg inhaled dose of atropine sulfate suspension and 1.9 \pm 1.5 h after a 3.4 mg inhaled dose of atropine sulfate suspension [13]

^eTmax was 8 min in eight patients who received 40 μ l of 1% atropine ophthalmic solution unilaterally to the inferior sulcus of the eye; however, the first samples were collected at 8 min [15]

Intravenously administered atropine has an initial distribution or (α) $T_{1/2}$ of about one minute, after which the concentration declines rapidly within the first 8–10 min. Ten minutes after IV injection, the amount of atropine that is present in the circulation is less than 5% of the intravenously administered dose [11, 14, 17]. After IV injection, over 50% of the drug is eliminated unchanged in urine [18].

After IM injection, peak plasma concentrations are reached by approximately 30 min; absorption is faster from the deltoid muscle than from the vastus lateralis or the gluteus maximus muscles [17]. The plasma concentration one hour after IM administration is virtually equal to the plasma concentration seen with the IV route one hour after IV infusion. Approximately one third of an IM dose of atropine is eliminated unchanged in urine [18, 19].

Inhaled atropine is being developed as a systemic and pulmonary treatment for the extended recovery period after chemical weapon exposures [12]. Dry powder inhalation is a high bioavailability route for attaining rapid and consistent systemic concentrations of atropine [12]. Atropine via metered-dose inhaler was investigated in a study in which eight subjects received 1.7, 3.4, and 5.2 mg of atropine sulfate by inhalation and 1.67 mg of atropine free base (equivalent to 2 mg of atropine sulfate) by IM injection [13]. Serum atropine sulfate concentrations were measured over a 24-h period. Mean peak concentrations were 4.9, 6.1, and 7.9 ng/mL for the inhaled doses and 8.4 ng/mL for the IM dose. Typical anticholinergic effects were seen after all doses [13].

Atropine is metabolized stereoselectively, predominantly in the liver. The biologically active enantiomer (*l*) is metabolized, whereas the biologically inactive enantiomer (*d*) is excreted unchanged in urine. The four atropine metabolites that have been identified in urine are tropine, noratropine, atropine-*N*-oxide, and tropic acid [20]. Metabolism of atropine, by microsomal monooxygenases, appears to be inhibited by organophosphate insecticides; no atropine metabolites were found in the urine of eight

organophosphate-poisoned patients who received high-dose atropine [21]. Children < 2 years of age and adults \geq 65 years of age have longer elimination half-lives than older children and adults < 65 years of age [10].

Contraindications, Adverse Effects, and Precautions

There are no absolute contraindications to administering atropine for treating life-threatening, cholinergic manifestations of OP or carbamate insecticide poisoning or OP military nerve agent poisoning. However, there are relative contraindications, potential adverse effects, and precautions about which the practitioner must be vigilant. Atropine is not indicated in those who lack significant muscarinic effects after exposures. Allergic reactions to atropine eye drops and anaphylaxis to IV atropine, administered during anesthesia, have been reported [22–24].

As of December 2014, the US Food and Drug Administration (FDA) requires removal of pregnancy categories from human prescription drug product labeling. Nevertheless, some references still list atropine preparations as pregnancy class B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women) [25, 26], whereas others list it as pregnancy class C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks) [27–30]. Atropine crosses the placenta and reaches the fetal circulation; in one study, atropine concentrations in the umbilical vein were 93% of maternal values, 5 min after intravenous injection [31]. With OP or carbamate poisoning, the dose required to effectively treat the mother is probably the optimal approach since usually the best treatment for the fetus is the best treatment for the mother.

Between November 1990 and March 1991, 268 children under the age of 16 years received injections of atropine from auto-injectors that had been distributed to the Israeli population in personal aid kits. In most of these exposures, the atropine was injected accidentally, typically into a finger or hand. In some instances, the auto-injector was administered by a parent under the false assumption of nerve agent exposure. Of the 240 atropine exposures for whom data were available, 43% had dilated pupils, 39% had tachycardia, 35% had dry mucous membranes, 20% had flushed skin, 4% had hyperthermia (defined as greater than 37.8 °C), and 5% had neurological abnormalities (described variously as irritability, agitation, confusion, lethargy, or ataxia). There were no reported fatalities, seizures, or life-threatening dysrhythmias; however, 22 had tachycardia between 160 and 190 beats per minute. Five were hospitalized for observation due to tachycardia or agitation [32].

The plasma elimination half-life is prolonged in patients \geq 65 years of age [10, 11]. Delirium, urinary retention, constipation, and ileus are potential adverse effects that are potentially more troublesome in the elderly. In the setting of OP or carbamate poisoning, renal or hepatic dysfunction is not a contraindication for atropine administration, and the dose should be titrated to achieve clinical therapeutic end points.

Treatment

As an antidote, atropine is used to treat OP and carbamate insecticide poisoning and poisoning from OP military nerve agents. Atropine has also been used therapeutically as premedication to prevent oropharyngeal secretions during anesthesia, to prevent vagal mediated bradycardia in procedures such as rapid sequence intubation, as a cycloplegic for a variety of ophthalmologic conditions and for treating diarrhea, irritable bowel syndrome, myasthenia gravis, vestibular disorders, and asthma.

Administration

Atropine is available as oral, parenteral, and ophthalmic preparations, as well as in solution for use in nebulizers. As an antidote, IV and IM are the preferred routes of administration. Intraosseous (IO), subcutaneous (SC), or endotracheal administration is possible. Atropine is formulated and supplied in multiple concentrations, which increases the possibility of dosing error. The most common concentrations are 0.05 mg/mL, 0.1 mg/mL, 0.4 mg/mL, 0.4 mg/0.5 mL, and 1 mg/mL. Preservative-free formulations are preferred for dosing that requires multiple boluses or continuous IV infusions because of the theoretical concern for toxicity from accumulation of benzyl alcohol [33].

Consensus does not exist as to the appropriate dosing regimen for cholinergic poisonings. Recommendations have varied widely; 33 different regimens were identified in a 2007 review of the topic [34] (level of evidence: III). There has been a recent trend recommending the increased speed of dose escalation [35] (level of evidence: III). A titrated dosing regimen has been proposed that involves administering an initial adult loading dose of 1.8–3 mg of atropine IV. The dose is then doubled every 3–5 min with the therapeutic end point of atropinization: defined as a clear chest on auscultation, heart rate greater than 80 beats per minute, pupils no longer pinpoint, dry axillae, and systolic blood pressure greater than 80 mmHg [36, 37] (level of evidence: II-2). The presence of small pupils alone does not warrant continued administration of bolus dose atropine if the other physiologic parameters have been met. Initial atropinization, followed by an atropine infusion starting at 10–20% of the total initial bolus per hour [37], produced fewer signs of atropine toxicity, such as delirium or hallucinations, compared to ad hoc dosing [36] (level of evidence: II-2).

For IM administration, generally under field conditions rather than in an ICU setting, a combined auto-injector that contains 2.1 mg atropine plus 600 mg pralidoxime chloride is available, as

Table 1 Classification of OP or carbamate insecticide or OP nerve agent-induced signs and symptoms

Mild	Severe
Eyes: Blurred vision Miosis Pain Lacrimation Airway and breathing: Rhinorrhea Salivation Chest pain or tightness Dyspnea Wheezing Cough Bronchorrhea Bronchospasm Cardiovascular: Bradycardia or tachycardia Gastrointestinal: Cramps Nausea Emesis Neuromuscular: Tremors Fasciculations	Airway and breathing: Severe bronchorrhea Severe dyspnea Respiratory distress Respiratory arrest Gastrointestinal: Defecation Diarrhea Genitourinary: Urination Peripheral neuromuscular: Fasciculation Weakness Paralysis Central nervous system: Altered mental status Confusion Convulsions Coma

Adapted from: Ref. [8], with permission

are atropine-only auto-injectors in 0.25 mg, 0.5 mg, 1 mg, and 2 mg doses. The package inserts and Advanced Hazmat Life SupportTM recommends administering atropine by IM auto-injector based on the age or the size of the patient and on the presence of signs or symptoms of toxicity (Tables 1 and 2) [8, 27–29] (level of evidence: III). For adults and children who weigh ≥ 40 kg with ≥ 2 mild signs of toxicity, administer one combined auto-injector as an initial dose; for those with any severe sign or symptom, administer three combined auto-injectors as an initial dose [8, 27, 28] (level of evidence: III). Table 2 details a weight- or age-based dosing regimen for administering atropine-only auto-injectors to children [8] (level of evidence: III).

Initial doses of atropine greater than 100 mg may be needed to achieve atropinization for OP and carbamate insecticide poisonings; more than 1000 mg may be required over the first 24 h to maintain atropinization. Such quantities may

Table 2 IM administration of atropine-only auto-injectors to pediatric patients

Pediatric patient weight and age	Initial IM dose of atropine for those with two or more mild carbamate or OP-induced signs or symptoms	Initial IM dose of atropine for those with any severe carbamate or OP-induced sign or symptom
≥41 kg ≥90 lb Generally ≥ 10 years of age	2 mg	6 mg
18–41 kg 40–10 lb Generally 4–10 years of age	1 mg	3 mg
7–18 kg 15–40 lb Generally 6 months to 4 years of age	0.5 mg	1.5 mg
<7 kg <15 lb Generally < 6 months of age	0.25 mg	0.75 mg

Adapted from: Ref. [8], with permission

deplete a hospital of its supply [38]. The US Department of Health and Human Services, through state, local, and tribal governments, has prepositioned atropine auto-injectors and multidose vials for use by emergency medical services or hospital personnel for multiple casualties produced by OP or carbamate insecticide poisonings or an attack with a military nerve agent [39]. Such supplies can be accessed through the state, local, or tribal health department or the regional poison control center.

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Calcium edetate (calcium disodium ethylenediaminetetraacetic acid [EDTA]) is the generic name for the chelating agent calcium disodium ethylenediaminetetraacetate. The drug also has been called *calcium disodium edathamil* and edetate calcium disodium. It is marketed in the United States under the brand name Calcium Disodium Versenate. (*Note:* Calcium edetate should not be confused with the disodium, trisodium, or tetrasodium salts of EDTA, which do not contain calcium and which may cause dangerous hypocalcemia.)

History

In 1950, EDTA (edetic acid), an industrial chemical widely employed to chelate cations in solution, was used clinically in the treatment of hypercalcemia. In 1952, investigators reported the first use of the calcium disodium salt of ethylenediaminetetraacetate (calcium edetate) in the treatment of lead intoxication in children [1] and adults [2]. The use of calcium edetate was associated with large increases in the urinary excretion of lead without the risk of hypocalcemia that had been encountered with the use of edetic acid. Within a few years, numerous accounts of the clinical utility of calcium edetate in the treatment of lead poisoning appeared in the medical literature. Its clinical use for this purpose has continued to the present.

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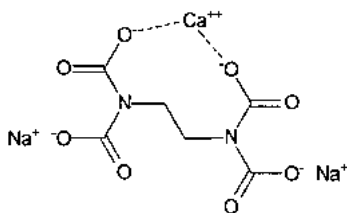


Fig. 1 Chemical structure of calcium disodium edetate

Chemical Properties

Calcium edetate ($\text{C}_{10}\text{H}_{10}\text{CaNa}_2\text{O}_8 \cdot \chi \text{H}_2\text{O}$; molecular weight 374.27 g/mol [anhydrous]) (Fig. 1) is a white, crystalline powder that is freely soluble in water. The compound forms stable, water-soluble complexes, or chelates, with numerous cations. Because the stability constant of the lead EDTA chelate ($K_{K2} = 18.2$) greatly exceeds that of the calcium EDTA chelate ($K_{K2} = 10.59$), lead ions react with calcium edetate *in vivo* to form a lead chelate that is excreted in the urine.

Pharmacodynamics

On absorption, calcium edetate forms complexes not only with lead but also with zinc, an essential trace metal. During the course of calcium edetate treatment, serum zinc levels may decline to approximately 60–70% of pretreatment values, and urinary zinc excretion may increase approximately 5- to 20-fold [3–6]. This increase may be associated with partial inhibition of zinc metalloenzymes (e.g., alkaline phosphatase). These indices of zinc status return to normal within a few days of cessation of calcium edetate treatment; their clinical significance is uncertain. Calcium edetate exerts no significant pharmacodynamic effects on cardiovascular, hepatic, or renal function.

Pharmacokinetics

Calcium edetate may be administered by either intramuscular injection or intravenous infusion. Oral absorption is poor, and oral administration is not recommended because it may increase

absorption of lead that may be present in the intestinal tract. The volume of distribution is 0.19 L/kg, consistent with distribution in extracellular water [7]. The serum elimination half-life is approximately 2 h in subjects with normal renal function. Calcium edetate is excreted unchanged in the urine, predominantly through glomerular filtration. Some data indicate that relatively greater metal excretion is achieved when the total daily dose is administered by continuous infusion over all or most of the day, as opposed to short-term infusion over 1 h [8, 9] (Grade III evidence). Renal clearance of calcium edetate and the mobilization of lead into the urine occur more slowly in patients with renal insufficiency [7, 10].

Contraindications and Precautions

Because calcium edetate and the metals it mobilizes are excreted in the urine, caution should be exercised in administering the drug to patients with renal insufficiency. In patients with moderate renal insufficiency, a reduction in dose proportionate to the deficit in creatinine clearance is appropriate. Some case reports suggest that calcium edetate can be used in conjunction with peritoneal dialysis, hemodialysis, or hemofiltration to enhance lead decorporation in lead-poisoned patients with renal failure [11–14]. A recommended protocol is to administer 1 g of calcium edetate in 250 mL normal saline intravenously over 1 h, followed immediately by 4 h of hemodialysis using a high flux dialysis membrane, such as the F160 [15] (Grade III evidence).

Calcium edetate was teratogenic when administered to pregnant rats at a dose of 4 mmol/m²/day (comparable to a therapeutic adult human dose of approximately 40 mg/kg/day) [16]. This teratogenicity may have been a consequence of zinc depletion, because the administration of a zinc chelate of EDTA was not teratogenic. Calcium edetate has diminished the adverse reproductive effects of lead in pregnant experimental animals [17] and in two isolated reports has been used to treat lead poisoning in the late stages of human gestation without apparent adverse effect [18, 19]. Calcium edetate is rated pregnancy

category B (pregnancy category means that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester) by the US Food and Drug Administration. If its use in pregnancy is necessary, maternal supplementation with zinc (e.g., 25 mg zinc sulfate orally during chelation and for one additional week) is advisable based on moderate evidence of the salutary effects of treatment of zinc deficiency during pregnancy [20] (Grade III evidence).

Adverse Effects

Calcium edetate generally is well tolerated, and adverse effects are rare. The drug has been associated with nephrotoxic damage to the proximal tubule in humans and animals, usually after administration of high or protracted doses [21, 22]. Moel and Kumar [23] reported four pediatric cases of oliguric acute renal failure among 207 courses of lead chelation that consisted of 5 days of combined treatment with calcium edetate, 50 mg/kg/day, and dimercaprol, 18 mg/kg/day. The oliguria developed 1–2 days after chelation was discontinued and lasted 2–4 days. Elevations in serum creatinine (3.9–8.4 mg/dL) normalized after 11–22 days. Although such nephrotoxicity from calcium edetate is uncommon, it is appropriate to monitor renal function (urinalysis, blood urea nitrogen, serum creatinine) at the onset of treatment and every 24–48 h during therapy. To reduce the risk of nephrotoxicity, a course of calcium edetate treatment should not exceed 5 consecutive days, and repeat courses should be separated by at least a 2-day interval. Maintaining urine output of approximately 1–2 mL/kg may optimize lead elimination and diminish the risk of nephrotoxicity, but care must be taken to avoid fluid overload in patients with lead encephalopathy and cerebral edema. Calcium edetate has been associated with mild reversible increases in hepatic transaminases, which are of minimal or no clinical significance [5].

Administration

Continuous intravenous infusion is the preferred route of calcium edetate administration. The drug should be diluted to a concentration of 2–4 mg/mL in normal saline or 5% dextrose. In adults with severe lead poisoning, the recommended dose is 2–4 g (30–50 mg/kg) intravenously per 24 h, as a continuous infusion. The pediatric dose is 1000–1500 mg/m²/24 h as a continuous intravenous infusion. To diminish the risk of nephrotoxicity, a course of treatment should not exceed 5 consecutive days.

Although intravenous administration is preferable, the daily dose of calcium edetate also can be administered by deep intramuscular injection in divided doses spaced 8–12 h apart. To minimize pain at the injection site, lidocaine can be added to the calcium edetate injection solution to achieve a final lidocaine concentration in the injectate of 5 mg/mL (0.5%). Calcium Disodium Versenate (edetate calcium disodium injection, USP) is supplied as 5-mL ampules containing 200 mg/mL of calcium edetate (1 g per ampule). Lower cost pharmaceutical-grade calcium disodium edetate bulk powder may also be obtained by hospital pharmacies for preparation of compounded intravenous solutions.

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Cyanide-Binding Antidotes: Dicobalt Edetate and Hydroxocobalamin

140

Vikhyat S. Bebarta

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Cyanide exposure can cause rapid death. The most common cause of cyanide toxicity is inhaled cyanide (hydrogen cyanide) from structure fires [1, 2]. While fortunately less common, the most interesting cause of cyanide toxicity come from suicidal and homicidal acts. There are as many deaths each year in the United States as from cardiac glycosides, beta blockers alone, or organophosphates [3]. The largest threat of cyanide toxicity is actually the result of terrorism and war [4]. Recent events have highlighted the need for preparedness against possible chemical terrorist attacks. Cyanide also creates an occupational hazard in industries such as electroplating, metal extraction, pest control, and oil field work. Several treatments are available to treat cyanide toxicity, and clinical practice guidelines are available [1, 5, 6]. The availability of antidotal therapy also is subject to impact from both market and regulatory forces [7, 8].

In the United States, the two most common antidotes used are hydroxocobalamin and sodium nitrite/sodium thiosulfate (Nithiodote, Hope Pharmaceuticals) [9]. In Europe, both hydroxocobalamin and 4-dimethylaminophenol (4-DMAP) are used. Dicobalt edetate is available in Germany but does not find widespread use elsewhere [10]. The cyanide antidote kit (Lilly Cyanide Kit, Eli Lilly, Indianapolis, IN) contains amyl nitrite, sodium nitrite, and sodium thiosulfate and was produced for over 50 years; however, this is no longer manufactured [11]. Guidelines in Australia, Europe, and the United Kingdom vary. However, most recommend hydroxocobalamin as

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the first-line agent for the management of cyanide toxicity [5, 6].

Cyanide antidotes are administered to patients suspected of suffering cyanide toxicity. This suspicion is most often based on the triad of altered mental, lactic acidosis, and hypotension, in concert with a clinical suspicion of cyanide exposure. Because bedside or field testing for cyanide is not available, the antidotes are often empirically administered. In patients who are not critically ill but likely intoxicated with cyanide, administration

of the antidote may reduce the incidence of persistent neurological effects [12, 13].

Cyanide toxicity is discussed in detail in ► Chap. 97, “Cyanide: Hydrogen Cyanide, Inorganic Cyanide Salts, and Nitriles.”

Pharmacodynamics

Cyanide antidotes work by different mechanisms (Tables 1, 2, and 3).

Table 1 Cyanide-binding antidotes

Antidote	Typical dose	Mechanism of action	Adverse effects
Dicobalt edetate (Kelocyanor)	300 mg IV	Chelation of cyanide. Dicobalt edetate complexes with cyanide forming cobalt cyanide, removing cyanide from the circulation and reducing toxicity	Severe hypotension, cardiac arrhythmias, convulsions. Gross edema after treatment with dicobalt edetate also has been reported. These effects are most common when infused in the absence of cyanide. Intravenous glucose may mitigate some of these adverse effects
Hydroxocobalamin	5–15 g IV	Chelation of cyanide. Cobalt complexes with cyanide to form cyanocobalamin (vitamin B ₁₂)	Minimal, transient reddish discoloration of the skin, mucous membranes, and urine, producing a increase in blood pressure Allergic reactions have been noted

IV, intravenously

Table 2 Methemoglobin inducer antidotes

Antidote	Typical dose	Mechanism of action	Adverse effects
4Dimethylaminophenol (4-DMAP)	5 mL of 5% 4-DMAP solution (250 mg or 3–4 mg/kg) IV for 1 min	Generates a methemoglobin concentration of 30–50% within a few minutes at these doses	Poor dose–response curve reproducibility. Hemolysis has been shown at therapeutic doses
Amyl nitrite pearls		Methemoglobin formation, which promotes a concentration-dependent movement of cyanide out of mitochondria	Methemoglobinemia and hypotension
Sodium nitrite	10 mL (30 mg/mL) IV	Methemoglobin formation, which promotes movement of cyanide out of mitochondria. Clinical effects are observed before significant levels of methemoglobinemia, however, suggesting an alternate mode of action	The mean of the peak amount of methemoglobin concentrations is 10% after administration of 300 mg of sodium nitrite. Hypotension may occur

Table 3 Sulfur donors – sodium thiosulfate

	Typical dose	Mechanism of action	Adverse effects
Sodium thiosulfate	50 mL (250 mg/mL) IV or 12.5 g/50 mL	Administer thiosulfate IV. Thiosulfate reacts with cyanide ion to form thiocyanate. Thiocyanate is nearly nontoxic and rapidly excreted renally	High thiocyanate concentrations (>10 mg/dL) have been associated with vomiting, psychosis, arthralgias, and myalgia

Cyanide Binders – Hydroxocobalamin and Dicobalt Edetate

Hydroxocobalamin is a precursor to cyanocobalamin (Vitamin B12) [14]. It is designed with a cobalt atom that binds cyanide, forming cyanocobalamin. This nontoxic product is excreted in the urine (Fig. 1). Hydroxocobalamin does not form methemoglobin; it binds directly to cyanide (Fig. 2). It is a single drug and is relatively safe. The elimination half-life is 24–48 h. In clinical and preclinical studies, it has shown to be effective after cyanide-induced apnea, hypotension, and cardiac arrest [15–17].

Dicobalt edetate is also an intravenous chelator of cyanide designed around a cobalt moiety [5]. It has a rapid onset of effect but has many adverse effects described below.

Methemoglobin Inducers

Several antidotes use methemoglobin induction to detoxify cyanide. Hemoglobin contains ferrous iron (Fe^{2+}) which is oxidized to ferric iron (Fe^{3+}) in methemoglobin by sodium nitrite, amyl nitrite, 4-DMAP, and other similar drugs [13]. Cyanide has a greater affinity for methemoglobin than hemoglobin. The resultant cyanomethemoglobin is less toxic than cyanohemoglobin. Significant methemoglobinemia occurs within about 30 min of administration of sodium nitrite with significant clinical

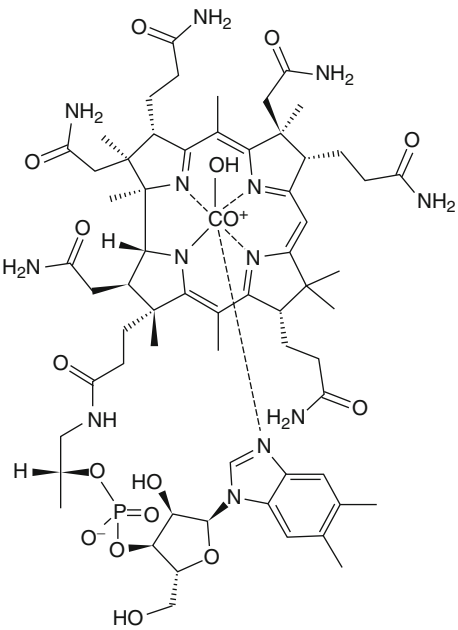


Fig. 1 Chemical structure of hydroxocobalamin

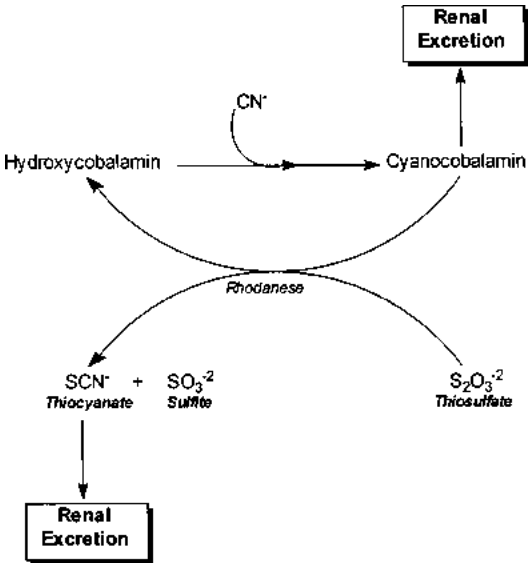
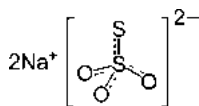


Fig. 2 Conversion of hydroxocobalamin and cyanocobalamin

benefit occurring within a few minutes of administration [18]. This timing suggests another, less well understood, effect of methemoglobin inducers may also contribute to overall therapeutic benefit.

Fig. 3 Chemical structure of sodium thiosulfate



Sulfur Donors – Sodium Thiosulfate

Sodium thiosulfate (Fig. 3) is thought to work primarily by sulfur donation to cyanide, producing the less toxic thiocyanate, which is renally eliminated [19]. This approach exploits rhodanese and similar innate ubiquitous enzymes, which serve to facilitate the detoxification of cyanide to thiocyanate.

Administration

Several antidotes are available for use in cyanide toxicity. In the United States, hydroxocobalamin is the most common agent stocked and used [8, 16, 20]. Sodium nitrite with sodium thiosulfate is also available. In the United Kingdom, dicobalt edetate is available and in Germany, 4-DMAP is used [6]. In most cases, administration of the antidote is done empirically based on initial laboratory testing (e.g., serum lactate) and clinical exam. In almost all cases, it is not appropriate to wait for the results of a cyanide level before beginning antidotal therapy (Level of Evidence (LOE) III). The overall treatment of cyanide poisoning is discussed more thoroughly in ► Chap. 97, “Cyanide: Hydrogen Cyanide, Inorganic Cyanide Salts, and Nitriles.”

Supplemental oxygen therapy must be initiated prior to administering cyanide antidotes (LOE II-2). Oxygen therapy alone is an important addition to the management of cyanide toxicity, and for mild or moderate cases of cyanide toxicity, oxygen alone may be sufficient [21]. This approach has not been validated in clinical studies but should be considered in circumstances involving many casualties or when availability of cyanide antidotes is limited (LOE II-3).

Hydroxocobalamin

Hydroxocobalamin is administered as 5 g over 30 min (70 mg/kg in a child) [1] (LOE I-1). If no

effect is observed after 5–15 min, an additional dose of 5 g may be given, up to a total dose of 15 g if needed. However, faster infusion rates may be used if needed in cases of cardiac arrest or severe clinical distress [17] (LOE-II). Hydroxocobalamin is contraindicated in patients allergic to vitamin B₁₂. Sodium thiosulfate may also be administered, though there is no clear additive benefit [10, 19] (LOE II-3). If both drugs are given, they should be infused separately [22].

Sodium Nitrite and Sodium Thiosulfate

These drugs are commonly administered together and are packaged together (Nithiodote, Hope Pharmaceuticals). The traditional cyanide antidote kit (amyl nitrite, sodium nitrite, sodium thiosulfate) is no longer manufactured. The dose for sodium nitrite is 300 mg (10 mg/kg) intravenously over several minutes. Methemoglobinemia of 15–20% is the goal, and the drug produces minimal adverse effects at usual doses [5]. A lower dose is required for children less than 25 kg and in anemic patients. The dose may be repeated in 30–60 min if an acceptable improvement in clinical effects is not detected. Use of sodium nitrite as a methemoglobinemia inducer is not preferred in patients with carbon monoxide toxicity; however, it is not contraindicated, and clinical judgment and experience should guide the decision [18, 19] (LOE II-3).

Sodium thiosulfate is a common sulfur donor. This drug converts cyanide into thiocyanate by donating sulfur and with the facilitation of rhodanese and other similar innate enzymes [23]. Thiocyanate is then cleared renally. The usual dose is 12.5 g (50 mL of 25% solution) intravenously; however, other formulations for intramuscular dosing have been studied and found to be effective. In children, the proper dose is 1 mL/kg intravenously (max of 12.5 g) [10]. Sodium thiosulfate dosing may be repeated in 30–60 min if adequate improvement is not observed. Sodium nitrite and sodium thiosulfate together may have a synergistic effect [13].

Amyl Nitrite

Amyl nitrite is a methemoglobin-inducing inhalant [24]. It was included in the Lilly Cyanide Antidote Kit, which is no longer manufactured. The ampule is crushed and the patient inhales the contents for 30 s. It can be inhaled through the nose or through the endotracheal tube. Amyl nitrite has traditionally been used as a prehospital therapy and as a temporizing measure prior to administration of parenteral antidotes. However, recent research suggests it may be effective alone for mild to moderate cyanide toxicity [25] (LOE II-2).

Dicobalt Edetate

Dicobalt edetate is administered as 300 mg (20 mL of 1.5% solution) intravenously over 1–5 min [5]. This dose is repeated if no improvement is observed after 5 min. Because of the potential for severe adverse effects, this antidote should only be administered when the diagnosis of cyanide toxicity is certain and other therapies are either unavailable or ineffective [5]. Co-administration of glucose (50 mL of 50% solution for adults) may help reduce some of the potential adverse effects (LOE II-2).

Dimethylaminophenol (4-DMAP)

Dimethylaminophenol is administered as 5 mL of 5% solution (250 mg) intravenously over 1 min [10, 26]. For children, the drug is administered intravenously at a dose of 3–4 mg/kg. 4-DMAP is discussed in detail in ► Chap. 144, “4-Dimethylamino Phenol.”

Hyperbaric Oxygen

In most published human reports, hyperbaric oxygen is offered after a combination of other therapeutic modalities, including antidote administration [22, 24]. Based on case reports and

preclinical data, the effectiveness of hyperbaric oxygen for treating cyanide toxicity remains controversial [27–29].

Future

Several novel cyanide antidotes are currently being evaluated. Nitrocobinamide is a small-volume antidote that contains cobalt in a formulation similar to hydroxocobalamin [30, 31]. One mole of nitrocobinamide can bind two moles of cyanide and has fewer side effects than hydroxocobalamin (Fig. 1). It has been studied in several animal species and appears effective for severe cyanide toxicity [30, 32, 33] (LOE I). Sulfanegen is another promising antidote that can be delivered intramuscularly in a small volume [34]. It is a prodrug for 3-mercaptopyruvic acid (3-MP) and detoxifies cyanide through its actions as a sulfur donor. Several studies have reported efficacy over several animal species and preclinical models [9]. Parenteral DMTS (dimethylsulfide) is a potential antidote for treating cyanide toxicity. It also works through sulfur donation (Fig. 4).

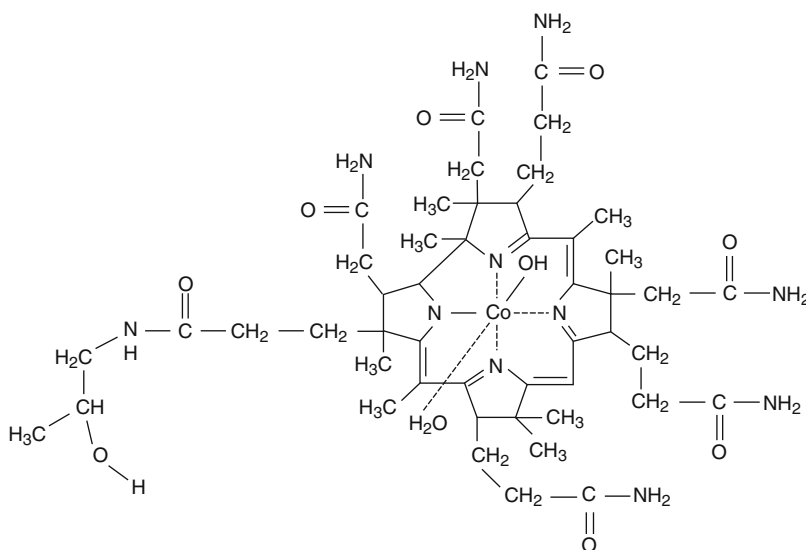
Adverse Effects

While antidotes are effective for the treatment of cyanide toxicity, all have some adverse effects. Hydroxocobalamin has the fewest serious adverse effects. New antidotes such as nitrocobinamide have even fewer associated adverse effects [33]. Knowledge of the adverse event profile prior to antidote administration may help guide the choice of best antidote selection and also may mitigate these effects in the complex, critically ill cyanide-toxic patient.

Hydroxocobalamin

Hydroxocobalamin is safe and has been approved for use in the United States since 2006 [10]. Adverse effects include a transient red

Fig. 4 Chemical structure of cobinamide



color of urine, tears, and skin and bright red blood [35, 36]. This color may be present for 2–3 days. The color change may affect results of colorimetric, spectrophotometric, and co-oximetric assays. The interference with co-oximetry may complicate, or render useless, measurement of carboxyhemoglobin in patients retrieved from structure fires. In addition, other blood tests that may be affected include lactate, alanine aminotransferase, aspartate aminotransferase, creatinine, bilirubin, and magnesium. Urine test results may also be affected. Blood color changes may also interfere with alerts on dialysis machines [37]. Elevated blood pressure occurs frequently with hydroxocobalamin administration and rare cases of anaphylaxis have also been reported [38].

Sodium Nitrite and Sodium Thiosulfate

The FDA placed a Black Box warning on sodium nitrite. Sodium nitrite produces methemoglobinemia of approximately 10% within 30 min of administration [39]. Higher levels of methemoglobinemia can be produced; however, this may also cause respiratory distress and hypoxia. In anemic patients (hemoglobin <14 g/dL), appropriate doses per weight of sodium nitrite should be used, up to a maximum dose of 10 mL

[40]. Hypotension and tachycardia may also occur and are typically transient [40]. Hemolysis rarely occurs and patients with G6PD deficiency are at greatest risk. The precise risk of hemolysis is unknown. Theoretically, inducing methemoglobinemia in a patient with an elevated carboxyhemoglobin level is potentially dangerous and some have recommended administering sodium thiosulfate alone in patients retrieved from structure fires. However, sodium nitrite is an effective and rapidly acting antidote for cyanide toxicity, and its administration should be given consideration if hydroxocobalamin is not available.

Sodium thiosulfate has few adverse effects. It detoxifies cyanide by converting it to thiocyanate. High levels of thiocyanate (>10 mg/dL) may cause arthralgias, psychosis, and vomiting [7]. Extracorporeal methods (e.g., hemodialysis) of thiocyanate removal may be necessary in patients with renal insufficiency or failure.

Dicobalt Edetate

The current recommended antidote for clinically severe cyanide toxicity in Australia and the United Kingdom is dicobalt edetate [5]. Significant adverse effects are associated with the use of this drug (see Table 150–1), many of which are

life threatening. These effects include seizures, anaphylaxis, dysrhythmia, and hypotension. Therefore, this antidote should be administered only when the diagnosis of cyanide poisoning is certain and other, safer, alternatives are not available. Administration of glucose may mitigate some of these adverse effects (LOE III).

4-Dimethylaminophenol

In Germany, 4-dimethylaminophenol (4-DMAP) is used as a methemoglobin generator in cyanide-poisoned patients because of its rapid onset of action within a few minutes of injection [5]. The adverse effect of methemoglobin formation is greater with 4-DMAP compared to sodium nitrite. It has poor dose–response curve reproducibility. Hemolysis as a result of 4-DMAP therapy has been reported both in overdose and following proper therapeutic doses [41]. Nephrotoxicity and reticulosis have been reported [41]. Methylene blue is often needed to reverse excessive methemoglobin caused by 4-DMAP, which adds additional risk as methylene blue may also increase cyanide release in cyanide-poisoned patients [42].

Special Populations

For pediatric patients sodium thiosulfate is safe to use in weight-based dose. Neonates and infants are more susceptible to severe methemoglobinemia after sodium nitrite. For children, administer the weight-based dose:

- Sodium nitrite – 0.2 mL/kg of a 3% solution (6 mg/kg or 6–8 mL/m² BSA) of sodium nitrite at the rate of 2.5–5 mL/min not to exceed 10 mL (300 mg)
- Sodium thiosulfate – 1 mL/kg of body weight using a 25% solution (250 mg/kg or approximately 30–40 mL/m² of BSA) not to exceed 50 mL (12.5 g) total dose immediately following administration of sodium nitrite

For pediatric patients, the dose safety of hydroxocobalamin has not been determined; however, reports have been published that recommend it and the dose used is 70 mg/kg parenterally [43] (LOE III).

For pregnant patients, the data on cyanide antidotes is limited. Sodium thiosulfate and sodium nitrite are Pregnancy Category C (<http://www.hopepharm.com/prescribing/>- package insert). Hydroxocobalamin is also assigned Pregnancy Category C. Use these antidotes with benefit outweighing the possible risk of their use. Since cyanide toxicity can be lethal and severely damaging to the fetus, and antidote use can be lifesaving, often the benefit outweighs the risk (LOE III).

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Cyproheptadine is a first-generation piperidine antihistamine that is an antagonist at H₁ receptors and some serotonin receptor subtypes [1, 2]. Labeled uses of cyproheptadine include those related to its antihistaminic properties, such as allergic rhinitis and urticaria. Off-label, it has been used for its antiserotonergic properties including appetite stimulation in chronic disease, migraine prophylaxis, treatment of pruritus and spasticity associated with spinal cord injury, and management of serotonin syndromes [2–4]. Its use as an adjuvant in the treatment of baclofen withdrawal has also been reported [5–8]. The focus of this chapter is the use of cyproheptadine for the management of serotonin syndrome.

History

In the USA, a patent for cyproheptadine was issued to Merck & Co. in 1961. The drug was originally marketed under the brand name “Periactin[®],” which is no longer available in the USA, although cyproheptadine can be obtained in both tablet and liquid forms from generic manufacturers [9, 10].

Physicochemical Properties

The empirical formula of the anhydrous salt is C₂₁H₂₁N·HCl. The sesquihydrate form of the drug has a molecular weight of 350.89 g/mol

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[11]. Cyproheptadine hydrochloride USP is a white to slightly yellow crystalline solid which is freely soluble in methanol, soluble in chloroform, slightly soluble in water, sparingly soluble in ethanol, and nearly insoluble in ether [11, 12].

Pharmacodynamics

Current human and animal studies suggest 5-HT_{2A} receptors are responsible for the more severe and life-threatening effects of serotonin syndromes, such as hyperthermia and hypertonicity or a hyperserotonergic state. 5-HT_{1A} receptors are probably responsible for less-severe effects such as hyperactivity and anxiety [4]. The nonspecific 5-HT₂ antagonist activity of cyproheptadine provides the basis for the suggestion that it may be clinically useful in managing states associated with serotonin excess.

When the serotonin precursor 5-hydroxy-L-tryptophan (5-HTP) is administered to rats in which monoamine oxidase activity is blocked with clorgyline, a hyperserotonergic state resulting in serotonin toxicity (i.e., serotonin syndrome) is induced. This model allows for the study of the efficacy of various serotonin antagonists, administered either before or after induction of serotonin syndrome. Nisijima used this model of serotonin syndrome in a rat study in which various drugs were given intraperitoneally (IP) prior to serotonin syndrome induction in order to evaluate their efficacy in preventing life-threatening effects [13]. Serotonergic effects attributed to 5-HT_{1A} agonism included tremor, forepaw treading, and Straub tail while those attributed to 5-HT_{2A} included increased norepinephrine levels in the anterior hypothalamus, hyperthermia, hypertension, and shock. The 5-HT_{2A}, but not the 5-HT_{1A}, effects were associated with death. Only the drugs with 5-HT_{2A} antagonist effects prevented death. And, in these cases, death was prevented only when sufficiently high doses of less-potent 5-HT_{2A} drugs were given. The 5-HT_{2A}-specific antagonists pipamperone and ritanserin consistently prevented hypothalamic increases in norepinephrine, hyperthermia, and death while 5-HT_{1A} antagonists did not; the authors concluded the most

serious serotonin effects appeared to be mediated by 5-HT_{2A} receptors. Therefore, it was reasoned that successful treatment of more serious toxicity required 5-HT_{2A}-antagonist drugs. Cyproheptadine, a less specific 5-HT antagonist drug than pipamperone or ritanserin, inhibits 5-HT_{2A} receptors. In this study, a 10 mg/kg IP dose of cyproheptadine was successful in preventing hyperthermic death in rats, whereas a smaller 5 mg/kg IP dose was not.

Using the same model of serotonin syndrome, Ma administered cyproheptadine after serotonin syndrome was induced in rats [14]. Cyproheptadine, when given as a 10 mg/kg IP dose, prevented hyperthermic death in rats with serotonin syndrome when given 15 min after induction of toxicity, but before the onset of hyperthermia. In contrast, death was slowed, but not prevented, when cyproheptadine was given 60 min after induction, by which time severe hyperthermia had already developed.

Zhang administered 10 mg/kg IP cyproheptadine to rats after serotonin syndromes were induced with 5-HTP and clorgyline and noted that the efflux of serotonin from the hypothalamus and cortex were attenuated, confirming prior work demonstrating the ability of cyproheptadine to antagonize 5-HT_{2A} receptors is the most likely mechanism for effectiveness in managing serotonin excess [15]. The authors theorized two separate but related mechanisms led to serotonin excess in significant cases: the initial augmentation caused by increased synthesis, and decreased breakdown of serotonin, followed by secondary activation of a 5-HT and NMDA neural circuit, amplifying the increase in 5-HT in the central nervous system. For activation, the secondary mechanism required the primary increase in serotonin first reach a threshold level.

Rats given doses of citalopram sufficient to induce seizures and death were protected by 17.1 mg/kg cyproheptadine or by 1.77 mg/kg diazepam IP [16].

A PET scan done in 2 patients given either 4 mg or 6 mg of cyproheptadine 3 times daily for 6 days showed that 5-HT₂ receptors in the prefrontal cortex are 85% blocked at a 12 mg/day dose and 95% blocked at 18 mg/day [17].

The animal studies reviewed above are of good quality, with appropriate controls and effective dose-finding. (Level of evidence [LOE] II-1) Human research in serotonin syndrome management is based entirely on case reports and reviews. (LOE Grade III) The pharmacodynamics and pharmacokinetics may differ between rodents and humans [4, 18, 19]. The timing with regard to onset of serotonin syndrome and administration of antidote is rarely, if ever, as ideal in humans as in rodent research. Additionally, serotonin syndrome is not always easily diagnosed with certainty and in most instances resolves quickly. For these reasons, it is difficult to assess the efficacy of any antidote given to manage serotonin syndrome. Therefore, while it is logical that administration of cyproheptadine to humans may alleviate or entirely resolve the effects associated with serotonin syndrome, it has not been demonstrated whether this occurs reliably at the doses currently administered to humans.

Pharmacokinetics

The pharmacokinetic profile of cyproheptadine in humans is not well studied. The drug is well absorbed after oral administration, but <15% of an 8 mg sublingual dose is absorbed. The peak level of glucuronidase-incubated cyproheptadine after oral ingestion of 8 mg occurred at 4 h [20]. Cyproheptadine distributes so rapidly into tissues that neither the parent compound nor the desmethylycyproheptadine metabolite is detected in plasma well under 2 h postingestion. Cyproheptadine is almost entirely metabolized, followed by renal metabolite elimination, mostly as glucuronide and sulfate conjugates. When radioactivity of any compound containing cyproheptadine in the plasma was measured after the administration of radioactive cyproheptadine, the peak radiation measurement occurred in 6–9 h after a 5 mg oral dose of solution [18]. Cyproheptadine undergoes hydroxylation of the aromatic ring, then glucuronidation, N-demethylation, and heterocyclic ring oxidation [19]. Metabolic studies indicate that $\geq 60\%$ of conjugates are glucuronides, with approximately 10% as sulfates

[18]. Roughly two thirds of a cyproheptadine dose is eliminated as metabolites in the urine, with approximately 25% eliminated in feces [18]. Predictably, elimination of metabolites is slowed in renal dysfunction [11].

Contraindications

Contraindications to cyproheptadine use include known hypersensitivity to the drug and circumstances in which anticholinergic effects would be significantly disadvantageous (e.g., pyloroduodenal obstruction, urinary obstruction, angle-closure glaucoma, and stenosing peptic ulcer) [2, 11]. Careful risk-benefit analysis should take place before use of cyproheptadine in patients with benign prostatic hypertrophy, and if it is to be used in young children or the elderly, who are more likely to have adverse effects when given anticholinergic medications [11, 12].

Concomitant use of cyproheptadine and monoamine oxidase inhibitors (MAOIs) is listed as being contraindicated in the cyproheptadine package insert. The listed concerns are an increase in anticholinergic effects, decrease in efficacy of MAOI antidepressants, and the hypothetical potential for toxicity. These concerns are based on a single unconvincing case report in which a patient developed irritability and visual hallucinations 2 months after beginning cyproheptadine therapy for phenelzine-induced anorgasmia [21, 22]. As cyproheptadine is expected to decrease serotonergic excess-related toxicity caused by the combined use of MAOIs with other serotonergic agents, this reported contraindication should probably not be a deterrent to using cyproheptadine to manage serotonin toxicity associated with MAOIs.

Adverse Effects

Most information about the adverse effects of cyproheptadine is derived from therapeutic use. Cyproheptadine is associated with increase in appetite and associated weight gain; sedation; anticholinergic effects (dry mouth, glaucoma,

urinary retention); and sometimes central nervous system stimulation (agitation, confusion, and visual hallucinations) [23].

Adverse effects of cyproheptadine are more likely with higher dosing, but the occurrence and severity of these effects appears to show individual variability [24, 25]. Sedation is the most common effect consistently reported [26–30] and more likely with higher doses. In a study evaluating the use of cyproheptadine given for blepharospasm, 8–24 mg daily in divided doses caused drowsiness and dry mouth [24]. The effect of increased appetite is often used for therapeutic intervention in patients requiring weight gain [27, 28]. Dizziness and sedation were reported in adult cancer patients given cyproheptadine 8 mg three times daily for anorexia or cachexia [25]. In addition to the more common adverse effects of sedation and increased appetite, some less common reported effects include agitation, confusion [28], psychosis [31], and acute hepatitis with prolonged anicteric cholestasis [32].

The therapeutic dose of cyproheptadine for children is 2 mg 2–3 times daily in 2- to 6-year-olds (maximum 12 mg/day) to 4 mg 3 times daily in 7- to 14-year-olds (maximum 16 mg/day) [2]. In pediatric overdoses, cyproheptadine causes anticholinergic effects similar to other first-generation antihistamines. In one case report of a 4-year-old child who ingested 22.5 mg, disorientation, ataxia, irritability, athetosis, mydriasis, tachycardia, hyperthermia to 38.8 °C, meaningless speech, and intermittent crying spells occurred, all lasting less than a day [33]. A 7-year-old hemodialysis patient taking cyproheptadine 4 mg nightly to increase his appetite was accidentally raised to 8 mg twice daily. This accidental overdose occurred 2 days after triprolidine/pseudoephedrine and ampicillin were added for an ear infection. After the accidental increase of cyproheptadine, the child developed hallucinations, tremors, and hearing difficulty that did not resolve completely for days after discontinuation [34].

Similar, but less severe, effects were reported when the drug was used therapeutically in children. The most common adverse effects associated with weeks-long use of cyproheptadine at a

dose of 0.04–0.62 mg/kg/day (median 0.19 mg/kg/d) for dyspepsia in children were somnolence (16%), irritability and behavioral changes (6%), increased appetite and weight gain (5%), and abdominal pain (2%) [25]. Anticholinergic toxicity was reported in a 9-year-old prescribed cyproheptadine 4 mg twice daily for migraine headaches. He developed “mean” behavior, then agitation, confusion, and hallucinations with tachycardia [35]. Headache and vertigo may be related to use [29, 30]. One case reported violent aggression in a 5-year-old boy taking 6 mg/day for months. The child was given cyproheptadine and levothyroxine to stimulate growth, then became more agitated and aggressive after cyproheptadine was added. The effects began to decrease within a few days of discontinuation of cyproheptadine and significantly decreased in just over a month. The levothyroxine was initiated 3 months prior to the cyproheptadine and discontinued more than a week after the cyproheptadine was discontinued, therefore the levothyroxine likely did not play a significant role. Also, the thyroid hormone levels were normal throughout. One additional confounder is a change in psychotherapy 2 weeks prior to the cyproheptadine discontinuation. The treatment team believed the temporal association favored cyproheptadine as the most likely cause of enhanced aggression in this child [36].

With repeated therapeutic dosing, cyproheptadine causes significant sedation and increase in appetite, even in doses as small as 4 mg in adults. Dry mouth, irritability, confusion, nausea, and abdominal pain have also been reported. Other effects that are less common but may be related to therapeutic use include headache, vertigo, violent aggression, and acute hepatitis with anicteric cholestasis. Sedation is more severe initially and with increasing doses. In cases of pediatric overdose, tachycardia, mydriasis, ataxia, disorientation, hallucinations, athetosis, and hyperthermia have been reported, as with overdoses of other antihistamines.

When cyproheptadine is used for the management of serotonin syndrome, mydriasis [37], blurry vision [37], and urinary retention [38] have been reported in adults. Interestingly, sedation has not been reported as an adverse effect in

this context. However, it may be difficult to observe sedation in patients with serotonin syndromes treated with cyproheptadine. Compared with the effects of the serotonin syndrome, minor to moderate sedation from cyproheptadine would likely go unnoticed. Additionally, other sedatives are often given to patients with serotonin syndrome, so any observed sedation could be due to the other sedatives given or the combination of cyproheptadine with the other sedatives. Any sedation noted would either be considered beneficial or possibly not be attributed to the cyproheptadine, making it unlikely most case reports and studies involving serotonin excess would mention sedation due to cyproheptadine.

High doses of cyproheptadine are used for the management of serotonin syndrome, making adverse effects more likely. However, the clinical significance of the adverse effects is questionable. The potential for anticholinergic effects is worth consideration in the subset of patients previously mentioned (e.g., pyloroduodenal obstruction, urinary obstruction, angle-closure glaucoma, and stenosing peptic ulcer). However, this does not mean the use of cyproheptadine for serotonin syndrome is contraindicated in these patients.

Treatment

The dosing of cyproheptadine for treatment of allergic conditions is typically 4 mg three times daily, increased as needed, up to 0.5 mg/kg/day, to a maximum dose of 32 mg/day. However, dosing for off-label indications can begin with doses as low as 2 mg every 12 h [39].

The best dosing regimen of cyproheptadine for the management of serotonin syndromes has not been formally studied or determined.

Two reviews recommend consideration of an initial dose of 12 mg, followed by 2 mg every 2 h until resolution of the effects of serotonergic excess, followed by 8 mg every 6 h for maintenance. These reviews did not specify whether, when, or how long maintenance dosing is recommended [3, 40]. In the original source review [3], it appears this recommendation is based on a combination of typical maximum

daily dosing for therapeutic use of cyproheptadine and a brief account of research involving positron emission tomography (PET) scans in two adult male volunteers. In this study, the researchers evaluated the antagonistic effect of two different doses of cyproheptadine on 5-HT_{2A} receptors in the prefrontal cortex using PET scan. The subjects took cyproheptadine (either 4 mg or 6 mg) three times daily for 6 days. Scan results were compared before and after 6 days of cyproheptadine. After 6 days of cyproheptadine use, the 4 mg dose (12 mg/day) blocked 85% of 5-HT_{2A} receptors, while the 6 mg dose (18 mg/day) blocked more than 95% of these receptors [17]. It is unclear how it was decided to recommend giving 12 mg in one initial dose based on the information provided. While not dangerous, an initial dose of 12 mg for an adult may not be necessary. The level of evidence supporting this dosing regimen is low (LOE III).

In a third review, the authors recommend titrating 4–8 mg doses until clinical improvement is noted, suggesting as much as 16–20 mg may be required. No timeframe for the titration is provided. The authors proposed a pediatric dose of 0.25 mg/kg/day divided into two or three doses [41]. Another author managed a child with serotonin syndrome by first loading with approximately 0.25 mg/kg (the equivalent of 16 mg in an adult), then giving 0.25 mg/kg/day in three divided doses thereafter [42]. The reported justification was that a higher dose was needed to block 5-HT_{2A} receptors more completely and more quickly. The level of evidence supporting this relatively high dosing is still low (LOE III).

Although reviewers suggest that a higher initial dose of 12 mg, followed by 2 mg every 2 h until clinical resolution, with possible maintenance of 8 mg every 6 h is reasonable, many patients have had a good response with only 4–8 mg. Some of these patients received maintenance doses while others did not [38, 43–48]. Once again, all evidence is low (LOE III).

Patients who respond well usually do so within the first hour after cyproheptadine treatment if the dose is sufficient [6, 38, 44, 46, 48, 49] though some required an additional hour or two [45, 47, 50, 51]. With or without therapeutic intervention,

serotonin syndrome usually resolves in hours to days with discontinuation of the offending agent(s) [3, 40, 52]. For those who fail to respond to cyproheptadine within 4 h of initiation, there is little justification for further dosing. Patients will likely recover with discontinuation of serotonergic agents and supportive care alone. For severe cases, aggressive sedation, with or without neuromuscular blockade and intubation, is required.

Which patients may benefit most from cyproheptadine antidotal therapy for serotonin excess is unclear. Based on rodent studies, cyproheptadine is most useful for moderate to severe toxicity when given prior to onset of significant hyperthermia. However, based on human case reports, patients with mild to moderate toxicity appear to derive the greatest benefit. Most cases of apparent cyproheptadine success involve patients who have not suffered seizures and are not severely hyperthermic. As cyproheptadine is only available in oral formulations, it must be administered through a nasogastric or orogastric tube in critically ill patients, and these patients must have a functioning gastrointestinal tract. Use is most reasonable for mild to moderately ill patients. However, use may be considered in more severely intoxicated patients as long as other necessary measures are not delayed. Any use of cyproheptadine in humans for serotonin syndrome is based on low-level evidence (LOE III).

In consideration of the information available to date, it is reasonable to give cyproheptadine 8 mg once, then to give an additional 4 mg in 1–2 h if serotonergic signs do not improve substantially within 2 h. Subsequent doses (4 mg) are indicated if previously resolved clinical effects return (LOE III). If there is no response to a total cyproheptadine dose of 12 mg within the first 4 h, it is unlikely further dosing will add significant benefit, and other therapeutic approaches such as the use of benzodiazepines or propofol are indicated as needed. Further, if there is no response to cyproheptadine, reevaluation of the diagnosis of serotonin syndrome is warranted.

The goal of cyproheptadine therapy is to decrease the effects of serotonin excess

substantially within the first few hours of dosing, enabling a shorter and more comfortable course for the patient, and to reduce the risk of complications that may accompany severe syndromes (see ► Chap. 24, “Serotonin Syndrome”). As with all antidotes, cyproheptadine is not a substitute for good supportive care. Sedation, intubation, aggressive cooling, or other supportive measures should not be delayed while waiting for cyproheptadine to be effective.

Administration

In the USA, cyproheptadine hydrochloride is available for oral use only as 4 mg tablets or 2 mg/5 ml syrup [9, 10]. If the patient is unable to voluntarily take the medication, cyproheptadine syrup or crushed tablets may be administered through a nasogastric tube [3, 41, 42, 45, 53–56].

Pediatrics

Cyproheptadine is given therapeutically to children 2 years of age and older for allergic conditions in doses of 2 mg 2–3 times daily in 2- to 6-year-olds (maximum 12 mg/day) to 4 mg 3 times daily in 7- to 14-year-olds (maximum 16 mg/day). Alternatively, dosing may be based on weight for a total daily dose of 0.25 mg/kg divided [2]. Cyproheptadine was used to manage serotonin syndrome in two cases involving young children. A 2-year-old was given 0.25 mg/kg divided into 3 doses given every 8 h (1 mg loading dose then 1 mg every 8 h) [49]. A 9-year-old was given a larger loading dose of 0.25 mg/kg followed by maintenance doses of 0.25 mg/kg (8 mg then 2.5 mg every 8 h) [42]. It is reasonable to treat children 2 years of age and older with the therapeutic dose 0.083 mg/kg (0.25 mg/kg in 3 divided doses), which is the therapeutic dose for allergic conditions and the dose that successfully managed one pediatric case of serotonin syndrome (LOEIII).

Pregnancy

Cyproheptadine is a Pregnancy Category B drug. The theoretical reason for serotonergic excess and harm is accumulation of serotonin in the estrogen-sensitized myometrium, leading to uterine contractions and decrease in placental blood flow, leading to abortion [57, 58]. Most, but not all, studies of pregnant animals failed to show harm. Limited human data appear to support safety (LOE II-1, II-3, III).

Studies in rabbits, mice, and rats do not reveal maternal fertility issues or fetal harm when the drug is given in doses up to 32 times the maximum recommended human dose orally or subcutaneously. However, rats dosed with 2–50 mg/kg given intraperitoneally exhibited fetal toxicity affecting multiple different organ systems [11, 12]. Weinstein failed to show teratogenic effects in rats given 0.5–5 mg/kg/day doses of cyproheptadine during their 3 weeks of pregnancy [59]. Pfeifer demonstrated the safety and efficacy of cyproheptadine 5 mg/kg doses given to pregnant rats to prevent fetal death after excessive in utero exposure to serotonin induced by the monoamine oxidase inhibitor pargyline.

Doses of 4 - 16 mg/day of cyproheptadine were given to 29 women (31 pregnancies) to prevent abortion. Prior to the study, these women had 2-12 spontaneous abortions. The drug was given “early” in pregnancy through the end of month seven. The birth rates in these women increased from 14% to 90% with 23 normal babies and 4 surviving premature babies, none of whom displayed teratogenic effects. Adverse effects in mothers were minor and included drowsiness, diplopia, and weight gain [60]. Two successful pregnancies were reported in patients with Cushing’s syndrome taking 12–32 mg/day of cyproheptadine. Both were born healthy. One died 4 months later due to gastroenteritis [61, 62].

Warnings about use in neonates and premature babies suggest cyproheptadine is contraindicated. This information can be traced back to package inserts with similar warnings for multiple

anticholinergic drugs including antihistamines [11, 12]. These warnings may be based on concern for greater toxicity in premature babies and neonates with regard to antihistamine and anticholinergic effects including seizures and excessive drowsiness and apnea.

Based on the apparent safety in most animal studies, the apparent efficacy managing serotonin excess induced by a monoamine oxidase inhibitor given in pregnant animals, the efficacy in preventing human abortions in a small study of women used as their own controls, as well as the apparent safety and possibly efficacy in two human case studies involving use in pregnant women with Cushing’s Syndrome, cyproheptadine seems relatively safe in pregnant women in all trimesters. However, human data are limited.

Use in pregnant women with serotonin excess is reasonable when indicated based on the same criteria as in nonpregnant individuals (LOE II-1, II-2 and III).

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Dantrolene is a unique, noncentrally acting, nondepolarizing muscle relaxant used primarily to treat malignant hyperthermia associated with inhaled anesthetics. It is also used in the management of chronic muscle spasticity caused by upper neuron disorders such as stroke, spinal cord injury, cerebral palsy, and multiple sclerosis.

History

Snyder and colleagues [1] first described the possible muscle-relaxing properties of dantrolene in 1967, while studying the ability of substituted furans to inhibit hind-limb flexor reflexes in cats. Shortly thereafter, dantrolene was shown to alleviate muscle spasticity effectively in animals [2] and humans [3]. In 1972, Ellis and colleagues [4, 5] showed that dantrolene uncoupled the excitation-contraction process during skeletal muscle stimulation. Because malignant hyperthermia was thought to result from continuous muscle contraction, perhaps through an abnormality in the excitation-contraction coupling mechanism, the compound was tested as a treatment for this condition. In 1982, the first human data were published showing that dantrolene could significantly reduce mortality associated with malignant hyperthermia [6]. Since then, dantrolene has been tried in the treatment of other medical conditions associated with muscle spasm, such as tetanus [7, 8], neuroleptic malignant syndrome [9], lethal catatonia [10], drug-induced rigors [11, 12], black widow spider envenomation

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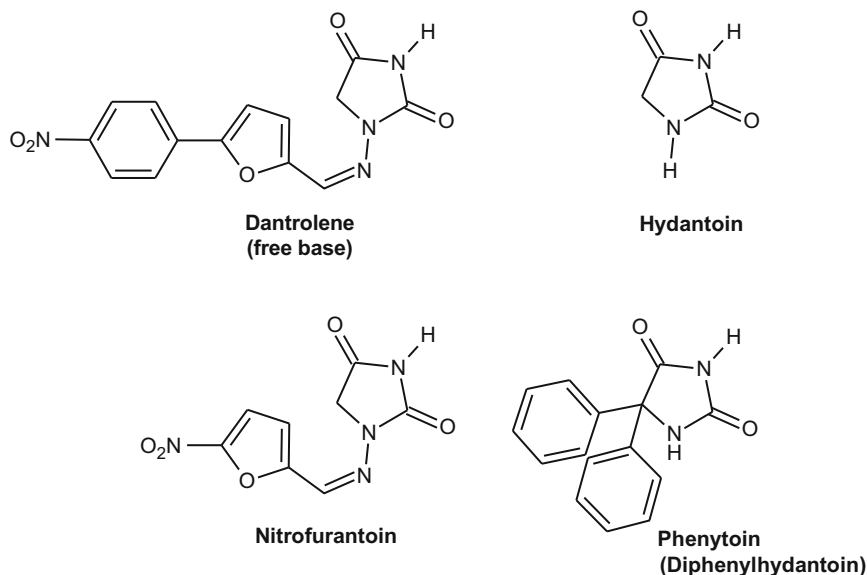


Fig. 1 Chemical structures of dantrolene and, for comparison, hydantoin, nitrofurantoin, and phenytoin

[13], 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”) intoxication [14], phenelzine poisoning [15], theophylline poisoning [16], muscle rigidity associated with carbon monoxide poisoning [17], and organophosphate poisoning [18]. Dantrolene protected mice envenomated with *Androctonus australis hector* scorpion venom [19]. It also has been used as a treatment for neurogenic bladder obstruction associated with external urethral sphincter spasm [20] and as a potential treatment for cerebral vasoconstriction [21–23].

By the early 1990s, there was growing evidence that nerve injury may be mediated by elevated intracellular calcium. Dantrolene prevents release of calcium stored in endoplasmic and sarcoplasmic reticula. Recent studies have focused on using dantrolene as a possible neuroprotective agent for treating Alzheimer’s disease [24, 25] and neurotoxicity secondary to subarachnoid hemorrhage [22, 26].

to phenytoin and nitrofurantoin (Fig. 1). Anhydrous dantrolene sodium has a molecular weight of 336 g/mol. Medicinal dantrolene is an orange hemiheptahydrate sodium salt with a molecular weight of 399 g/mol. It is a weak base (pKa 7.5) that is only slightly soluble in water [27, 28]. Dantrolene is available commercially as 25, 50, and 100 mg oral capsules and as 20 mg (Dantrium[®], Revonto[®]) and 250 mg vials (Ryanodex[®]) for intravenous administration (brand names and formulations shown are those for products available in the USA and may be different in other countries). Sodium hydroxide and mannitol are added to the intravenous products to enhance solubility. Ryanodex[®] is formulated as a nanocrystalline suspension instead of as a standard lyophilized powder [29]. It can be reconstituted much faster and delivered in a much smaller total volume than traditional injectable dantrolene [30] (Table 1).

Properties

Dantrolene (1-[[[5-(4 nitrophenyl)-2-furanyl] methylene] amino]-2,4-imidazolidinedione) is a hydantoin derivative with structural similarities

Pharmacodynamics

Dantrolene is a ryanodine receptor antagonist. Ryanodine receptors (RyR) exist on the surface of endoplasmic and sarcoplasmic reticula. They

Table 1 Comparison of injectable forms of dantrolene

Brand name (manufacturer)	Dosage form	Reconstituted dantrolene concentration	Mannitol content per vial (mg)	Vials required for loading dose ^a	Loading dose ^a total volume (mL)	Reconstitution time for loading dose ^a
Dantrium IV [®] (JHP Pharmaceuticals) Revonto [®] (US WorldMeds)	Injectable solution	0.33 mg/mL (20 mg/60 mL)	3000	9	525	180 s [27]
Ryanodex [®] (Eagle Pharmaceuticals)	Injectable suspension	50 mg/mL (250 mg/5 mL)	125	1	3.5	5 s [30]

^aBased on 2.5 mg/kg loading dose for 70 kg adult

exist in three isoforms with varying tissue expression. RyR1 are found primarily in skeletal muscle tissue. RyR2 are expressed primarily within cardiac muscle while RyR3 are expressed primarily in the brain and smooth muscle [31, 32]. RyR are ligand-gated and ligand-modulated. In skeletal muscle, RyR1 are activated by a physical interaction with dihydropyridine receptors. In other tissues RyR1, RyR2, and RyR3 are activated by increases in cytoplasmic calcium concentrations [33, 34]. Dantrolene inhibits RyR1 and RyR3 receptors but not RyR2 receptors. Dantrolene binds to the N-terminus of RyR1 stabilizing it in a closed state thereby preventing the release of calcium from sarcoplasmic reticulum, which in turn prevents activation of troponin C and subsequent interaction of actin and myosin [35, 36]. The relaxation of skeletal muscle allows body heat to be released more efficiently (Fig. 2) [37]. There is growing evidence that dantrolene may also inhibit store-operated calcium channels, the channels that allow intracellular calcium entry so endoplasmic reticula may be replenished [38]. Dantrolene does not affect pretubular steps of skeletal muscle excitation-contraction. It has weak muscle relaxant effects on smooth muscle and only depresses cardiac contractility when used in higher than therapeutic doses [39–41].

Tissue cell and animal research suggests that dantrolene may be beneficial in preventing nerve cell loss in certain neurodegenerative diseases such as Alzheimer’s disease, amyotrophic lateral sclerosis, spinocellular ataxia, and reperfusion injury [31]. A common pathway for injury in each of

these diseases is a triggering event leading to a rise in intracellular calcium within nerve cells. The elevated intracellular calcium then leads to destruction of key intracellular structures, lysosomal autophagy, improper protein folding apoptosis, and eventually neural cell necrosis. Dantrolene’s inhibitory effects on RyR1 and RyR3 in the brain may impart neuroprotective effects.

Pharmacokinetics

Approximately 70% of an oral dose of dantrolene is absorbed in humans. In animals, dantrolene is absorbed primarily in the small intestine [42]. Peak blood concentrations occur 4–8 h after ingestion in healthy human volunteers [43]. Therapeutic blood concentrations are 0.3–0.6 $\mu\text{g/mL}$ (1–1.9 $\mu\text{mol/L}$) for treatment of spasticity [43–45] and 2–3 $\mu\text{g/mL}$ (6.4–9.5 $\mu\text{mol/L}$) for treatment of malignant hyperthermia [46, 47]. When given intravenously to healthy adult volunteers, dantrolene followed a two-compartment distribution model. The initial volume for a 69.5 kg adult was 3.24 L and the final volume was 22.9 L. Distribution from the initial compartment to the final compartment occurs quickly. The intracompartment distribution half-life ($t_{1/2a}$) was 1.6 min [48]. Dantrolene crosses the placenta in humans with a fetal-to-maternal serum concentration ratio of 0.4–0.7 [49, 50].

When distributed, dantrolene is metabolized in the liver by 5-hydroxylation of the hydantoin ring, resulting in 5-hydroxydantrolene (Fig. 3), which is

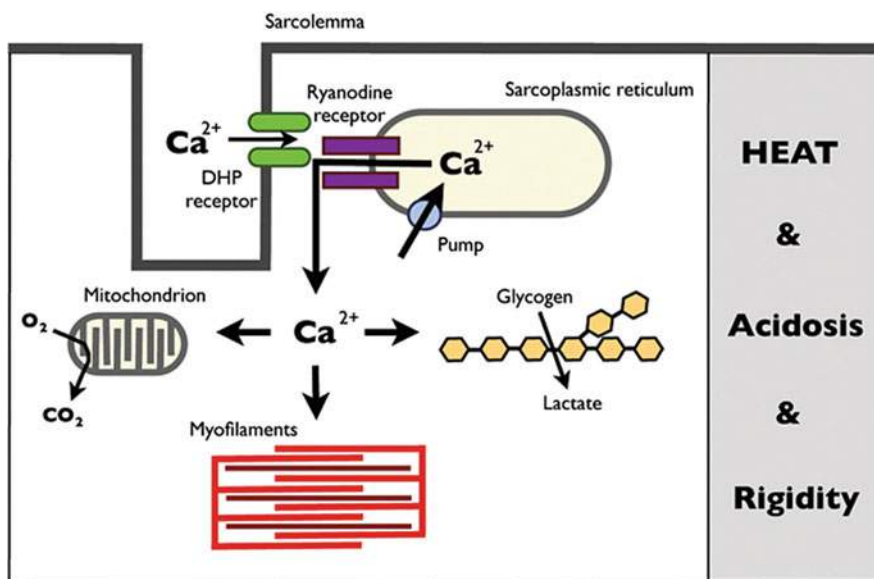


Fig. 2 Schematic of excitation-contraction coupling in skeletal muscle in relationship to malignant hyperthermia. A somatic motor neuron impulse propagates along the sarcolemmal membrane into the transverse tubule. The impulse activates the dihydropyridine (*DHP*) receptor which in turn physically interacts with ryanodine receptors to cause release of calcium ions from the sarcoplasmic reticulum. Free calcium leads to muscle contraction,

acidosis, and increased body temperature. Dantrolene stabilizes the ryanodine receptor in the closed position thereby preventing abnormal release of calcium from sarcoplasmic reticula (Adapted from Fig. 3, Oliver Bandschapp, Thierry Girard: Malignant hyperthermia, Swiss Med Wkly. 2012;142:w13652. Used with permission from EMH Swiss Medical Publishers, Ltd.)

about half as potent in inhibiting twitch contractions as the parent compound [51]. In children, steady-state concentrations of 5-hydroxydantrolene are 30–50% those of dantrolene [52]. Dantrolene also may undergo reduction of the phenyl nitro group to form aminodantrolene. Aminodantrolene is acetylated further to the pharmacologically inactive reduced aminodantrolene (see Fig. 3) [51].

Approximately, two-thirds of the absorbed dose of dantrolene appears in bile. The remaining one third appears in the urine, with 79% as the 5-hydroxydantrolene metabolite, 17% as the reduced acetylated metabolite, and 4% unchanged [39, 42, 52]. The renal clearance of dantrolene in healthy volunteers is 1.8–7.8 L/h. Dantrolene's serum half-life is 6–9 h in adults with spasticity [39, 45]. The mean half-life of dantrolene in patients with malignant hyperthermia is 12 h

[53]. In children, the half-life is 7–10 h [52, 54]. In neonates, the half-life is 20 h [52].

Pharmacokinetics of Dantrolene

Volume of distribution: two compartment; initial $V_d = 0.047$ L/kg; final $V_d = 0.33$ L/kg

Oral bioavailability: 70%

Time to peak blood levels: 4–8 h

Therapeutic range: 0.1–0.6 $\mu\text{g/mL}$ (spasticity); 2–3 $\mu\text{g/mL}$ (malignant hyperthermia)

Metabolism: extensively metabolized in liver by hydroxylation or acetylation

Route of clearance: 70% biliary, 30% renal

Clearance: 1.8–7.8 L/h

Half-life: healthy adults, 6–9 h; adults with malignant hyperthermia, 12 h; children, 7–10 h; neonates, 20 h

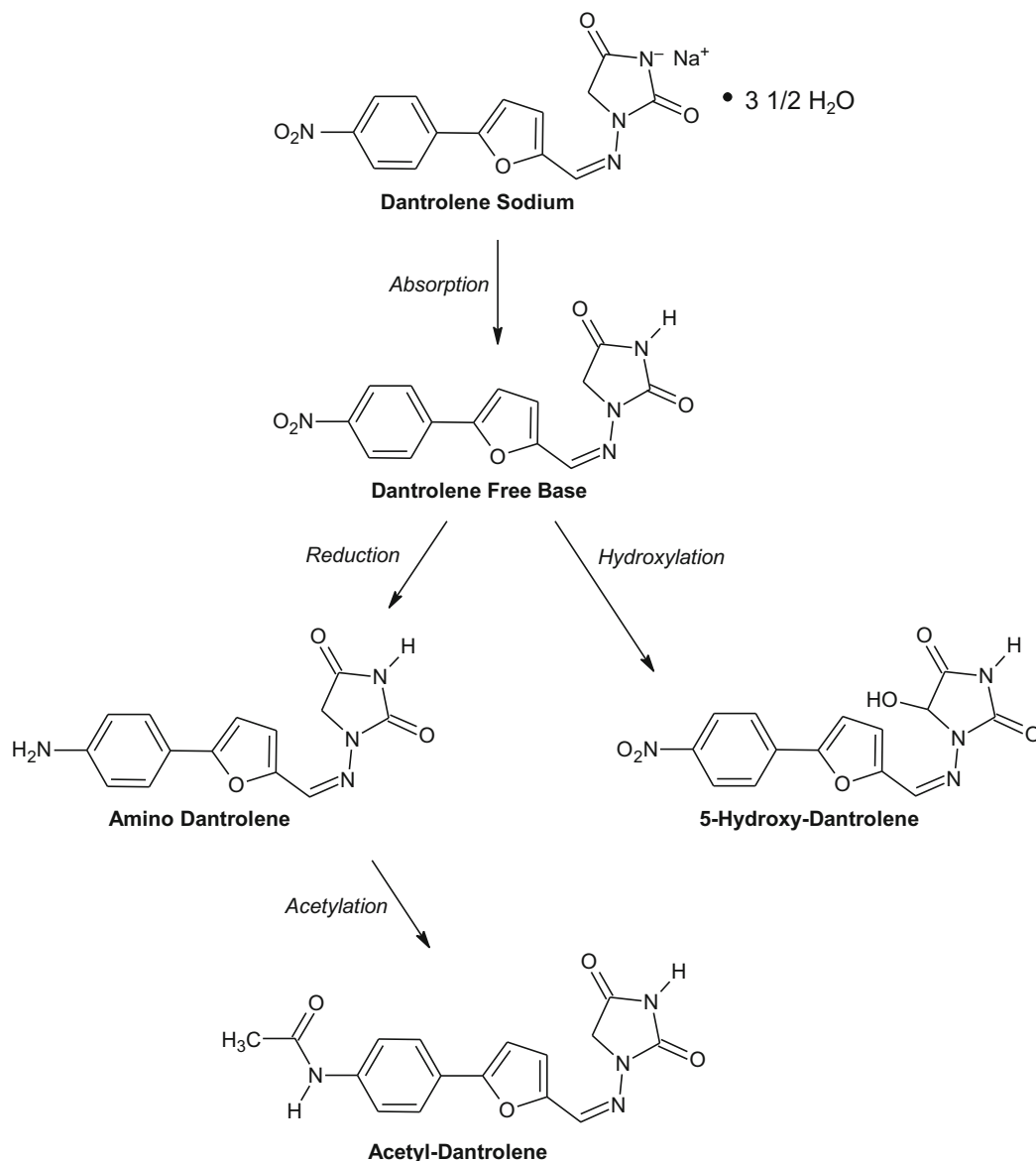


Fig. 3 Metabolic pathway for dantrolene sodium

Special Populations

Pediatric and Geriatric Patients

There is little published dosing experience with dantrolene in neonatal or geriatric populations. Current dosing guidelines apply to children 5 years old and older. It is likely that dantrolene

accumulates in patients with renal, hepatic, or biliary impairment. Dosage reductions should be considered in these patients, especially if the drug must be continued for more than 2 or 3 days. Signs of dantrolene toxicity include muscle weakness, lethargy, vomiting, diarrhea, and crystalluria.

Pregnant and Breast-Feeding Patients

The US Food and Drug Administration (FDA) has assigned dantrolene to pregnancy category C, meaning that there have been teratogenic effects reported in animal studies. The safety of dantrolene use during pregnancy has not been established. Minor skeletal abnormalities not attributable to teratogenicity were observed in offspring of rats and mice given 60 mg/kg of dantrolene by mouth [55, 56]. No adverse effects were observed in sheep given therapeutic doses or in their offspring [57]. There are several case reports where dantrolene was used during pregnancy without apparent harm to the fetus [58, 59]. In two small case series involving pregnant women, dantrolene crossed the placenta but caused no apparent harm to the mothers or the neonates. Neonatal dantrolene serum concentrations were 40–70% those of the mothers [49, 50]. Dantrolene also has been detected in breast milk of a mother who was being treated for malignant hyperthermia after an emergency cesarean section. Her peak breast milk concentration was 1.2 $\mu\text{g/mL}$ (3.8 $\mu\text{mol/L}$) 36 h after birth. The half-life of dantrolene passing through breast milk was 9 h [60].

Contraindications

Other than prior allergic reactions, there are no contraindications for short-term intravenous use of dantrolene. Long-term oral therapy (>45 days) is contraindicated in patients with active hepatic disease because of the possibility of exacerbating liver damage. Dantrolene also is contraindicated in patients who depend on spasticity to maintain posture or locomotion.

Precautions

Intravenous dantrolene has a pH of 9.5. It can cause irritation to peripheral veins and significant tissue loss if extravasation occurs. During the infusion, care must be taken to ensure that the

catheter tip is placed within a large nonmovable vein and that the solution is infused slowly enough to prevent backflow into surrounding tissue.

Each 20-mg vial of dantrolene contains 3 g of mannitol. This source of mannitol should be considered when a patient receives additional mannitol to preserve renal function. Patients should be monitored carefully for evidence of dehydration and pulmonary edema while receiving dantrolene. Patients with impaired cardiac or pulmonary function may be particularly susceptible to developing acute respiratory distress syndrome (ARDS) during intravenous therapy.

On the day of intravenous administration, patients may experience difficulty swallowing, so they should be monitored carefully during meals for choking. Because dantrolene's muscle relaxant effects may last 48 h after intravenous administration, patients who recover quickly should avoid ethanol and sedative drugs, and be cautioned not to drive or operate heavy machinery.

Dantrolene should be avoided in patients taking calcium channel antagonists. Anesthetized swine given therapeutic intravenous doses of both verapamil and dantrolene developed rapid-onset third degree atrioventricular block, hyperkalemia, and cardiovascular collapse [61]. Similar results were seen in dogs [62]. There is a single human case report of hyperkalemia and myocardial depression after concomitant administration of dantrolene and verapamil. A 60-year-old man treated with verapamil for coronary artery disease was given dantrolene 30 min before surgery. At 2.5 h after the infusion finished (45 min after surgery was completed), his cardiac index decreased from 2.1 to 1.9 L/min/m² and his serum potassium increased to 7.1 mmol/L, despite an otherwise uneventful hemicolectomy. He was treated with insulin, and his condition improved over 4 h. Six months later, the same patient received dantrolene before another surgical procedure. He had been switched to nifedipine 2 weeks before surgery and this time did not develop hyperkalemia or myocardial depression [63]. The exact mechanism

responsible for this adverse effect is unknown. It is possible that myocardial depression results from a combination of slow calcium channel blockade and suppressed calcium release within the myocardium. Hyperkalemia may result from an enhanced release of potassium from muscle secondary to a direct effect of dantrolene on muscle or from decreased potassium uptake by the liver, skeletal muscle, and kidneys as a result of decreased cardiac output. Even though the interaction has only been seen with verapamil, the cautionary warning has been extended to all calcium channel antagonists.

Dantrolene may potentiate vecuronium-induced muscle block. A 60-year-old woman given dantrolene and vecuronium before a breast biopsy had a longer recovery period, based on 75% recovery of evoked twitch tension, compared to eight control subjects [64]. Dantrolene may prevent presynaptic neurotransmitter release at the neuromuscular junction through a calcium-mediated process.

Dantrolene can also potentially increase methotrexate and carbamazepine serum concentrations. A 16-year-old girl had elevated methotrexate plasma concentrations after receiving her first dose of methotrexate (12 g/m²) for treatment of osteosarcoma. The patient had received intravenous nalbuphine for 4 days and oral dantrolene for 1 day before methotrexate was started. Her plasma methotrexate concentration rose at 24 h post dose (418 μ mol/L) and she subsequently developed clinical and biological manifestations of methotrexate toxicity. Dantrolene was stopped and the patient eventually was treated successfully with low dose methotrexate. It is thought that dantrolene or 5-hydroxydantrolene reduced serum binding and impaired methotrexate renal elimination [65]. In addition, a 37-year-old woman taking carbamazepine developed elevated serum carbamazepine concentrations with symptoms of intoxication while taking dantrolene and oxybutynin. It is unclear whether oxybutynin, dantrolene, or the combination of the two triggered the apparent reduction in carbamazepine metabolism [66].

Adverse Effects

The adverse effects of dantrolene depend on the dose, route, and duration of therapy. For short-course (3–5 days) intravenous or oral therapy, typical during treatment or prophylaxis for malignant hyperthermia, patients often develop generalized muscle weakness, drowsiness, dizziness, light-headedness, diarrhea, nausea, malaise, and fatigue (24–30% incidence of combined findings) [42, 67, 68]. These effects subside within 2–4 days of continued therapy and are alleviated by reducing the daily dose [69, 70]. Nine percent of patients receiving intravenous dantrolene also may experience phlebitis near the infusion site [67]. Deep vein thrombosis has also been reported [71]. The more serious side effects associated with short-course intravenous therapy are anaphylaxis, respiratory failure, ARDS, and hyperkalemia. There has been one case of anaphylaxis and “rare reports” of dantrolene-associated pulmonary edema, according to the manufacturer. Large diluent and mannitol doses as well as serious underlying cardiovascular disease may have contributed to the development of pulmonary edema. The true incidence of drug-induced anaphylaxis and pulmonary edema is unknown.

Long-term oral therapy has been associated with drowsiness (30%), dizziness (14%), nausea (9%), vomiting (9%), fatigue, and malaise [42]. In addition, patients may experience either constipation (4%) or persistent diarrhea (2.5%). Other, less frequent side effects include constipation, gastrointestinal bleeding, anorexia, swallowing difficulty, gastric irritation, abdominal cramps, speech disturbances, seizure, headache, light-headedness, visual disturbances, diplopia, alteration of taste, insomnia, tachycardia, erratic blood pressure, mental depression, confusion, increased nervousness, crystalluria, hematuria, difficult erection, difficulty urinating, feeling of suffocation, abnormal hair growth, acne-like rash, pruritus, urticaria, sweating, chills, fever, and excessive tearing [72]. Dose-dependent respiratory failure may also occur even in patients without underlying respiratory disease [73]. Urinary retention [74] and pharyngeal spasticity [75] have

also been reported. The two most serious side effects associated with chronic dantrolene therapy are hepatotoxicity and eosinophilic pulmonary effusion; neither of these two effects has been reported with short-course therapy.

Dantrolene-associated hepatotoxicity tends to occur after 1–6 months of long-term oral therapy, usually in patients taking more than 200–300 mg/day. There is a single case of hepatotoxicity after intravenous administration, but this was in a patient who was recovering from orthotopic liver transplantation [76]. Fatalities have clustered in patients older than 35 years of age, women, those with a primary diagnosis of multiple sclerosis, and patients taking dantrolene longer than 6–10 months [77, 78]. These observations are based on two overlapping case series composed almost entirely of voluntary reports to the US Food and Drug Administration. It is impossible to characterize true risk of dantrolene-associated hepatotoxicity without knowing the size and characteristics of the chronic dantrolene user population and without comparing the dantrolene population with a similarly matched control population.

The best estimate of the incidence of dantrolene-associated hepatotoxicity is derived from a review of safety data from premarketing clinical trials involving 1044 patients taking dantrolene for at least 60 days. In this group, 1.8% of patients taking dantrolene on a long-term basis developed abnormal liver function tests, 0.6% showed clinical manifestations of hepatotoxicity, and 0.3% died as a direct result of hepatotoxicity [77]. Large doses were used regularly in these trials, so it is possible that the true incidence of hepatotoxicity is lower with current dosing. In a subsequent series of 243 patients taking ≤ 400 mg daily, one patient developed hepatotoxicity. This patient had chronic hepatitis B and was taking 400 mg dantrolene daily [68].

Clinical manifestations are not sensitive indicators of hepatotoxicity during long-term dantrolene therapy. In four patients undergoing liver biopsy after suspected dantrolene-induced hepatotoxicity, two patients had no clinical symptoms but had marked hepatic necrosis on biopsy specimen [79]. Both asymptomatic

patients were identified through routine screening. When dantrolene produces liver injury, serum transaminase enzymes are mildly elevated (100–600 IU). Fatality is more common with total serum bilirubin in the range of 15–19 mg/dL (257–325 $\mu\text{mol/L}$) [78]. Liver biopsy specimens usually show changes consistent with chronic active hepatitis, submassive necrosis, massive necrosis, or bridging necrosis [77–80]. The underlying mechanism for dantrolene-associated hepatotoxicity is poorly understood. Studies in rats have shown that dantrolene or one of its metabolites inactivates mixed-function oxidase and binds strongly to hepatic proteins. This activity is enhanced when reduced glutathione stores are depleted [81, 82].

The treatment for dantrolene-induced hepatotoxicity is discontinuation of the drug. In most instances, serum transaminases and bilirubin return to normal within 1–12 months [77].

Another rare, but serious, side effect of long-term dantrolene therapy is eosinophilic pleural effusion. Fifteen cases have been published to date [83–91]. In two instances, the patients also had drug-induced pericarditis. The onset ranges from 2 months to 15 years. Patients usually present with cough, dyspnea, shortness of breath, low-grade fever (38–38.5 °C), and moderate peripheral and pleural eosinophilia. The chest radiograph showed unilateral or bilateral pleural effusion. In all instances, the patients recovered after discontinuation of the drug. None of the patients underwent dantrolene rechallenge. There is no discernible pattern in dose, gender, or age. The exact pathophysiology of this adverse effect is unknown.

Indications

Injectable dantrolene sodium is approved by the US Food & Drug Administration for treatment of malignant hyperthermia crisis. The injectable product has been used off-label for treating MDMA intoxication, neuroleptic malignant syndrome, tetanus, and heat stroke. Oral dantrolene sodium has been approved by the FDA for treatment of chronic spasticity and for treatment of

Table 2 Strength of evidence supporting clinical use of dantrolene

Use	FDA approval	Highest level of evidence supporting use	Efficacy	Reference(s)
Malignant hyperthermia crisis	Yes	II3	Effective	[6]
MDMA intoxication	No	III	Effective	[14]
Neuroleptic malignant syndrome	No	II2	Inconclusive	[94–96]
Tetanus	No	II3	Effective	[7]
Heat stroke	No	I	Inconclusive or potentially ineffective	[97, 98]
Spasticity (all causes)	Yes	I	Inconclusive or potentially effective	[99]
Spasticity, multiple sclerosis	Yes	I	Inconclusive or of limited effectiveness	[100, 101]
Spasticity, cerebral palsy	Yes	I	Inconclusive	[102]
Spasticity, stroke	Yes	I	Inconclusive or potentially effective	[103, 104]

malignant hyperthermia. Table 2 shows the strength of evidence supporting FDA approved and other uses. The beneficial impact of intravenous dantrolene is clearer for malignant hyperthermia than for treatment of chronic spasticity. For malignant hyperthermia, the mortality rate decreased from 64% in the 1960s [92] to 9.5% [93] in 2012 with use of dantrolene. Dantrolene's use in the treatment of chronic spasticity is based on double-blind placebo controlled clinical trials conducted in the 1970s and 1980s. These trials usually had nonvalidated outcome measures, unclear diagnostic criteria, poorly described randomization methods, and potential threats to blinding. In addition, these trials were of short duration (<6 weeks). The reduction in spasticity was often associated with significant muscle weakness, limiting dantrolene's use to a small group of tolerant patients.

Administration

The preparation of intravenous dantrolene varies by brand. Dantrium[®] and Revonto[®] brands of dantrolene for injection are prepared by adding 60 mL of sterile water for injection to each 20-mg vial of lyophilized product. The vials are shaken

until the contents are clear. The reconstituted product should then be administered by continuous intravenous push into a large nonmovable vein. Reconstituted drug can also be administered by transferring the appropriate dose to a sterile plastic bag (not glass) that is protected from light. Each Ryanodex[®] vial contains 250 mg of lyophilized dantrolene that is reconstituted with 5 mL of sterile water. Each Ryanodex[®] vial should be shaken until there is a uniform suspension without particulate matter. The reconstituted product is either administered into an IV line where 0.9% sodium chloride or 5% dextrose are already running freely, or, into a patent flushable indwelling catheter. Ryanodex[®] should not be transferred to another container or diluted before use. Only sterile water should be used for reconstitution of intravenous dantrolene products. Intravenous dantrolene should be stored at 15–25 °C and must be used within 6 h of reconstitution.

The dosage of dantrolene for treating suspected malignant hyperthermia is 2.5 mg/kg given by rapid intravenous administration until end-tidal carbon dioxide concentration, temperature, muscle stiffness, and heart rate decline. This dose may be repeated as frequently as needed until the patient responds. Most patients will respond to

cumulative doses of <10 mg/kg; however, larger doses are sometimes needed for patients with persistent contractures or rigidity. After an appropriate loading dose has been infused, the patient should be started on a maintenance regimen to prevent recrudescence of malignant hyperthermia. The maintenance regimen consists of multiple infusions of 1 mg/kg every 4–6 h or a continuous infusion of 0.25 mg/kg/h with a total duration of at least 24 h [105, 106]. Longer infusions and higher administration rates are sometimes needed [107]. Since recrudescence occurs in 20% of cases, continuous monitoring is needed for 48–72 h after the initial incident [105, 108]. A pharmacokinetically based regimen has also been proposed that increases maintenance infusion rates with the size of the loading dose required [48]. Dantrolene’s ability to prevent complications associated with malignant hyperthermia diminishes with time. Ideally, it should be administered within 10 min of event detection. In one study, dantrolene was ineffective in preventing malignant hyperthermia complications if given beyond 50 min of the onset of clinical effects [109]. Dantrolene should not be used prophylactically [28]. The use of dantrolene in the treatment of this condition is discussed in greater detail in ► Chap. 29, “Malignant Hyperthermia.”

Oral dantrolene has been administered through a nasogastric tube when intravenous dantrolene was not available. One patient was treated with 4 mg/kg of dantrolene as a suspension in 50 mL sterile water given twice within 30 min [110]. This technique should be used only as a last resort since dantrolene’s absorption may be erratic, and the onset of action will be delayed.

A dantrolene oral suspension can be prepared by mixing the contents of an appropriate number of dantrolene capsules into a simple syrup containing citric acid (150 mg/100 mL final product) with or without preservative (0.15% methyl hydroxybenzoate). This suspension is stable at 5 °C, 25 °C, and 40 °C (104 °F, 41 °F, and 77 °F) for 150 days. It should be dispensed in high-density polyethylene bottles and should be shaken before use. Fawcett and associates recommended assuming a shelf life of 30 days for the suspension [111].

Table 3 Typical dose titration regimens for treating spasticity

Adults	Children
25 mg once daily for 7 days	0.5 mg/kg twice daily
25 mg three times daily for 7 days	0.5 mg/kg three to four times daily
50 mg three times daily for 7 days	Incrementally increase each dose by 0.5 mg/kg
100 mg three times daily for 7 days	Do not exceed 3 mg/kg four times daily or 400 mg/day

The oral doses of dantrolene used for treating spasticity vary by age and by patient response. Adults are given 25 mg/day initially [112]. The dose should be increased in 7-day increments until limb functionality is improved. Dosage should not exceed 400 mg/day. Pediatric patients are given 0.5 mg/kg twice daily. Children may be gradually titrated to larger daily doses by increasing the dosing frequency first and then increasing each dose. The total maximum pediatric dose should be no greater than 12 mg/kg/day or 400 mg/day [72, 113]. For all patients, the lowest effective dose should always be used [72] (Table 3).

Dosages used to treat neuroleptic malignant syndrome (Level of evidence II2) are 1–2.5 mg/kg intravenously, followed by 1 mg/kg every 6 h for 48 h, followed by tapering oral doses of 25–600 mg/day depending on response [114]. Most patients respond within 12 h [39]. See ► Chap. 31, “Neuroleptic Malignant Syndrome” for more information.

The Malignant Hyperthermia Association of the United States recommends that all anesthetizing suites be stocked with enough dantrolene to treat a 70 kg patient with 10 mg/kg of drug [115].

Azumolene

Azumolene is an equipotent analogue of dantrolene. It is 30 times more water soluble than traditional injectable forms of dantrolene sodium (e.g., Dantrium[®], Revonto[®]). It was created by substituting the *para*-nitrophenyl group of dantrolene with a *para*-bromophenyl group. Based on in vivo animal studies and a small

number of in vitro human muscle tests, azumolene appears to have the same pharmacodynamic properties as dantrolene [38, 116]. Efforts to advance azumolene as a potential replacement for dantrolene ceased due to concerns about its hepatotoxic effects [30].

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Deferoxamine is a chelator used for acutely ill iron-poisoned patients. It can also be used as an aluminum chelator and in the treatment of transfusional iron overload states. Its use in critically-ill patients is, however, almost always confined to patients with acute iron overdose. The treatment of acute iron toxicity is discussed in detail in ► [Chap. 67, “Iron.”](#) This chapter focuses on the clinical pharmacology of deferoxamine for the treatment of acute iron poisoning.

History

In 1964, ferrioxamine D, which is an iron chelate of deferoxamine, was isolated from *Streptomyces pilosus* [1]. Several animal studies verified the efficacy of deferoxamine as a chelator in iron poisoning [2]. In 1966, a clinical series of 172 iron-poisoned children treated with deferoxamine was published [3]. Five years later, the same author published a series of 472 iron-poisoned patients, providing the largest clinical series available on the treatment of iron poisoning with this agent [4], (level of evidence grade II-2).

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Properties

Chemical

Deferoxamine (Fig. 1) has a molecular weight of 561 g/mol. It typically is supplied as desferoxamine mesylate (*N*-[5-[3-[(5-amino-pentyl) hydroxycarbonyl] propionamido] pentyl]-3-[(5-(*N*-hydroxyacetamido) pentyl) carbonyl] propionhydroxamic monomethane sulfonate (salt). Its molecular formula is $C_{25}H_{48}N_6O_8$.

Physical

Deferoxamine is usually supplied as a lyophilized powder with a white to off-white color. It is highly water soluble. It has no odor, or its odor is subtle. The melting point of deferoxamine is 148–149 °C.

Pharmacodynamics

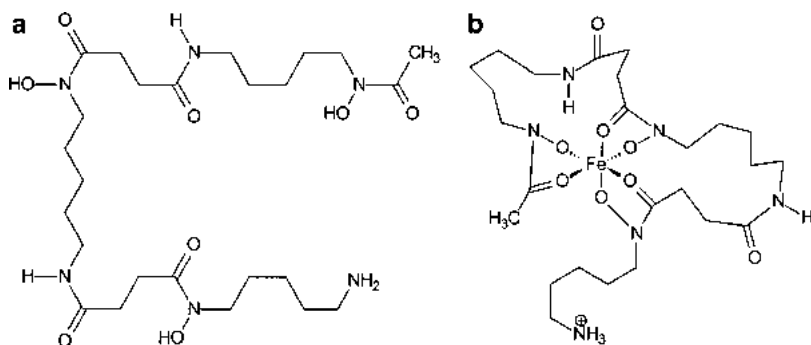
Deferoxamine binds ferric (Fe^{3+}) iron in a 1:1 M ratio with an affinity constant approximating 10 [31, 1, 4]. Deferoxamine has low affinity for other common ions (with the exception of aluminum), including ferrous (Fe^{2+}) iron [1]. The structure of the deferoxamine-iron chelate ferrioxamine is shown in Fig. 1.

There is some uncertainty regarding the compartment from which deferoxamine removes iron. Given its hydrophilic nature and molecular weight of 561 g/mol, its cellular permeability is likely

limited [1, 5–7]. In addition to the various molecules for which it has a physiologic function, such as hemoglobin, myoglobin, and cytochrome oxidase, iron is stored in the form of ferritin and transported in the blood primarily bound to transferrin. After absorption from the gastrointestinal tract as ferrous iron, it is oxidized to the ferric form and bound to transferrin. Under normal conditions, almost all circulating iron is bound to transferrin, and it is this bound form which is generally reflected in routine serum iron determinations. Transferrin has a molecular weight of approximately 90,000 d, and each molecule is capable of binding two ferric ions. Typically, only about one third of transferrin's iron-binding sites are occupied, and it serves as a natural chelator when free serum iron is present. Normally, there is some iron release, particularly from the reticuloendothelial system, where hemoglobin and red blood cells are broken down. In this situation, the iron is released in the form of ferritin in small amounts.

In iron toxicity, the iron-binding capacity of transferrin is exceeded. Deferoxamine does not remove significant amounts of transferrin-bound iron [8]. Non-transferrin-bound iron usually has a serum half-life of 60–120 min. It is therefore assumed that deferoxamine's major mode of action is its ability to chelate non-transferrin-bound serum iron [9], level of evidence grade II-1. It is intuitively apparent that deferoxamine has the capacity to chelate the fraction of serum iron that, being unbound, may be most likely to be responsible for intercellular transport and toxicity. A dose of 100 mg of deferoxamine has the capacity to bind 8.5 mg of iron. The fraction of

Fig. 1 Chemical structures of deferoxamine (a) and the ferrioxamine B chelate (b)



deferoxamine that enters cells may chelate unbound or weakly-bound intracellular iron.

There are no prospective controlled studies verifying deferoxamine's efficacy in the treatment of acute iron poisoning. Considerable data exist, however, in patients treated for iron overload states, indicating that iron reduces serum ferritin and, when given on a long-term basis, reduces intracellular iron deposition [10].

Pharmacokinetics

The pharmacokinetic profile of deferoxamine in acute iron poisoning is poorly characterized. There is a small body of data from patients with transfusional iron overload states and from studies with volunteers, however, which allows for some conclusions concerning relevant pharmacokinetic parameters. Deferoxamine is poorly absorbed orally and should not be given by this route. In the case of acute iron ingestion, it is possible for ferrioxamine, the deferoxamine-iron chelate, to form in the gastrointestinal tract after oral administration of deferoxamine. However, this situation may enhance iron toxicity because of the greater absorption of iron in the chelated form and the intrinsic toxicity of ferrioxamine.

Pharmacokinetics of Deferoxamine

Oral absorption: poor

Volume of distribution: 0.6–1.33 L/kg

Excretion in breast milk: unknown

Mode of clearance: metabolism followed by renal metabolite elimination

Elimination half-life: 3–6 h

Cleared by extracorporeal techniques: yes

Although clinically significant deferoxamine concentrations are achievable by all parenteral routes, only the intravenous route generally is used in the case of acute iron poisoning. The pharmacokinetic correlation of deferoxamine in relation to the hemodynamic perturbations associated with acute iron poisoning has not been characterized for the intramuscular or subcutaneous routes, and administration by these routes

should be avoided if possible. After intravenous administration, deferoxamine follows a two-component elimination profile, consisting of a fast initial distribution half-life of 5–10 min followed by an elimination half-life of approximately 3 h [11]. Steady-state was achieved in 6–12 h in volunteers receiving an intravenous deferoxamine infusion [11]. In a canine model, a steady-state serum concentration of 10.7 µg/mL was achieved with an infusion dose of 10 mg/kg/h [12].

Deferoxamine not renally cleared has two potential fates. One is to complex with iron to form ferrioxamine; the other is to be metabolized hepatically [11, 13–15]. The degree of metabolism depends on the chelatable iron status of the patient. The primary metabolite of deferoxamine is called *metabolite B*. When formed, deferoxamine metabolites are excreted renally. In healthy volunteers, renal clearance accounts for 30% of total deferoxamine clearance [16].

Deferoxamine has been reported to have a volume of distribution of 0.6–1.33 L/kg [1, 13, 17]. It distributes into the intracellular compartment and can chelate intracellular iron [1, 5–8]. Deferoxamine is removable by hemodialysis and other extracorporeal drug removal techniques [18, 19].

Ferrioxamine has a volume of distribution of only 0.2 L/kg and has an initial half-life of 2.3 h, followed by a terminal half-time of 5.8 h in volunteers [16]. Similar to deferoxamine, ferrioxamine can be removed by extracorporeal techniques [20–22].

Special Populations

Pregnant and Breast-Feeding Patients

There have been several cases of treatment of iron-poisoned pregnant women with deferoxamine without an evident harmful effect to the fetus [23–25]. In women with thalassemia being treated with deferoxamine, there seemed to be no adverse effects on the fetus [25–27, level of evidence grade III]. Deferoxamine is a highly charged molecule and is unlikely to cross the placenta, a prediction verified in an ovine model

[28]. The logical conclusion, therefore, is that based on the current state of our knowledge iron poisoning in pregnancy should be treated in a fashion similar to that in nonpregnant patients (Grade III recommendation). It is unknown whether deferoxamine is excreted in breast milk; it is prudent, therefore, to suspend breast-feeding during administration of this agent.

Contraindications

As with all agents, a known allergic reaction to deferoxamine should be considered to be a contraindication. Because deferoxamine and ferrioxamine are excreted renally, patients with renal failure should receive this agent only in association with hemodialysis. If the renal failure is prerenal, aggressive fluid resuscitation can be followed by standard deferoxamine therapy. Because hypotension is a major acute complication of deferoxamine administration, it is prudent to closely monitor the hemodynamic status of patients with renal insufficiency during deferoxamine infusions. Patients with compromised renal function may not be able to tolerate infusion rates that are appropriate to those who can excrete deferoxamine and ferrioxamine normally.

Precautions

The precautions associated with deferoxamine therapy for acute iron poisoning relate to the potential adverse effects described in detail below.

Adverse Effects

The major adverse effects associated with the use of deferoxamine in the treatment of iron poisoning are hypotension, acute renal failure, a pulmonary syndrome, *Yersinia* sepsis, and allergy. Many additional effects have been reported with long-term use of deferoxamine as an iron chelator for the treatment of iron overload states such as thalassemia major, hemosiderosis, or

hemochromatosis. These effects have little relevance to the use of deferoxamine in the treatment of acute iron intoxication and are not discussed further in this chapter. For additional information regarding these toxicities, the reader is referred to an excellent review on this topic by Bentur et al. [29] (level of evidence grade III).

Hypotension and Shock

There have been several reports of hypotension and shock associated with intravenous deferoxamine therapy [4, 30, 31]. Most sources recommend that hypotension can be avoided if doses of deferoxamine do not exceed 15 mg/kg/h. It is likely, however, that the intravascular volume depletion associated with iron poisoning may contribute to the hypotension, and substantially higher doses may be tolerated (Grade III recommendation). The dose rate is best determined based on the clinical response in an appropriately volume-resuscitated patient. It also is possible that histamine release may contribute to the hypotension [31, 32]. One article reported, however, that the use of H₂ antagonists did not prevent deferoxamine-induced hypotension [31, level of evidence grade II-2].

Acute Renal Failure

Acute renal failure has been reported after deferoxamine administration [33–35]. It seems that this renal injury is related to decreased renal perfusion associated with intravascular volume depletion as is typically seen in acute iron poisonings. A study of intravenous deferoxamine administration to dogs showed that it causes decreased renal perfusion independent of changes in systemic blood pressure, an effect preventable in this model by intravascular volume expansion [33]. Based on this, intravascular volume resuscitation should be started before deferoxamine administration; this should be accomplished by a bolus rather than delaying therapy by a slow infusion (Grade III recommendation).

Acute Respiratory Distress Syndrome

Beginning around 1990, several reports [36–38] described a pulmonary syndrome in patients who received high doses of deferoxamine for prolonged periods for the treatment of iron overload states [36, 37] or iron poisoning [38]. This syndrome occurred within 32 h to 9 days of continuous high-dose deferoxamine therapy and was associated with noncardiogenic pulmonary edema, tachypnea, hypoxia, fever, eosinophilia, cough, and diffuse pulmonary infiltrates. Some of the patients had urticaria before the development of the syndrome. Pulmonary function tests in one of the patients being treated for thalassemia major showed a restrictive pattern; however, the interpretation is confused by the high incidence of pulmonary abnormalities in patients with thalassemia [37]. In the early 1990s, several reports appeared of fatalities in patients with acute respiratory distress syndrome after deferoxamine treatment for iron poisoning [38, level of evidence grade III]. Subsequently, several other reports also described acute respiratory distress syndrome in patients who had received prolonged or high-dose deferoxamine therapy [34, 39, 40]. Because these patients generally were treated for prolonged periods, it is unlikely that 24 h of deferoxamine therapy, even at high doses, represents an increased risk for the development of acute respiratory distress syndrome. If treatment is continued for more than 48 h, it is prudent, based on the above, to monitor patients carefully for the development of this syndrome.

Yersinia Sepsis

There have been several reports [41, 43] of patients being treated with deferoxamine for acute iron poisoning or iron overload secondary to thalassemia major who developed infections due to *Yersinia enterocolitica*. Although patients with thalassemia have increased susceptibility to *Y. enterocolitica*, it is likely that the deferoxamine enhances the possibility of sepsis by this organism

[42, 44–47]. Normally, *Yersinia* proliferation is limited by its iron dependency. Deferoxamine can substitute for iron, however [42]. It also is possible that the excess iron from an iron overdose may stimulate *Yersinia* virulence, even in the absence of deferoxamine therapy.

Allergy

Several reports of apparent allergic and anaphylactoid reactions to deferoxamine therapy have been published. The early studies by Whitten and associates [31] reported that deferoxamine induces release of histamine, which may play a role in these reactions. A patient with an apparent anaphylactic reaction, including laryngospasm [48], subsequently was desensitized and was able to continue receiving deferoxamine therapy for thalassemia.

Interference with Iron Assays

Deferoxamine interferes with iron determinations by several routine assays [49, 50]; this occurs not because of deferoxamine-related interfering color but because its chelating qualities interfere with the iron-binding reagents used in the assays. Atomic absorption and plasma emission spectrophotometric assays are unaffected by the presence of deferoxamine and are recommended for iron quantitation during deferoxamine therapy. A deferoxamine-insensitive modification of the routine automatic clinical analyzer method of iron determination has been published [51].

Administration

As reviewed previously and in ► Chap. 67, “Iron,” deferoxamine should be administered by the intravenous route in all patients with acute systemic iron poisoning. Because of the concern for hypotension in these often volume-depleted patients, it is important to administer fluid resuscitation aggressively to these patients as soon as

possible. It is not necessary to complete fluid resuscitation before starting deferoxamine therapy; both can be accomplished simultaneously (Grade III recommendation).

The rate of deferoxamine infusion, as described earlier, is best individualized on the basis of patient tolerability. Although a maximal rate of intravenous infusion of 15 mg/kg/h is often cited, there is little empirical justification for this recommendation. In a severely iron-poisoned patient who is able to tolerate higher doses, there is no reason to restrict the rate of infusion to this parameter. Most acutely iron-poisoned patients require less than 48 h of deferoxamine treatment [52]. Because of concerns for deferoxamine-induced acute respiratory distress syndrome, as described earlier, treatment with this agent should be restricted to less than 48 h if possible.

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In normal intermediary metabolism, six adenosine triphosphates (ATPs) are created by passing two pairs of electrons down the respiratory chain from two reduced nicotinamide adenine dinucleotides to molecular oxygen. In the course of this mitochondrial ATP synthesis, the iron in cytochrome *aa₃*, the terminal oxidative respiratory enzyme, is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form. Cyanide has a special affinity for the ferric heme, blocking oxygen consumption and oxidative phosphorylation. Blood contains a great quantity of ferrous heme within hemoglobin that can be converted to the ferric form (methemoglobin) by the use of methemoglobin-generating agents. If methemoglobin is formed in excess of total body cytochrome *aa₃*, the cyanide ion binds to methemoglobin, restoring normal cellular respiration (Fig. 1).

The use of nitrite for methemoglobin formation was suggested by Chen and colleagues [1] in 1933, and nitrite is still used to treat cyanide poisoning. A theoretical disadvantage of nitrite therapy, however, is that methemoglobinemia is induced slowly. The originally suggested dose of 4 mg/kg intravenously results in 6% of methemoglobin after only 40 min [2]. A high dose of nitrite, if given too quickly, may lead to vasomotor relaxation and hypotension [3]. Amyl nitrite, which is administered by inhalation, creates little methemoglobin [4], but similar to nitrite, it has a vasodilating effect. Another cyanide antidote, dicobalt ethylenediamine tetraacetic acid (“cobalt EDTA”), can cause severe reactions, such as

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urticaria, hypotension, convulsions, and laryngeal edema [5, 6].

The antidote with the least side effects is hydroxocobalamin, which is discussed in the chapter on Cyanide-Binding Antidotes [7]. The latter is expensive, however, and has practical disadvantages. It can be given only in a large volume 5 gr in 250 mL, and the lyophilized powder must be first reconstituted. This process may be too time-consuming in a critically poisoned patient. A compound that quickly creates sufficient methemoglobin with few adverse effects would be preferable. 4-Dimethylaminophenol (4-DMAP) may have advantages regarding these criteria.

History

4-dimethylaminophenol was developed and studied in the laboratories of the Walther Straub Institute for Pharmacology and Toxicology of the Ludwig Maximilian University in Munich, Germany. The German army supported its development because it was thought that hydrogen cyanide might be used as a chemical warfare agent.

In 1969, Kiese and Weger [8] reported that 4-DMAP was the most potent methemoglobin-forming agent among a series of aminophenols tested in humans for the treatment of cyanide poisoning. 4-Dimethylaminophenol was used in human cyanide poisoning successfully by Daunderer et al. in 1972 [9]. Because severe cyanide poisoning has become rare, only single case reports have been published since. A series of 13 cases in which 4-DMAP was given to humans between 1973 and 1979 has been described in a thesis from our department; however, these cases have not been published elsewhere [10]. A further series of nine cases from our department, from 1981 to 1991, was published as an abstract [11]. We are aware of the use of 4-DMAP in Austria and the Netherlands [12]. 4-Dimethylaminophenol is registered as a pharmaceutical by the German authorities (BfArM). Permission for its use was extended in 2003. At the very moment, it is not acquirable as the firm has to

alter the way of synthesis. But stocks are still on most German emergency ambulances (Notarztwagen NAW). The producer of this drug is the company Dr. Franz Koehler Chemie GmbH, Bensheim, Germany.

Properties

The properties of 4-DMAP are summarized as follows:

Chemical name: Dimethyl (para) aminophenol hydrochloride (Fig. 2)

Chemical formula: $C_8H_{11}ON \cdot HCl$

Relative molecular mass: 173.5

Appearance: White crystals

CAS (Chemical Abstracts Service) number: 619-60-3

Raw material: White colorless crystals

Melting point: $145^\circ C \pm 1^\circ C$

Solubility: Soluble in water. The solution is oxidized by contact with air and changes from colorless to black-brown.

Pharmacodynamics

4-Dimethylaminophenol produces methemoglobin by catalytic transfer of electrons from ferroheme to oxygen. This process is terminated by binding of oxidized 4-DMAP to compounds that possess free SH groups (see Fig. 1).

In human volunteers, 3.25 mg/kg of 4-DMAP given intravenously oxidized about 30% of the total hemoglobin to methemoglobin (Fig. 3) [13]. The spontaneous reduction of methemoglobin back to ferroheme was 8% per hour at 30% to 20% of methemoglobin levels [14]. In vivo, 1 molecule of 4-DMAP is capable of converting 15 molecules of hemoglobin to methemoglobin [13]. Methemoglobin formation by 4-DMAP occurs rapidly. In experiments on seven volunteers [2], an intravenous bolus of 3.25 mg/kg of 4-DMAP resulted in 15% methemoglobin after 1 min and 28.5% after 10 min. The peak of 30% was attained after 20 min.

Fig. 1 Mechanism of action of cyanide, 4-DMAP, and methemoglobin. *Cyta₃* cytochrome *aa₃*

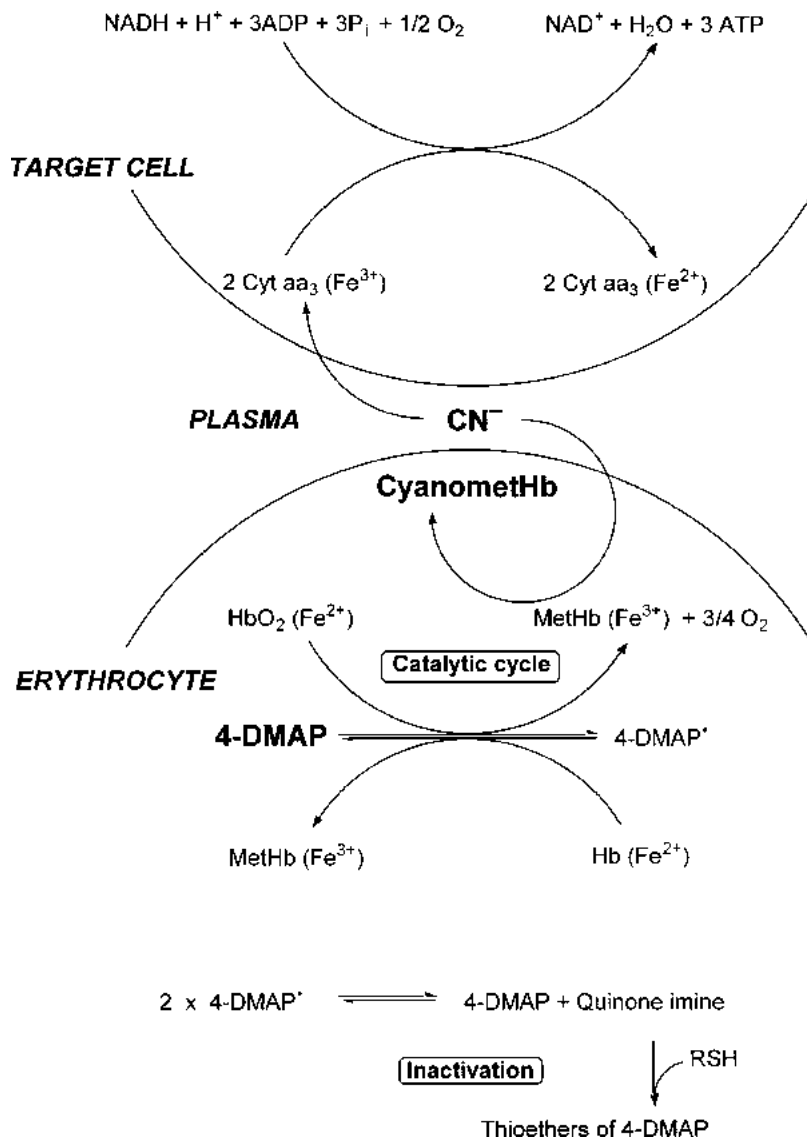
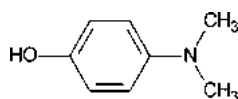


Fig. 2 Chemical structure of 4-dimethylaminophenol



4-Dimethylaminophenol can be administered intramuscularly or orally. The intramuscular injection of 3.5 mg/kg of 4-DMAP in human volunteers ($n = 6$) resulted in a maximal measured methemoglobin concentration of 30% after 45 min. The administration of 12 mg/kg of

4-DMAP orally ($n = 5$) created 27% methemoglobin within 30 min, but the actual oral bioavailability is uncertain [13].

4-Dimethylaminophenol (3.25 mg/kg) given intravenously to dogs 1 min after poisoning with potassium cyanide (4 mg/kg) that is twice the lethal dose in dogs [15] resulted in the survival of all dogs [16]. The peak concentration of methemoglobin was $32\% \pm 1.9\%$ [16].

4-Dimethylaminophenol has other effects on physiologic functions. Although the venous lactate

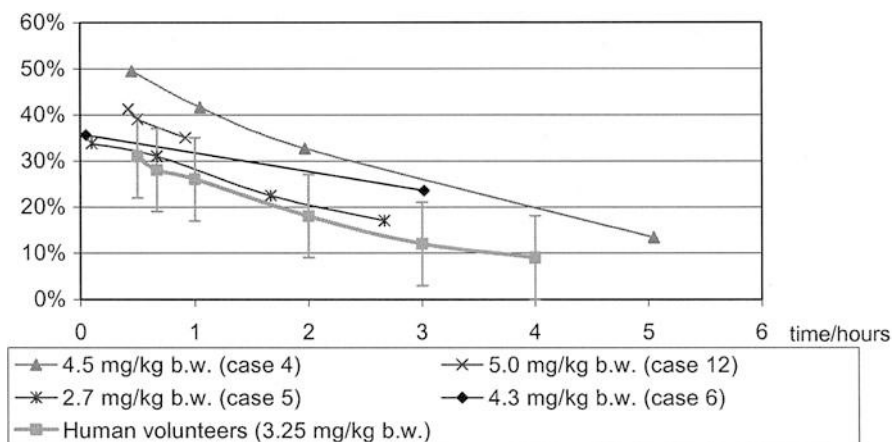


Fig. 3 Course of methemoglobin concentrations in cyanide-poisoned patients and human volunteers after intravenous administration of 4-DMAP [10]. *bw* body weight

concentration did not change, the pyruvate concentration increased by 30% after 4-DMAP administration. This effect also was found in canine blood in vitro, most probably caused by the lactate-induced methemoglobin reduction [14, 17].

In dogs [17], the mean arterial pressure after 4-DMAP (3.25 mg/kg intravenously) increased by 15% within 5 min, and the effect was maintained for 1 h. The respiratory minute volume increased by 30%. Both effects may be advantageous in cyanide poisoning. The arterial PO_2 increased within 1 min from 95 to 190 mmHg, after which it normalized by 10 min. This increase has been attributed to the release of oxygen from oxyhemoglobin during the formation of methemoglobin. It is possible that in a critically ill, cyanide-poisoned patient, this may improve tissue oxygenation [17]. When cerebral blood flow was measured in canine brain [18], 4-DMAP evoked a dose-dependent increase in cerebral blood flow. The positive cerebral blood flow response did not occur until at least 10% methemoglobin was formed. As long as the methemoglobin concentration was less than 40%, the canine brain could compensate for the diminished oxygen transport capacity by elevating oxygen use as indicated by a decrease of pO_2 in the sinus sagittalis. At higher methemoglobin concentrations, oxygen use no longer could be improved [18]. A 4-DMAP dose producing more than 40% methemoglobin is not

advisable. As long as methemoglobin is less than 40%, most physiologic reactions to 4-DMAP seem to be favorable for treating cyanide poisoning.

Pharmacokinetics

In humans and dogs, 4-DMAP (3.25 mg/kg intravenously) is cleared rapidly from the blood with a half-life of less than 1 min [19]. This rapid clearance is due to various first-pass effects [13]. Using [14]C-labeled 4-DMAP in canine experiments, approximately one third of 4-DMAP equivalents were found in red blood cells, and two thirds were found in plasma and the extracellular space (apparent volume of distribution 0.17 L/kg) [20]. To understand the particular pharmacokinetics of 4-DMAP, one must differentiate between the metabolism in erythrocytes and elsewhere, mainly in the liver.

Metabolism of 4-DMAP in Erythrocytes

The distribution of 4-DMAP between plasma and erythrocytes is not known because of the ultra-short lifetime of 4-DMAP within red blood cells. 4-Dimethylaminophenol is cooxidized quickly with oxyhemoglobin to form methemoglobin

and a phenoxyl radical. The phenoxyl radical oxidizes deoxyhemoglobin, sustaining the catalytic cycle of methemoglobin formation [21]. Alternatively, the phenoxyl radical disproportionates to form 4-DMAP and a quinone imine that is bound covalently to hemoglobin SH groups [22]. In the presence of high glutathione concentrations, such as occurs in erythrocytes, the quinoneimine undergoes sequential addition/oxidation reactions with formation of mono-glutathione, bis-glutathione, and tris-glutathione adducts of 4-DMAP [23]. The trisubstituted conjugate is not oxidized further but is actively excreted from the erythrocyte into plasma [24]. This conjugate has a half-life of about 1 h in plasma and is processed further by the kidneys and excreted mainly as a tris-cysteinyl derivative of DMAP [25], as has also been observed in dogs [20]. It has been calculated that probably all 4-DMAP thioethers excreted (15% of the dose) originate from the metabolism of 4-DMAP within the red blood cells. About the same amount of 4-DMAP is bound covalently to the hemoglobin SH groups.

Metabolism of 4-DMAP in the Liver

About 50% of the 4-DMAP administered intravenously to humans is transformed in the liver to the glucuronide and sulfate conjugate. In urine, 41% 4-DMAP glucuronide and 12% 4-DMAP sulfate were detected [13, 25]. This conjugation seems to occur rapidly, as shown in the isolated, hemoglobin-free perfused rat liver, in which covalent binding to liver proteins or formation of glutathione conjugates were of no importance [26]. The first-pass effect in the liver may be the reason for the much higher oral dose compared with the parenteral dose of 4-DMAP required to obtain an equivalent degree of methemoglobin [13].

Toxicity

The toxicity of 4-DMAP has been studied in mouse, rat, and dog. The median lethal doses are listed in Table 1. In all studies, the cause of death

Table 1 Median lethal doses in mice, rats, and dogs

Route/species	Median lethal dose (mg/kg)
Intravenous/mouse	50–70 [27, 28]
Oral/mouse	946 [28]
Intravenous/rat	57 [29]
Oral/rat	689–780 [28]
Intravenous/dog	26 [30]

was severe methemoglobinemia. Single intravenous injection of 4-DMAP (100 mg/kg) to rats was followed by a large amount of necrosis and inflammation of the convoluted tubules without affecting the glomeruli and papillae. No changes were found in the liver, heart, and spleen [27]. In isolated, hemoglobin-free perfused rat kidneys, 4-DMAP underwent a sharp increase of covalent binding to kidney proteins at concentrations greater than 15 μ M. Microautoradiography [14] showed that the high binding was particularly prominent in the proximal convoluted tubules [31].

Special Populations

No data for neonates or children are available. In our series of 23 patients in whom 4-DMAP was used, the eldest person was 66 years old (case 13) (Tables 2 and 3). This patient received 9.3 mg/kg of 4-DMAP. He developed mild hemolysis, with an increase in lactate dehydrogenase to 378 U/L, a decrease in hemoglobin from 13.8 to 10 g/dL within 5 days, and an increase in bilirubin to 3 mg/dL. Because this was nearly three times the recommended dose and hemolysis occurs in younger patients at similar doses, we could not detect a difference between elderly and younger people in reacting to this dose.

Contraindications

Patients with glucose-6-phosphate dehydrogenase deficiency who are unable to reduce methemoglobin by the pentose phosphate shunt are at risk of developing long-lasting methemoglobinemia after 4-DMAP and may have severe hemolysis.

To our knowledge, the drug was never used in such a case. On theoretical grounds, glucose-6-phosphate dehydrogenase deficiency is a contraindication for the use of 4-DMAP. Given the desperate situation of a potentially fatally poisoned patient, we recommend that this be considered only a relative contraindication in cyanide poisoning. If a glucose-6-phosphate dehydrogenase-deficient patient were treated with 4-DMAP, because the enzyme deficiency was unrecognized or it was thought that the treatment was mandated because of life-threatening cyanide poisoning, the induced hemolysis could be treated by transfusion or blood exchange. In whites in Europe, glucose-6-phosphate dehydrogenase deficiency is a rare disease.

Clinical Experiences with Use of 4-DMAP in Cyanide Poisoning

Limited data are available for the use of 4-DMAP in cyanide poisoning because of the rarity of such poisonings and because few such poisoned persons are found alive. Some single case reports are published [9, 12, 32–34] (Grade III evidence). All but one of these case reports describe patients who survived, probably reflecting a publication bias.

Since 1972, our department has accumulated 23 cases of cyanide poisoning treatment by 4-DMAP either before or at the time of admission and one case in which 4-DMAP was used by mistake (see Tables 2 and 3): 13 cases were published in a thesis by Werner in 1979 [10], 1 case (number 10) was published by Daunderer and coworkers [9], and 9 additional cases were published in an abstract [11].

In the original Werner series, the indications for administering 4-DMAP were less strict than they are today. Of the 13 patients, only 4 (see Table 2), found in coma, seemed to meet the absolute indications we use today. Three of these four patients survived. In two further cases (cases 8 and 9 in Table 2), the indications for 4-DMAP were questionable. One patient was somnolent and still arousable. The other patient was in a coma, but 5 h had elapsed since the poisoning. In 1981 (when the first author joined the

department), the indications for 4-DMAP administration were clarified. Cases of mild cyanide poisoning were treated with sodium thiosulfate. Since 1981, nine patients received 4-DMAP: five survived, three died, and one was dead for an unknown period before he was found. From the eight remaining cases, three had to be resuscitated at the scene. In all three cases, it was possible to restore circulation after the administration of 4-DMAP. Two of the patients died of irreversible brain damage or edema after brain death had ensued, and one fatally rearrested after 3 h. All patients who were found in deep coma without cardiac arrest or without severe circulatory failure survived. Of the group of 12 patients (excluding the one who was found dead, the one who got the antidote after 5 h, and all the cases in which the indication was doubtful), 8 survived and 4 died. 4-Dimethylaminophenol has not been studied in a controlled trial comparing its efficacy with other cyanide antidotes.

Dose

Considering the optimal 4-DMAP dose for a severely poisoned patient, the clinician has to keep in mind that exact dosing is difficult for the patient in extremis, the exact weight or height of the patient is unknown, and calculations under stress are difficult. We recommend that a standard dose, based on animal studies and clinical experience, be one ampule (equivalent to 3.25 mg/kg of 4-DMAP in a 76-kg person). As can be seen from Table 2, 125 mg was administered in 2 cases (cases 3 and 20), and 250 mg was administered in 13 cases. One patient (case 21) who could not be saved had mild hemolysis. One patient received 375 mg of 4-DMAP (case 19) in two divided doses and died on day 5 with severe hemolysis. All five patients (cases 7, 13, 14, 15, and 16) who were given 500 mg showed mild-to-severe hemolysis. One patient (case 18) received 1000 mg and developed severe hemolysis with a peak methemoglobin content of 73%; the patient survived. Another patient treated with 1000 mg of

Table 2 Data in 23 patients in whom 4-DMAP was administered^a

Case no./year	Cause/route of poisoning	4-DMAP dose/interval before administration	Indication	Adverse effects	Outcome
1/1975	Accident/transdermal	250 mg/12 min	None; not in coma	None	Recovery
2/1976	Accident/inhalation	250 mg/55 min	None; not in coma	None	Recovery
3/1976	Accident/transdermal	125 mg/2.5 h	None; not in coma	None	Recovery
4/1976	Accident/oral	250 mg/1.5 h	None; not in coma	None	Recovery
5/1977	Accident/inhalation	250 mg/5.5 h	None; not in coma	None	Recovery
6/1978	Accident/almond type with high amygdaline content (cyanogenic glycoside)	250 mg/9.5 h	None; not in coma	None	Recovery
7/1979	Accident/bitter almond	500 mg/2 h	None; not in coma	Severe hemolysis, Hb from 13 to 5.9 within 3 days	Recovery
8/1973	Suicidal/oral	250 mg/15 min	Questionable somnolence	None	Recovery
9/1978	Suicidal/oral	250 mg/15 min	Questionable blood level 3 mg/L	None	Recovery
10/1972 (published 1974)	Accident	250 mg/45 min	Yes; deep coma	Circulatory suppression due to additional cobalt EDTA	Recovery
11/1973	Suicidal/oral	250 mg/5 h	Yes; deep coma	None	Recovery
12/1977	Accident/transdermal	250 mg/2 h	Coma	None	Recovery
13/1979	Suicidal/oral	500 mg/?	Yes; coma	Mild hemolysis, Hb from 13.8 to 10 bilirubin (maximum): 3	Recovery
14/1985	Suicidal, oral	250 mg/10 min; 250 mg/3 h	Yes; deep coma	Mild hemolysis. Hb from 13.3 to 10.3 bilirubin (maximum): 4.7	Recovery
15/1987	Suicidal, oral	500 mg/1.5 h	Yes; coma	Mild hemolysis, Hb from 15 to 13.4 bilirubin (maximum): 4.4	Recovery
16/1989	Suicidal, oral	500 mg/20 min	Yes; deep coma	Hemolysis, Hb from 13.6 to 9 bilirubin (maximum): 9.3	Recovery
17/1991	Suicidal, oral	250 mg/15 min	Yes; deep coma	None	Recovery
18/1986	Accident, inhalation	1000 mg/15 min; 73 % MetHb	Yes; deep coma	Severe hemolysis, Hb from 13.9 to 7.3 bilirubin (maximum): 8.9	Recovery

(continued)

Table 2 (continued)

Case no./year	Cause/route of poisoning	4-DMAP dose/interval before administration	Indication	Adverse effects	Outcome
19/1977	Suicidal, oral	250 mg/1.5 h; 125 mg/5 h	Yes; deep coma	Severe hemolysis, Hb from 16.4 to 10.9 bilirubin (maximum): 18.4	Death after 4 days
20/1986	Suicidal, oral	125 mg (only)/1.5 h	Yes; resuscitation after 4-DMAP successful	None	Death after 4 days
21/1987	Suicidal, oral	250 mg/2 h	Yes; resuscitation after 4-DMAP successful	Mild hemolysis, Hb from 15.7 to 13.7 bilirubin (maximum): 4.4	Death after 5 days
22/1989	Suicidal, oral	250 mg/1 h	Yes; resuscitation after 4-DMAP successful	Too short to judge	Death after 3 h
23/1981	Suicidal, inhalation	500 mg/?	Dead for unknown time	Not possible to judge	Found dead

^aSodium thiosulfate was administered after 4-DMAP in all patients.

Hb hemoglobin, MetHb methemoglobin

4-DMAP was poisoned with parathion. This patient also survived with severe hemolysis and renal failure (not shown in Table 2 or 3).

Methemoglobin Formation

A dose of 250 mg of 4-DMAP (see Table 3, cases 4, 5, 6, and 12) seems to create methemoglobin concentrations between 33% and 49.5%, which disappeared with a half-life of around 140 min (see Fig. 3). The half-life is not influenced by the dose. In our patients, it was a little bit longer than in normal controls (117 min). As seen in case 7, 500 mg of 4-DMAP can lead to long-lasting methemoglobin formation. It is likely that most of the methemoglobin found in this case after 72 h stemmed from extracellular methemoglobin due to hemolysis.

From this limited experience, we conclude that in a healthy adult, 250 mg is theoretically sufficient, yet safe. Repeated 4-DMAP administrations do not seem to be necessary if sodium thiosulfate is administered subsequently.

Precautions

Before 4-DMAP is used in a patient, it should be certain to the degree practically possible that the patient is poisoned by cyanide. We recommend that 4-DMAP should be used only if the patient is in a coma (Grade III recommendation). We do not recommend its use in smoke inhalation patients because of the theoretical concern that carboxyhemoglobin and methemoglobin jointly may impair oxygen transport and delivery.

Table 3 Whole-blood cyanide and methemoglobin levels in 23 patients in whom 4-DMAP was administered

Patient	Cyanide level/time after intoxication	Dose 4-DMAP	Methemoglobin/time after 4-DMAP
1	Negative/1 h	250 mg	23 %/13 min
2	Not measured	250 mg; 4.38 mg/kg	Not measured
3	Negative/150 min	125 mg; 2.7 mg/kg	Not measured
4	Positive in breath/90 min	250 mg; 4.5 mg/kg	49.5 %/27 min
5	Positive in breath/5.25 h	250 mg; 2.7 mg/kg	33 %/9 min
6	0.18 mg/L/9 h	250 mg; 4.3 mg/kg	35.6 %/3 min
7	Not measured	500 mg; 8.3 mg/kg	35 %/72 h
8	1.5 mg/L/15 min	250 mg	Not measured
9	3 mg/L/15 min	250 mg; 4 mg/kg	14.7 %/1 h
10	Not measured	250 mg	Not measured
11	Not measured	250 mg; 3.57 mg/kg	22 %/13 min
12	2 ppm in breath/2 h	250 mg; 5 mg/kg	41.2 %/25 min
13	Not measured	500 mg; 9.3 mg/kg	Not measured
14	2.4 mg/L/2 h	250 mg/10 min; 250 mg/3 h	15.8 %/1 h; 37.7 %/155 min after second administration
15	6.0 mg/L/2.25 h	500 mg	Not measured
16	25 mg/L/1 h	500 mg	33.4 %/130 min
17	1.46 mg/L/130 min	250 mg	Not measured
18	Positive in breath	1000 mg	73 %/1 h; 46 %/3.5 h
19	2.65 mg/L	250 mg; 125 mg	Not measured
20	34 mg/L/1.5 h	125 mg	Not measured
21	10.9 mg/L/2 h	250 mg	19 %/15 min
22	14 mg/L	250 mg	14.8 %/45 min
23	Not measured	500 mg	Not measured

Adverse Effects

Two major adverse effects are related to the desired action of 4-DMAP: excessive methemoglobinemia and hemolysis. Our cases suggest that significant hemolysis does not occur at doses of 5 mg/kg body weight. The suggested dose of 3.25 mg/kg did not produce excessive methemoglobinemia. Only in one fatal case of cyanide poisoning was excessive methemoglobinemia observed using the recommended dose of 4-DMAP [12]. In vitro, the methemoglobin production rate at atmospheric oxygen pressure was only 60% of that at 40 mmHg, similar to that in venous blood [35]; this may be important in hypoxic patients when cardiopulmonary insufficiency is present. In our opinion, this fact should not lead to reducing the

dose in such circumstances as long as the patient is ventilated with a fraction of inspired oxygen of 1.

Some minor adverse effects are of little relevance in severely poisoned patients. Phlebitis was observed 6–7 days after 4-DMAP was infused in the antecubital vein. After an intramuscular injection of 4-DMAP, slight pressure was felt after 5–10 min at the site of injection, slowly growing in intensity and finally resulting in severe pain in one patient. In another patient, shivering, sweating, and fever occurred approximately 10 h after the injection. In volunteers, after the intravenous injection of 4-DMAP (3.25 mg/kg), the total bilirubin concentration increased by 140%, conjugated bilirubin increased by 180%, and iron increased by 200%. Within 24 h of an intramuscular injection of this dose, the total bilirubin

increased by 270% and then declined rapidly, whereas the conjugated bilirubin concentration increased by 120% and iron increased by 50% [13].

Treatment of Adverse Effects

Excess methemoglobinemia may be corrected by 2 mg/kg of toluidine blue or by 1 mg/kg of methylene blue intravenously [36]. We suggest that this should be done only if within 1 h after the administration of 4-DMAP the methemoglobin level exceeds 50% (Grade III recommendation). Otherwise, cyanide can be released, and thiosulfate infusion is mandatory. Exchange transfusion is needed if the methemoglobin level remains high as this means that methemoglobin comes from erythrocytes that have lysed and therefore cannot reduce MetHb.

Administration

4-Dimethylaminophenol should be administered in a dose of 3.25 mg/kg intravenously in a comatose, cyanide-poisoned person (Grade III recommendation). In adults, it seems reasonable to administer one ampule of 4-DMAP, which contains 250 mg, if the exact weight is not known. It is possible to administer 4-DMAP in the same dose intramuscularly in mass poisoning.

Final Evaluation

Animal experiments and limited clinical data suggest that 4-DMAP is an effective antidote against cyanide poisoning. Although in most cases it was used in combination with sodium thiosulfate and therefore it is difficult to distinguish the efficacy of the two drugs. Single cases have received DMAP only successfully. There was, in most cases, an improvement shortly after its administration and before the use of sodium thiosulfate, suggesting that 4-DMAP is effective. In cases of severe cyanide poisoning, 4-DMAP is probably lifesaving, if administered in time. 4-DMAP produces more

MetHb more rapidly than nitrites, although it has to be acknowledged that since both treatments have an equal chance of successful outcome, the speed of forming MetHb might not be of utmost importance. It should not be used in the case of smoke inhalation since the induced methemoglobinemia may be additive to CO poisoning. However, there is no evidence that it has ever been tested in such circumstances. The possibility to administer 4-DMAP intramuscularly might make it an appropriate antidote for severe cases in the industrial environment and for use in treatment of mass casualties, e.g., in terror attacks [37].

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Dimercaprol is the generic term for 2,3-dimercaptopropanol. Because British investigators developed dimercaprol during World War II as an antidote to the war gas lewisite, it also came to be known as the *British anti-lewisite* or *BAL*.

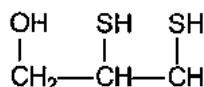
History

The development of dimercaprol as an antidote to the organoarsenical agent lewisite (dichloro [2-chlorovinyl] arsine) extended earlier observations that the action of arsenoxide drugs involved biochemical interaction with the thiol groups of enzymes and that this process could be mitigated by a large excess of sulfhydryl reagents. After screening many monothiol and dithiol chemicals, Peters and coworkers [1] found that the dithiol compound 2,3-dimercaptopropanol was most effective at preventing lewisite-induced inhibition of pyruvate oxidase and protecting experimental animals from lewisite's vesicant and lethal effects. A penetrating oily liquid dimercaprol initially was conceived of as a topical treatment for lewisite burns to the eyes and skin. Subsequent studies found that topical and intramuscular injections of dimercaprol alleviated severe dermatologic and systemic complications associated with organoarsenical antibiotics used in the treatment of syphilis [2]. Within 3 years, the use of dimercaprol extended to treatment of poisoning by inorganic heavy metals, particularly inorganic arsenic

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Fig. 1 Chemical structure of dimercaprol (2,3-dimercaptopropanol)



and mercuric salts [3]. It still is used for this purpose today.

Chemical and Physical Properties

Dimercaprol (Fig. 1) ($\text{C}_3\text{H}_8\text{OS}_2$; molecular weight 124.2) is an oily, colorless liquid with a skunk-like mercaptan odor. Although soluble in water to 6% (weight/volume), the vicinal thiol groups are readily oxidized in aqueous solutions. To achieve greater stability, the pharmaceutical product is prepared as a 10% solution (100 mg/mL) in peanut oil that also contains 20% (200 mg/mL) benzyl benzoate. Dimercaprol forms 1:1 or 2:1 complexes with several metals *in vitro*; however, the nature of metal complexes formed by dimercaprol or its metabolites *in vivo* has not been determined.

Pharmacodynamics

Dimercaprol increases the urinary excretion of certain toxic metals (particularly arsenic, lead, and mercury). In animal studies, it has been shown to redistribute mercury and arsenic to the brain, however [4, 5]. Dimercaprol increases elimination of copper, an essential trace mineral. In human studies, dimercaprol injection results in a transient increase in blood pressure and heart rate, but it otherwise has no clinically significant pharmacodynamic impact on cardiovascular, hepatic, or renal function.

Pharmacokinetics

In humans exposed to arsenicals, intramuscular dimercaprol is associated with an increase in urinary arsenic excretion that peaks in 2–4 h [6] and then quickly declines. Pharmacodynamic effects, such as increased blood pressure and pulse, peak

at approximately 30 min and resolve within 2 h [7]. Limited observations such as these imply that dimercaprol is absorbed, distributed, and excreted rapidly. After intramuscular injection of radio-labeled dimercaprol to rats, 80% of the radioactivity entered the bloodstream within 1 h [8]. The radiolabel was distributed rapidly and widely to most soft tissues, with the highest levels measured in the kidneys and the liver. Some intracellular distribution has been inferred from the ability of dimercaprol to traverse cell membranes *in vitro* [9], but the drug's volume of distribution has not been determined. After injection in animals, an altered form of dimercaprol is excreted in the urine, with minor amounts in the bile or feces, within 6–12 h [8, 10]. It was observed consistently in rats and rabbits that unchanged dimercaprol was not excreted in the urine. In rabbits, dimercaprol seemed to be metabolized partly to an unspecified thiol compound [11]; in rats, no free thiols were excreted [12].

Contraindications and Precautions

Because it is dissolved in peanut oil, dimercaprol should not be administered to patients who are allergic to peanuts. Dimercaprol has been associated with hemolysis in two patients with glucose-6-phosphate dehydrogenase deficiency [13]; susceptible patients should be monitored for hemolysis during treatment.

Because the metabolites of dimercaprol and the metals it mobilizes are excreted predominantly in the urine, caution should be exercised in administering dimercaprol to patients with severe renal insufficiency. Such caution may include initiating treatment at low dose (i.e., 3 mg/kg every 6 h) and closely monitoring patients for adverse effects and evidence of metal excretion. A few reports suggest that dimercaprol or its metabolites may be dialyzable and that dimercaprol may increase the dialysis clearance of mercury in patients with renal failure [14–16]. Although increased mortality was found when massive doses of dimercaprol were given to animals with acute hepatic damage from carbon tetrachloride [17], no relevant

clinical experience implicates hepatic insufficiency as a contraindication.

Dimercaprol (0.3 mg/kg) did not redistribute radiolabeled mercury to the fetus when administered to pregnant mice concurrently exposed to mercuric chloride [4]. Dimercaprol was teratogenic and embryotoxic, however, at a dose of 125 mg/kg/day in a mouse model, and it seems less effective than succimer or unithiol in averting the adverse reproductive effects of arsenic or mercury [18, 19]. Dimercaprol is rated pregnancy category C by the US Food and Drug Administration.

Adverse Effects

The adverse effects of dimercaprol are dose dependent. Reactions are relatively mild and infrequent at doses of 3 mg/kg intramuscularly or less but occur in two thirds of patients receiving 5 mg/kg intramuscularly. Transient elevation in blood pressure, with an increase in diastolic pressure of 10–40 mmHg, is common at doses of 4 or 5 mg/kg intramuscularly. The blood pressure usually normalizes within 2 h [7]. Compared to adults, children are prone to tachycardia rather than blood pressure elevation after dimercaprol injections [20]. In 60 healthy adults and 61 adults with complications of organoarsenical antisyphilitic therapy, dimercaprol doses of 4–5 mg intramuscularly were associated with the following adverse effects, in decreasing order of frequency: nausea, vomiting, and headache; a burning sensation of the lips, mouth, throat, and eyes, sometimes with accompanying lacrimation, rhinorrhea, or salivation; generalized muscular aches; burning and tingling of the extremities, with sweating of the forehead and hands; pain in the teeth; and a sense of constriction in the chest, with a feeling of anxiety and general agitation. These symptoms appeared within 10–30 min of the injection and subsided within 30–50 min. Fever was observed after the second or third dimercaprol injection in two thirds of children receiving doses greater than 3 mg/kg [20], but this seems to be uncommon in adults. Convulsions and transient coma occurred in three

children who accidentally received dimercaprol injections of 25 mg/kg [20].

One anecdotal report suggested that 25 mg of ephedrine administered (to an adult) 0.5 h before dimercaprol injection may diminish the severity of subsequent adverse effects [21]. This has not been a consistent observation, however, and ephedrine conceivably might aggravate the pressor response of dimercaprol. Intramuscular injections of dimercaprol frequently are perceived as painful and may be complicated by sterile or pyogenic abscesses. Prior local injection of procaine has been suggested as a means to diminish the pain associated with intramuscular dimercaprol injection [22].

Administration

Dimercaprol (BAL in oil) is supplied as 3 mL ampules containing dimercaprol (100 mg/mL) and benzyl benzoate (200 mg/mL) in peanut oil. For the treatment of systemic poisoning by relevant heavy metals, it can be administered only as a deep intramuscular injection. The initial dose ranges from 2.5 to 4 mg/kg intramuscularly every 4–6 h depending on the nature and severity of the poisoning being treated. It is common to progressively taper the amount and frequency of dimercaprol administered during the initial days of therapy. Dimercaprol injections have been used as an experimental topical treatment for vesicant burns to the skin and eye induced by lewisite [23, 24]. A 5% solution prepared by diluting the 10% ampules in vegetable oil should be applied *immediately* to the exposed surface of the eye, conjunctivae, and skin. Systemic effects should be treated parenterally.

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Ethylene glycol and methanol toxicity has the potential to cause morbidity and mortality [1, 2]. Along with supportive care and hemodialysis, ethanol has been utilized as a treatment option for many years, first investigated and used in the 1940s and 1950s [3–5].

Although in the past few years the use of ethanol has largely been supplanted by the alcohol dehydrogenase inhibitor, fomepizole [6], it is not always available either because of cost or lack of easy access. Given the need to inhibit formation of the toxic metabolites of ethylene glycol and methanol, initial use of ethanol may be necessary either as a temporizing measure until fomepizole is available or to complete treatment.

Ethanol (C_2H_5OH) is a colorless, hygroscopic, volatile two-carbon alcohol (Fig. 1) with a molecular weight of 46.07 g/mol. It can be synthesized from carbohydrates by the enzyme zymase, found in yeast cells. Ethanol also can be formed through the hydration of ethylene or through the hydration of acetylene to form acetaldehyde, which is further reduced to form ethanol [7].

Ethanol therapy generally mandates an intensive care unit admission regardless of the patient's clinical status. Therefore, it is important that the critical care medicine physician be familiar with the safe and effective use of ethanol in this clinical setting.

Ethylene glycol and methanol poisoning are discussed extensively in their respective chapters.

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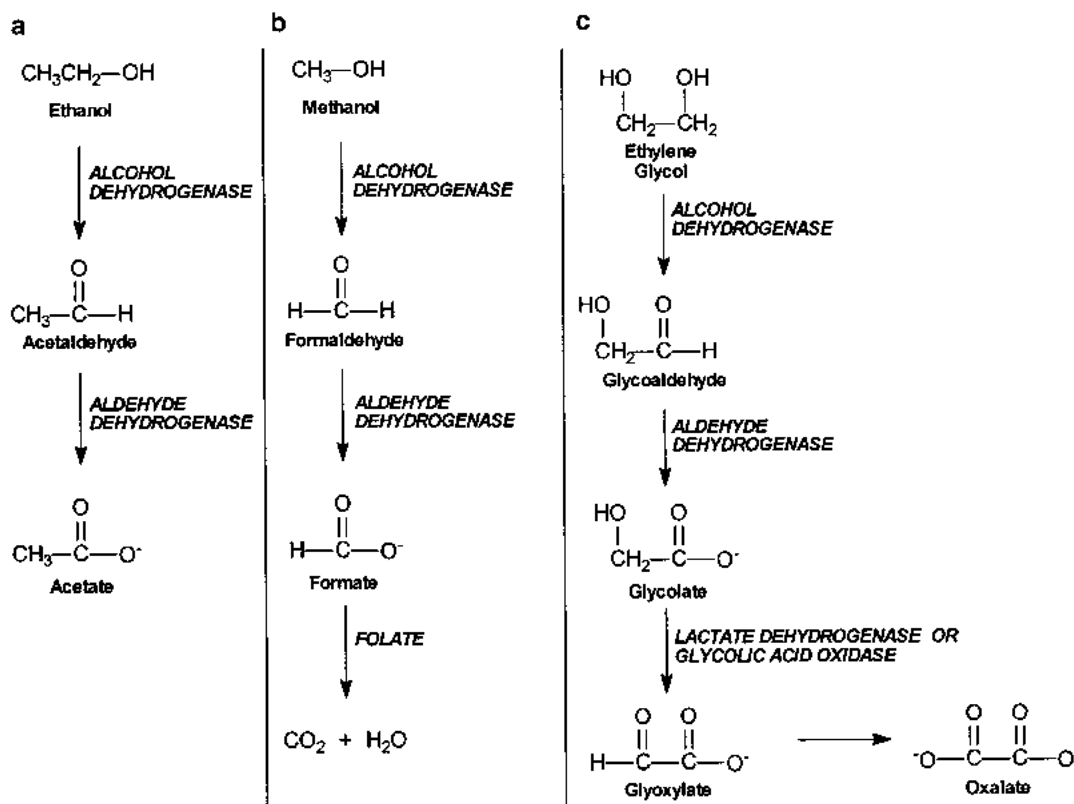


Fig. 1 Metabolic pathways for ethanol (a), methanol (b), and ethylene glycol (c)

The clinical pharmacology of fomepizole is addressed in ► [Chap. 150, "Fomepizole."](#)

Pharmacodynamics

The most prominent clinical effect of ethanol is initial central nervous system excitation and inebriation, followed by depression. The mechanism of ethanol's effect on the central nervous system is a matter of some debate. Being an amphipathic solvent, the lipophilic portion of ethanol increases the fluidity of cellular membranes. It is not known, however, if this alteration in membrane fluidity is related to the observed effects at clinically relevant concentrations. Ethanol can also cause ataxia, loss of coordination, and mood change. It also modulates the activities of multiple ion channels in the central nervous system.

Pharmacokinetics

Absorption

Ethanol is absorbed directly from the stomach, but primarily from the duodenum and jejunum [8]. In volunteer studies, peak absorption of ethanol was shown to occur at 104 min after a 700-mg/kg ethanol dose in men and 84 min after administration of the same dose in women [9, 10]. Factors such as gender and the presence of food may alter the absorption kinetics of ethanol. Women achieve higher serum concentrations of ethanol than men after oral administration of equivalent doses. This has been somewhat controversially attributed to increased levels of gastric alcohol dehydrogenase in men [11, 12]. Food also decreases gastric emptying which slows ethanol absorption. The area under the curve for ethanol is lower when food is present rather than on an

empty stomach. This is the same whether the food contains fat or carbohydrates [13, 14].

Distribution

Ethanol has a volume of distribution of approximately 0.6–0.7 L/kg. It distributes with total body water and does not bind to plasma proteins or other tissues. Women have a slightly lower V_d than men likely because the average woman has less water and more fat than the average man [15].

Metabolism

The primary enzymes responsible for the metabolism of ethanol are hepatic alcohol dehydrogenase and aldehyde dehydrogenase (Fig. 1a) and, to a much lesser extent, the cytochrome P450-2E1-dependent ethanol-oxidizing system [16]. Some orally ingested ethanol does not enter the systemic circulation because of first-pass metabolism via gastric ADH. The extent of this first-pass metabolism still remains a point of debate. Some studies have shown significant first-pass metabolism while others did not show as large of a change [17–19]. If ethanol is rapidly passed into the duodenum without food present, gastric first-pass metabolism is eliminated, and higher blood alcohol concentrations are observed [16].

Elimination

The average physiologic range of ethanol elimination is 10–25 mg/dL (2.17–5.43 mmol/L) although there is considerable variability. In those with liver disease or who are malnourished, elimination can be as slow as 8–9 mg/dL (1.74–1.95 mmol/L), while in moderate drinkers 15 mg/dL (3.26 mmol/L) is a good average value. For patients who are binge drinkers or alcoholics, elimination can be as high as 25–35 mg/dL (5.43–7.6 mmol/L) [20].

Women tend to eliminate ethanol more rapidly than men; however, this is unlikely significant

enough to merit gender-specific rates [20, 21]. Ethanol undergoes Michaelis-Menton elimination kinetics at low ethanol levels while at levels greater than 10–20 mg/dL (2.17–4.34 mmol/L) elimination follows a zero-order process [20].

Precautions and Adverse Effects

Ethanol can cause a dose-related decreased level of consciousness, ranging from mild inebriation to coma. Rarely this can result in loss of airway protection and respiratory depression requiring intubation, airway management, and assisted ventilation. Although there are many anecdotal case reports describing hypoglycemia after exposure to ethanol especially in children [22–24], retrospective medical record reviews and case series have questioned the actual incidence of this effect [25–28]. Frequent blood glucose measurement is beneficial in recognizing hypoglycemia, which can be treated with supplemental dextrose as necessary.

In a retrospective review of ethanol therapy in cases of pediatric methanol toxicity, no clinically relevant episodes of hypoglycemia were reported. Some children were reported to be drowsy, but none required any type of airway intervention. Hypotension was rare, and there were no children with ethanol-associated hypothermia or hepatotoxicity [29]. Adverse events were more common in two other studies, mostly involving adults, with central nervous system depression and coma, some requiring intubation, and manifesting hypotension, tachycardia, and, in some cases, agitation [30, 31]. These studies also reported difficulty keeping the serum ethanol level within the desired range, a well-documented problem in cases where ethanol is used therapeutically.

During intravenous administration of ethanol, close observation and reevaluation of the IV site is important to prevent local vein irritation, phlebitis, and extravasation. Gastritis and nausea after exposure to oral ethanol are well described. There is also an increased risk for vomiting after oral administration of therapeutic doses of ethanol in children and other ethanol-naïve patients, given the high concentrations and frequent doses

administered. Although allergic reactions, described as anaphylactoid, after ethanol administration are rare, dermatitis and asthma-associated wheezing have been reported [32].

Ethanol should be used very carefully in pregnancy. 1–2 h after maternal ethanol ingestion, fetal alcohol concentrations reach levels nearly equivalent to maternal levels. Ethanol elimination by the fetus is impaired because of reduced metabolic capacity and reabsorption via amniotic fluid [33]. Both ethanol and fomepizole are Pregnancy Category C (there are no well-controlled studies that have been done in pregnant women; it should be used only if the possible benefit outweighs the possible risk to the unborn baby); however, we would recommend the use of fomepizole as it does not have the same clinical effects expected of ethanol.

Treatment

The toxicity of ethylene glycol and methanol are due primarily to the formation of toxic metabolites. In the presence of sufficient concentrations of ethanol, the metabolism of ethylene glycol and methanol to these toxic metabolites is inhibited as a result of competitive inhibition of alcohol dehydrogenase [1]. Compared with methanol, ethanol has approximately 20 times the affinity for alcohol dehydrogenase. Ethylene glycol has an even weaker affinity for alcohol dehydrogenase than methanol, and its metabolism, like that of methanol, can be effectively blocked by ethanol administration. In clinical practice, serum ethanol concentrations of 100–150 mg/dL (21.7–32.5 mmol/L) are targeted for therapeutic ADH-blockade, although this is an empiric range dating back to early investigations of ethanol as an antidote [34, 35] (Grade III evidence). A serum ethanol concentration of 100 mg/dL (21.7 mmol/L) significantly prolongs the elimination half-life of ethylene glycol and methanol from approximately 4 h and 8 h to approximately 18 h and 52 h, respectively [36, 37].

The indication for ethanol therapy is the same for the initiation of fomepizole in the treatment of methanol or ethylene glycol toxicity. These

indications are discussed in detail in the chapters on Methanol, Ethylene Glycol, and Fomepizole.

The most frequently used biological matrices in which ethanol concentrations are measured are serum, blood, and breath. During therapeutic administration of ethanol for ethylene glycol and methanol poisoning, frequent monitoring (every 1–2 h) of serum ethanol concentration (the most common matrix utilized in hospitals) is mandatory to ensure that concentrations are maintained at greater than 100 mg/dL (>21.7 mmol/L) and to avoid development of toxicity.

Administration

Both intravenous and oral ethanol can be used in the treatment of ethylene glycol and methanol toxicity. Some advantages to intravenous ethanol are complete and rapid absorption, bypass of first-pass metabolism, and avoiding the gastrointestinal upset associated with oral ethanol. A maximum concentration of IV ethanol of 10% is generally recommended and well tolerated. The loading dose of ethanol is usually administered over 30–60 min. Although less-concentrated solutions such as 5% may be helpful in decreasing the risk of venous irritation, fluid overload is also possible due to the large volume required. When oral ethanol is used, it is generally recommended that solutions should be diluted to 20% and administered over 30 min to decrease the risk of gastritis and vomiting. This is particularly important in children and other ethanol-naïve patients.

There are different approaches to the dosing of ethanol. Based on pharmacokinetic parameters, one recommendation has been to use a loading dose of 600 mg/kg (13 mmol/kg or 6 mL/kg of ethyl alcohol [EtOH] 10%) [35, 37, 38]. These authors also recommend maintenance doses of 109 mg/kg/h (2.4 mmol/kg/h or 1.1 mL/kg/h of EtOH 10%). (Grade III recommendation) As ethanol is also dialyzable, doses during hemodialysis of 237 mg/kg/h (5.1 mmol/kg/h or 2.4 mL/kg/h of EtOH 10%) are recommended.

However, because of the variations from ongoing metabolism, many clinicians use larger doses. One approach utilizes an ethanol

loading dose of 700–1000 mg/kg (15.2 mmol/kg to 22 mmol/kg or 7 mL/kg of EtOH 10%). This is followed by a maintenance dose of 60–130 mg/kg/h (2.7–3.3 mmol/kg/h or 1.25–1.5 mL/kg/h of EtOH 10%) for a nonchronic drinker and 100–154 mg/kg/h (2.2–3.4 mmol/kg/h) for more ethanol-tolerant patients. If the patient is also undergoing hemodialysis, the maintenance dose is generally increased to 250–275 mg/kg/h (5.4–6 mmol/kg/h or 2.5–2.75 mL/kg/h of EtOH 10%) [38, 39] (Grade III recommendation).

In the absence of pharmaceutical-grade ethanol, other alcohol sources, such as vodka, can be used for oral ethanol therapy. Vodka, or other 80-proof alcoholic beverage, provides a 40% ethanol solution. An approximate oral ethanol loading dose is 2.5 mL/kg, with maintenance doses from 0.2 to 0.4 mL/kg/h. It is useful to dilute this with juice or another mixer to make it more palatable to ethanol-naïve patients. Nonsedating antiemetics such as ondansetron are recommended for ethanol-associated nausea.

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The influence of insulin on the heart was studied as early as the 1920s [1]. Efficacy of insulin and glucose as a possible antidote for beta-blocker and calcium channel blocker-induced cardiogenic shock was demonstrated by Kerns and Kline in the 1990s. These early animal studies confirmed not only improved hemodynamics but also improved survival over glucagon and epinephrine in xenobiotic-induced myocardial depression. Subsequently, a report of high-dose insulin therapy used as a treatment for drug-induced cardiovascular shock in humans was reported [2–4]. Since then, insulin and dextrose have been used to treat not only calcium channel blocker and beta-blocker overdoses but also polypharmacy overdoses with myocardial depression.

Currently, the only formulation of insulin or glucose demonstrated as an effective antidote for drug-induced cardiovascular shock is intravenous (IV) regular human insulin and dextrose. Therefore, this chapter will not discuss other formulations of insulin or glucose. All references to insulin in this chapter refer to IV regular human insulin, and all references to glucose refer to IV dextrose solutions.

History

In 1921, Dr. Frederick Banting, at the University of Toronto, created a pancreatic extract by isolating “isletin” from pancreatic islet cells. Isletin

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later became known as insulin. Banting first tested his extract in dogs, and then in 1922, insulin was successfully used to treat a 14-year-old patient with diabetes who lay dying in Toronto General Hospital. Insulin was then administered to other children with diabetes and had a phenomenal response in waking children from diabetic coma. Banting was awarded the Nobel Prize in Physiology or Medicine, and the patent for insulin was sold to University of Toronto for one dollar [5].

Insulin's beneficial effects beyond simple control of hyperglycemia soon became apparent, and the use of the drug expanded into the management of critical care issues such as sepsis, heart failure, and cardiac drug toxicity.

Positive inotropic effects of insulin were described as early as 1927 by Visscher et al. [1]. Research in the 1970s went on to examine the effects of glucose, insulin, and potassium (GIK) on myocardial free fatty acid substrate metabolism. These studies demonstrated the ability of high-dose insulin to increase left ventricular function in patients with myocardial infarction/ischemia and to increase cardiac index in patients with cardiac shock following cardiac bypass surgery [6, 7].

Insulin's mechanisms of action in drug-induced cardiovascular shock are complex and not completely understood. However, the three primary suggested mechanisms of action of high-dose insulin in xenobiotic-induced cardiovascular shock that result in increased inotropy are increased myocardial glucose utilization, vasodilation, and calcium signaling. Each of these mechanisms is discussed more in depth below.

Augmentation of myocardial contractility through exogenous administration of supplemental glucose alone has not been shown to be of benefit in experimental models [8]. Under normal conditions the heart uses free fatty acids as its primary source of energy [9]. In times of stress, myocytes and other cells shift to utilization of carbohydrates for their primary cardiac energy source [9]. One example of this is calcium channel antagonist toxicity. Calcium channel antagonists block L-type calcium channels in

myocardial cells, smooth muscle cells, and beta cells resulting in bradycardia, conduction delays, peripheral vasodilation, hypoinsulinemia, hyperglycemia, metabolic acidosis, and shock. Hypoinsulinemia may result in decreased uptake of glucose by myocytes causing a loss of inotropy and decreased peripheral resistance. Exogenous insulin administration increases glucose uptake by myocytes leading to improved inotropy, decreased peripheral vascular resistance, increased lactate uptake by cells, and reversal of acidosis [10–12].

The second mechanism by which high-dose insulin therapy is thought to result in increased inotropy is through peripheral vasodilation. High-dose insulin does not increase mean arterial pressure (MAP) through vasopressor activity. Insulin is actually a vasodilator of the systemic, coronary, and pulmonary vasculature [13]. Vasodilatory effects are due to enhancement of endothelial nitric oxide synthase [13]. In cases of beta antagonist or calcium channel antagonist overdose, significant myocardial depression is observed, resulting in decreased cardiac output and a decrease in MAP. While vasopressors increase MAP, afterload is also increased resulting in increased cardiac workload and oxygen demand. These effects acting on an already struggling heart could result in cardiac arrest. High-dose insulin causes peripheral vasodilation, allowing for increased mechanical efficiency of the heart, increased cardiac output, and an increase in both macrovascular and microvascular perfusion without increasing workload or oxygen demand [1, 3, 10].

The third proposed mechanism for the inotropic effects of high-dose insulin is the result of increased calcium signaling. Insulin helps to facilitate transmembrane calcium influx by accelerating the reverse mode of the sodium/calcium exchanger, resulting in increased inotropy [14]. Calcium is the major intracellular signal required for pyruvate dehydrogenase activation. Inhibition of mitochondrial calcium entry at the sarcolemma and mitochondrial membrane decreases pyruvate dehydrogenase activity. Decreased availability of pyruvate for the Krebs

cycle results in lactate accumulation and metabolic acidosis [4, 15–18].

High-dose insulin also regulates/reduces cytosolic calcium concentrations. Insulin enhances activity of sarcoplasmic–endoplasmic reticulum calcium ATPase, which improves contractility by increasing binding of troponin I and protein C in myofibrils, enhancing excitation coupling [19].

High-dose insulin therapy has multiple other effects which are just beginning to be understood, such as suppression of tumor necrosis factor α , interleukin 6, pro-inflammatory cytokines, and free radical production, all of which contribute to hypotension [20]. Insulin facilitates the release of nitric oxide and regulates interleukins 4 and 10 possibly protecting against apoptosis as well as ischemic and reperfusion injury associated with shock [21]. Insulin's role in increased expression of β 1-adrenoreceptors and intramyocardial calcium-handling genes in human myocardial cells is also being explored [22, 23].

Properties of Regular Human Insulin

Amorphous insulin was the first form made available for clinical use. Further purification afforded crystalline insulin that is now commonly called regular human insulin.

Physical: Recombinant human insulin is an off-white powder.

Regular human insulin is crystalline zinc insulin dissolved in a clear solution.

Chemical: Insulin injection USP is a solution made from crystalline zinc insulin.

Regular human insulin is a 51-residue peptide hormone composed of two amino acid chains covalently linked by disulfide bonds. Recombinant insulin is synthesized by recombinant DNA technology with a molecular formula of $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5807.69 Da. This recombinant human insulin is chemically, physically, and biologically identical to pancreatic human insulin [24–26] [24. Level of Evidence: III] [25. Level of Evidence: II-3] [26. Level of Evidence: II-3].

Pharmacodynamics

Insulin pharmacodynamics refers to the metabolic effect of insulin. The pharmacodynamic effects of IV regular human insulin are significantly different than subcutaneous administration [26] [26. Level of Evidence: II-3].

In insulin overdose, the duration of action is extended and the peak effect delayed [27] [27. Level of Evidence: III]. The reasons for these pharmacodynamic effects include accumulation effect of insulin and extended insulin half-life secondary to insulin receptor saturation with exogenous insulin [28] [28. Level of Evidence: III].

The dosing of insulin when it is used as an antidote for drug-induced cardiovascular shock is significantly different than how it is dosed for treatment of diabetes or diabetic ketoacidosis. Insulin when used as an antidote for drug-induced cardiovascular shock is typically given as a 1 u/kg IV bolus, and then an IV infusion of 1–2 u/kg/h is started and may be titrated up to 10 u/kg/h. Given the significantly higher dosing of insulin when used as an antidote for drug-induced cardiovascular shock, it would be expected that insulin's duration of action and half-life may be much longer than that when administered for diabetic diagnoses.

Pharmacokinetics

Pharmacokinetics of IV Regular Human Insulin

- Onset, 10–15 min [29]
- Peak, 15–30 min
- Duration, 30–60 min

Level of Evidence: II-3

Although recombinant human insulin is chemically, physically, and biologically identical to pancreatic human insulin, the pharmacokinetics of exogenously administered regular human insulin

does differ from endogenous insulin released by the pancreas. The main reason is that the pancreas releases insulin into the portal vein where it undergoes a first-pass effect with more than 50% of released insulin being extracted by the liver. As a result, hepatic exposure to insulin is high, and peripheral (muscle, fat) exposure to insulin is low. On the other hand, exogenously administered insulin is distributed throughout the circulation, exposing the peripheral organs to relatively high concentrations due to its lack of first-pass effect and relatively lower concentrations to the liver [29] [29. Level of Evidence: II-3].

IV bioavailability, 100%

Volume of distribution, 0.15 L/kg:

- The volume of distribution is equal to the volume of the extracellular fluid (i.e., approximately 20% of the body weight.)
- Insulin is present in plasma as a free monomer. It diffuses into tissues and crosses the blood–brain barrier [30] [30. Level of Evidence: II-3].

Protein binding, 5%

Pregnancy category: B

- Studies show that endogenous insulin only crosses the placenta in minimal amounts. Recombinant human insulin is identical to endogenous hormone and would not be expected to produce teratogenic effects.

Excretion in breast milk: endogenous insulin is present in human milk. Insulin orally ingested is degraded in the gastrointestinal tract. No adverse reactions have been associated with infant exposure to insulin through the consumption of human milk.

Elimination half-life, 6 min (in healthy subjects and patients with diabetes)

- Insulin is inactivated by several enzymatic biotransformations: hydrolysis by metalloproteinases

and reduction, i.e., cleavage of disulfide bonds [31] [31. Level of Evidence: II-3].

- Renal insulin elimination is low because after filtration it is reabsorbed by the tubule [31] [31. Level of Evidence: II-3].
- The kidneys and liver account for the majority of insulin degradation. With endogenous release of insulin from the pancreas, approximately 60% is metabolized hepatically and 35–45% renally [32, 33] [32. Level of Evidence: II-3] [33. Level of Evidence: II-3].
- Exogenously administered insulin metabolism is slightly different as it is not delivered directly to the portal vein. Renal degradation accounts for approximately 60% and hepatic metabolism about 30–40% [32, 33] [32. Level of Evidence: II-3] [33. Level of Evidence: II-3].
- Renal impairment will reduce the clearance of insulin and prolong its effect. This decreased clearance is seen with both endogenous and exogenous insulin administration. In general, this decreased clearance is not clinically relevant until renal function is significantly diminished [32, 33] [32. Level of Evidence: II-3] [33. Level of Evidence: II-3].

Cleared by extracorporeal techniques:

- Plasma insulin appears to be removed by hemodialysis [34] [34. Level of Evidence: I].

Contraindications

The major specific contraindication to insulin administration is hypoglycemia.

Adverse Effects

The most significant adverse effect of insulin is hypoglycemia. True allergic reactions and cutaneous reactions are rare [Level of Evidence: III].

Hypoglycemia

Signs of hypoglycemia (nausea, vomiting, sweating, hyperventilation, tachycardia, labile blood pressure, hyperventilation) and neuroglycopenia (abnormal behavior, altered level of consciousness, lethargy, coma, cerebral edema, hypertonia, hyperreflexia, extensor plantar response) may occur [27] [Level of Evidence: III].

Electrolyte Disturbances

Hypokalemia, hypomagnesemia, and hypophosphatemia may occur. Cardiac adverse effects associated with hypokalemia and hypomagnesemia may cause prolonged QTc. Fluid overload with resultant hyponatremia may also occur.

Pharmacokinetics of Dextrose

Dextrose is a rapidly metabolized source of calories and fluids in patients with hypoglycemia or increased needs of carbohydrates. By increasing blood glucose concentration, dextrose may decrease body protein and nitrogen losses, promote glycogen deposition, and decrease or prevent ketosis if sufficient doses are given [35] [Level of Evidence: II-3].

Parentally injected doses of dextrose undergo oxidation to carbon dioxide and water. Dextrose solutions >5% may be irritating if given by peripheral infusion. Solutions above 10% should be given only by central venous catheter [35].

IV bioavailability, 100%

Volume of distribution:

- May vary depending on concentration administered

Onset:

- Immediate

Peak:

- Immediate

Duration of action:

- Unknown

Pregnancy risk category: C

- Animal reproduction studies have not been conducted with dextrose. It is also not known whether dextrose can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dextrose should be given to a pregnant woman only if clearly needed.

Excretion in breast milk:

- It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dextrose injection is administered to a nursing mother.

Metabolism:

- Metabolized to carbon dioxide and water

Elimination half-life:

- Unknown

Cleared by extracorporeal techniques:

- Glucose is removed by hemodialysis [34] [34. Level of Evidence: I].

Pharmacodynamics of Dextrose

Dextrose is a rapidly metabolized source of calories and fluids for patients [35, 36] [(35) [Level of Evidence: II-3] 36. Level of Evidence: II-3]. While increasing blood glucose levels, dextrose may have a protein- and nitrogen-sparing effect on the body while also promoting glycogen deposition and decreasing ketosis. Parentally injected

doses of dextrose are oxidized to carbon dioxide and water. A 5% solution is isotonic and can be administered peripherally. More concentrated dextrose infusions provide increased caloric intake with less fluid volume but are irritating if given peripherally. Solutions above 10% should be given only by central venous catheter.

Contraindications to Dextrose

- Hypersensitivity to corn products
- Intracranial or intraspinal hemorrhage

Precautions with Dextrose

- Concentrated dextrose solutions >10% should be administered via central vein only after suitable dilution.

Adverse Effects with Dextrose

- Parenteral dextrose is hypertonic and may cause phlebitis and thrombosis at the site of injection.
- Significant hyperglycemia and possible hyperosmolar syndrome may result from too rapid administration.

GIK Treatment

Insulin as an antidote has been reported in both human and animals to treat drug-induced cardiovascular shock. A recent systematic review concluded that although low quality, the strongest evidence for pharmaceutical intervention supports high-dose insulin for calcium channel blocker-induced cardiovascular shock [37] [37. Level of Evidence: III].

GIK Administration

Regular human insulin is administered IV. It is strongly recommended that a central line be placed for dextrose administration as

concentrations >10% are extremely irritating to the veins [12, 38, 39, 42] [12. Level of Evidence: III] [38. Level of Evidence: II-3] [39. Level of Evidence: III] [42. Level of Evidence: III]. Also, concentration of administered fluids will likely need to be considered to avoid pulmonary edema.

Dextrose

If blood glucose is <200 mg/dl, administer 25 g of dextrose to adults or 0.25 g/kg for children (given as 10–25% dextrose IV push). Blood sugars should be monitored every 10 min while titrating insulin. Once the insulin infusion and blood glucose concentrations are stabilized, monitor glucose concentrations every 30–60 min. No human studies currently exist to verify the frequency at which blood glucose concentrations should be monitored when using high-dose insulin as an antidote. Therefore the author recommends monitoring blood glucose concentrations every 10 min to avoid any significant or sustained hypoglycemia. In the authors' opinion, glucose levels should be maintained between 100 and 200 mg/dl while insulin is being used as an antidote. Although this blood sugar concentration is higher than what is typically desired for a critical care patient in the intensive care unit, short-term hyperglycemia within this range (100–200 mg/dl) likely has more benefits than risks in this situation allowing for flexibility while administering insulin and decreased incidences of hypoglycemia in the patient. Dextrose infusions should be started to maintain a blood glucose > 100 mg/dL (5.6 mmol/L). Additionally, concentrated dextrose infusions >10% administered through a central line may be required to maintain normal glucose concentrations. No equation exists that can accurately calculate the amount of dextrose a patient will need while receiving high-dose insulin therapy. Variability depends on the patient, the medications taken in overdose, and the amount of insulin administered. However, in an insulin dosing study by Cole et al., the author found that the hypoglycemic effects of high-dose insulin therapy actually saturated in his study; the

animals administered 5 u/kg/h of insulin required more dextrose than the animals that received 10 u/kg/h [40] [40. Level of Evidence: I]. Patients receiving 5–10 u/kg/h doses of insulin may require 150 g or more of dextrose per hour. Administration of this amount of dextrose requires administration of a concentrated dextrose solution through a central line to avoid phlebitis as well as pulmonary edema and fluid overload. The pharmacy should be contacted to help prepare a concentrated dextrose solution. Concentrated dextrose solutions of 50% or greater have been used by the author in this type of situation given through a central line.

Insulin

Administer an insulin bolus of 1 u/kg IV push; then start an IV continuous infusion of regular human insulin at 1–2 u/kg/h. The insulin infusion can be titrated up by 2 u/kg/h every 10 min up to a maximum of 10 u/kg/h if desired cardiac output or clinical improvement is not obtained. In general, no human dosing studies were available at the time this chapter was written for high-dose insulin therapy. Dosing is based off of animal studies and case reports [38, 40] [38. Level of Evidence: II-3] [40. Level of Evidence: I].

In Cole et al.'s dosing study, the maximum dose of insulin studied was 10 u/kg/h based off of prior canine studies by Kerns and Kline [2, 3, 10, 40] [2. Level of Evidence: I] [3. Level of Evidence: I] [10. Level of Evidence: I] [40. Level of Evidence: I]. However Cole et al. did not see a plateau in MAP or CO in this study at a dose of 10 u/kg/h. Therefore the maximum response dose is unknown and may require doses higher than 10 u/kg/h. Engebretsen et al. reported a therapeutic misadventure in which a patient received 23 u/kg/h of insulin by mistake. Upon attempts to decrease the insulin infusion, the patient could not be titrated down to 10 u/kg/h and required a dose of 17 u/kg/h for more than 24 h to treat his toxin-induced cardiac shock [41] [41. Level of Evidence: III].

Potassium

Monitor potassium every 60 min while titrating insulin and dextrose solutions to avoid significant hypokalemia. Once insulin infusions have stabilized, monitor potassium concentrations every 6 h. Supplement potassium if concentrations drop below 2.8–3 mEq/L (2.8–3 mmol/L). Typical ICU guidelines may routinely allow for potassium supplementation when potassium concentrations decrease to less than 3.5 mEq/L. However, in high-dose insulin therapy, potassium is shifted intracellularly and does not reflect a true potassium loss from the body. Therefore aggressive replacement of potassium is not recommended in order to prevent hyperkalemia upon discontinuation of high-dose insulin therapy. Caution should be noted in patients who have bradycardia and a prolonged QTc. These patients may be at increased risk of torsades de pointes. Since potassium plays a crucial role in QTc prolongation and torsades de pointes, the author recommends maintaining potassium concentrations in the normal range (3.5–5 mEq/L) in this case to avoid increased risk of torsades de pointes.

Other

Magnesium and phosphorous concentrations also need to be monitored during high-dose insulin therapy. These electrolytes play an important role with potassium in the body. High-dose insulin therapy may significantly affect potassium concentrations and therefore, these electrolytes need to be monitored as well as potassium.

Goals

Perfusion of essential vascular beds and organs needs to be maintained (assessed not by increased BP or mean arterial pressure alone) [42] [42. Level of Evidence: III]. Instead, if possible, assess by mental status, skin warmth and color, peripheral pulses, urine output, and vital signs.

Insulin's action as an inotrope and a vasodilator typically results in minimal effects on systolic blood pressure. Traditional hemodynamic parameters such as maintaining a mean arterial pressure >60 mmHg, a systolic blood pressure >90 mmHg, and an HR >50 may not be obtainable. Noninvasive cardiac output monitoring, if available, will add significant data to assess the efficacy of HDI on contractility and cardiac output of the heart.

Discontinuing Insulin Dextrose Infusions

Currently there are no evidence-based recommendations on the best way to discontinue insulin and dextrose therapy. The insulin infusion may be titrated down or turned off. It is expected that with the administration of high-doses of insulin, the duration of action and half-life may be extended, and hypoglycemia may occur up to 24 h after the insulin infusion has been stopped [43] [41. Level of Evidence: III].

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Flumazenil (Romazicon®) (US brand names are given here as examples. These may be the same or different in other countries.) is a specific benzodiazepine receptor antagonist that has generated debate regarding its clinical indications since its initial release in the USA in 1991. A major argument against the use of flumazenil in the management of benzodiazepine intoxication is the relatively high safety index (i.e., toxic-to-therapeutic dose ratio) of benzodiazepines, even in cases of overdose. In addition, the anticonvulsant effects of benzodiazepines may be advantageous in individuals simultaneously poisoned with proconvulsant substances, such as tricyclic antidepressants. Another significant concern regarding the clinical use of flumazenil in the emergent management of poisoning is the possibility of precipitating acute withdrawal in individuals with pharmacodynamic tolerance to benzodiazepine receptor agonists. Withdrawal from benzodiazepines is associated with a spectrum of effects, which can include epileptic seizures [1]. These safety concerns have prevented flumazenil from gaining widespread clinical acceptance as a component of the initial pharmacologic management of coma.

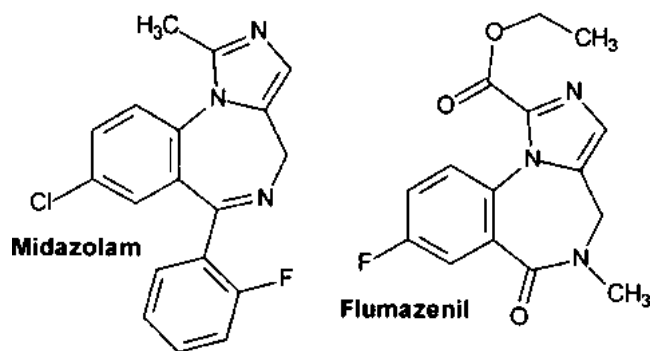
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Pharmacodynamics

Flumazenil is an imidazobenzodiazepine similar in structure to midazolam (Fig. 1). It is formulated for intravenous administration primarily because

Fig. 1 Chemical structures of midazolam and flumazenil



it undergoes extensive first-pass metabolism after oral administration [2]. Flumazenil was discovered during the screening of compounds for effects at the central nervous system benzodiazepine site on the γ -aminobutyric acid (GABA) receptor complexes of the GABA_A subtype. The latter functions as a ligand-gated chloride (Cl^-) channel [3]. Ligand interactions at the benzodiazepine receptor are of three types: agonists (such as benzodiazepines), which bind to the receptor and enhance the GABA_A-mediated Cl^- influx; inverse agonists, such as certain β -carboline derivatives (Fig. 2), which decrease GABA_A-mediated Cl^- cell entry [4]; and competitive antagonists, such as flumazenil, which prevent binding of agonists and inverse agonists in a dose-dependent manner, suppressing both agonist and inverse agonist effects on the GABA_A receptor (Fig. 3) [5].

Flumazenil has been shown to bind the benzodiazepine receptor based on displacement of radiolabeled diazepam and other benzodiazepines in vitro [6]. In this regard, it is a competitive antagonist of the benzodiazepine receptor that prevents the binding of an agonist to the receptor. Flumazenil's antagonist properties were confirmed when it reversed the effects of patients intoxicated with benzodiazepines [7, 8]. In addition, flumazenil also reverses the sedative hypnotic effects of non-benzodiazepine drugs (e.g., zolpidem, zopiclone, zaleplon) that bind to the benzodiazepine receptor [9–11].

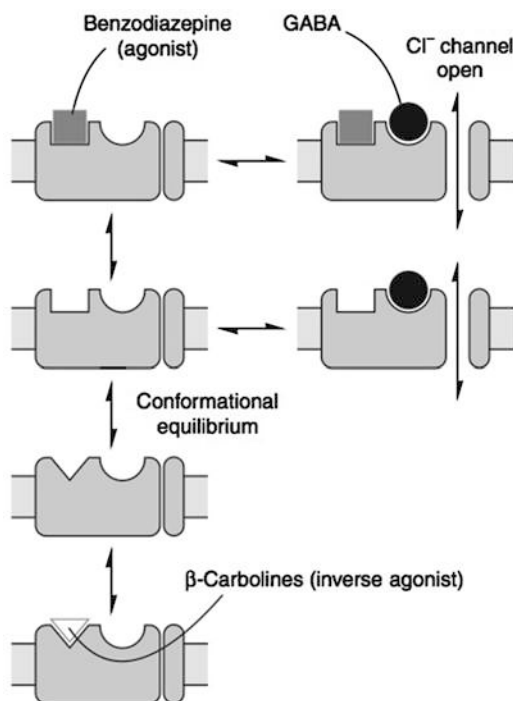


Fig. 2 Model of benzodiazepine/ γ -aminobutyric acid (GABA) receptor interaction. Benzodiazepine agonists (e.g., diazepam) and antagonists (e.g., flumazenil) are believed to bind to a site on the GABA receptor distinct from the GABA-binding site. A conformational equilibrium exists between states in which the benzodiazepine receptor exists in its agonist-binding conformation (above) and in its antagonist-binding conformation (below). In the latter state, the GABA receptor has a greatly reduced affinity for GABA, and as a result the chloride (Cl^-) channel remains closed (From Rang HP, Dale MM, Ritter JM, Gardner P: *Other transmitters and modulators*. In: *Pharmacology*, 4th ed. Philadelphia, Churchill Livingstone, 2001)

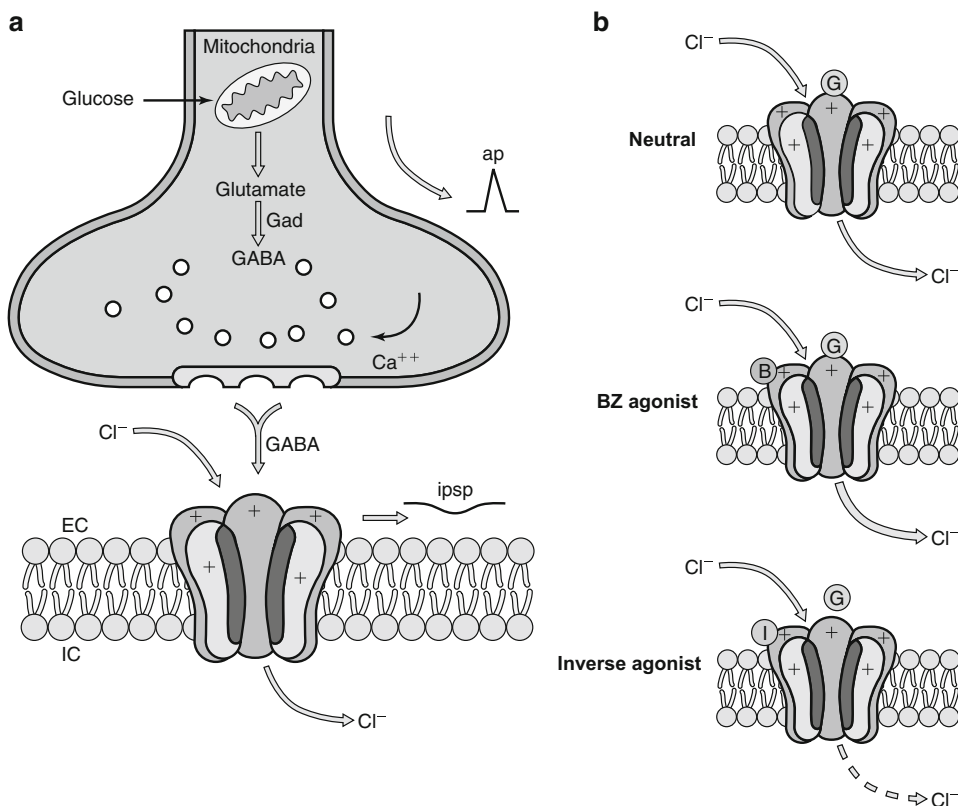


Fig. 3 Idealized model of γ -aminobutyric acid (GABA)-benzodiazepine (BZ)-chloride (Cl^-) channel at axosomatic (postsynaptic) inhibitory synapses. (a) Presynaptic and postsynaptic elements. *ap* action potential, *EC* extracellular, *Gad* glutamic acid decarboxylase, *IC* intracellular, *ipsp* inhibitory postsynaptic potential. (b) GABA-BZ receptor interactions influencing permeability of Cl^- channels. *Neutral*: GABA receptor binds GABA (G) with moderate affinity in the absence of BZ ligand. *BZ agonist*: direct BZ

agonist (b) enhances GABA affinity for its receptor, resulting in maximal Cl^- permeability. *Inverse agonist*: inverse agonists bound to BZ receptor result in poor GABA affinity and markedly reduced Cl^- permeability (From Rech RH: *Drugs to treat anxieties and related disorders*. In Brody TM, Lerner J, Minneman KP [eds]: *Human Pharmacology: Molecular to Clinical*, 3rd ed. St. Louis, Mosby, 1998, p 367)

Acute toxicity studies in rodents revealed oral median lethal dose values of flumazenil of 4300–6000 mg/kg [12]. Evaluation in human volunteers showed no serious toxicity in flumazenil doses of 600 mg orally [13] and 100 mg intravenously [14–16]. Positron emission tomography imaging has shown benzodiazepine receptor occupancy of 50% in human adults after an intravenous flumazenil dose of 1 or 2 mg [17].

Pharmacokinetics

Volume of distribution: 1 L/kg

Protein binding: 50%

Oral bioavailability: 16%

Onset of effects: 1–2 min

Peak effects: 6–10 min

Mechanism of clearance: hepatic metabolism to inactive metabolites

Elimination half-life: 0.8 h

Clinical Use

Initial use of flumazenil was limited to reversal of benzodiazepine effects after conscious sedation and regional or general anesthesia [18–30]. Numerous evaluations in patients undergoing procedural sedation with benzodiazepines have shown effective reversal of sedation with flumazenil. It also has been effective after orthopedic, urologic, and other surgical procedures, including studies that enrolled elderly and other high-risk patients [18–31].

Flumazenil may be used with limited risk in the setting of pure benzodiazepine overdose in a non-benzodiazepine-tolerant individual. In this circumstance, flumazenil may be used to reverse the sedative effects of excessive benzodiazepine doses [5, 7, 8, 15, 32, 33]. Controversy exists regarding flumazenil's reversal of benzodiazepine-induced respiratory depression due to the diversity of findings in the few studies performed [34]. In general, studies of effort-dependent respiratory function, such as vital capacity, have supported improvement with flumazenil [35]. This effect may, however, be due merely to improved conscious control of breathing. Studies of effort-independent respiratory parameters, such as the carbon dioxide respiratory response curve, have not consistently shown improvement after administration of intravenous flumazenil [26, 36]. Overall, flumazenil is not indicated for primary reversal of intravenously administered benzodiazepine-associated respiratory depression [26, 34].

The use of flumazenil in the comatose undifferentiated overdose patient is more controversial. Of particular concern are patients who present after concomitant overdose of benzodiazepines and proconvulsant drugs, such as tricyclic antidepressants. Reports of seizures in temporal association with the empiric use of flumazenil in the management of suspected benzodiazepine overdose emerged early in clinical use [37–43]. Seizures following flumazenil administration are most likely to result from three possible mechanisms: (1) removal of the benzodiazepine-mediated anticonvulsant protection against the proconvulsant effects of other drugs, (2) the

precipitation of acute benzodiazepine withdrawal in the benzodiazepine-tolerant individual, or (3) due to reversal of the anticonvulsant effect of a drug in a patient with a history of seizures [38]. Accordingly, overdose patients considered at risk for flumazenil-associated seizures include patients who are benzodiazepine tolerant, who are treated for seizures or have a seizure disorder, or who have ingested a proconvulsant drug [38].

Given the concern for flumazenil-associated seizures, one retrospective study stratified 35 comatose overdose patients into two groups – one considered “low risk” (i.e., flumazenil use was considered safe and effective) and the other “non-low risk.” The authors defined “low risk” based on the following criteria: no clinical findings consistent with stimulant exposure, no known chronic benzodiazepine use, no known seizure disorder, and no QRS or QT prolongation on ECG. Patients who did not meet these low-risk criteria were categorized as “non-low risk.” In the low-risk group were four patients, and the use of flumazenil resulted in no adverse outcomes; however, 5/31 (16%) of patients in the non-low-risk group had a seizure. Based on the authors' criteria, few comatose patients are likely to meet low-risk criteria for safe flumazenil administration [39].

Clinicians should be aware of the possibility of seizures or acute benzodiazepine withdrawal, manifested by agitation, and peripheral hyperadrenergic signs after flumazenil administration [44–47]. Should seizures occur after flumazenil administration, we recommend initial treatment with standard dosing of benzodiazepines or another GABAergic agent, such as barbiturates. In cases of persistent seizure activity after flumazenil administration that have been treated with standard benzodiazepine or barbiturate dosing, we recommend administration of higher doses of these medications [38].

Administration of flumazenil to overdose patients has been rarely temporally associated with cardiac dysrhythmias [37]. Isolated reported cardiac complications of flumazenil administration have included cardiac arrest [48], ventricular tachycardia [49], and complete heart block [50]. Although there is a temporal association between these reported complications and the

use of flumazenil, other operational criteria used to assess the likelihood of a cause-and-effect relationship were not fulfilled in these cases.

A recent meta-analysis of 13 randomized clinical trials that involved the administration of flumazenil or placebo to patients who had verified or suspected benzodiazepine overdose identified a higher rate of serious adverse effects in patients administered flumazenil. This meta-analysis included studies involving both pure benzodiazepine overdose and polysubstance overdose patients. In this review, 12/498 patients (2.4%) administered flumazenil experienced a serious adverse event, which includes seizures ($n = 3$), arrhythmias ($n = 8$), and hypotension ($n = 1$). In the placebo group, 2/492 patients (<1%) experienced a serious adverse event, both of which were arrhythmias. No patients died. Based on these data, the authors concluded that judicious use of flumazenil is warranted [51].

Despite these studies, other retrospective and prospective studies of undifferentiated acutely poisoned patients who received flumazenil reported a low seizure rate after flumazenil administration [52–56]. While the use of flumazenil in the patient with undiagnosed coma has been reported to obviate the need for further diagnostic studies [52, 54], other data suggest that the use of flumazenil in both pure and mixed benzodiazepine overdoses has not been shown to affect patient outcome, number of procedures, or duration of hospital stay [57] and has also not been shown to be cost-effective [58]. Given the low morbidity and mortality associated with benzodiazepine overdose [59], the benefit gained from flumazenil administration in these patients should be weighed against the potential risk.

The application of flumazenil to clinical settings other than benzodiazepine overdose has also been studied. Lethargy and sedation in patients with hepatic encephalopathy seems to be related, to some extent, to increased levels of endogenous, centrally active benzodiazepine receptor ligands [60] and increased GABAergic tone [61]. Human case reports and studies involving patients with hepatic encephalopathy have reported improved mental status in these patients after the administration of flumazenil [62–65]. The improvement

in mental status after flumazenil administration in these patients is temporary, typically lasting 1–2 h [64, 65]. In a randomized, prospective placebo-controlled study of 527 cirrhotic patients with grade III and IVa hepatic encephalopathy (HE) in which 265 of these patients received flumazenil, 17.5% of those patients with grade III HE and 14.7% of those with grade IVa HE had neurologic improvements compared with 3.8% and 2.7% of the respective HE groups treated with placebo [63]. Administration of flumazenil to a carefully selected group of cirrhotic patients with severe HE may be useful (grade I recommendation), but data are lacking to support the use of flumazenil in all patients with HE. Seizures have not been described following flumazenil use in treatment of hepatic encephalopathy [66]. Flumazenil has also been studied for the potential reversal of ethanol intoxication, and flumazenil administration does not significantly reverse sedation in ethanol-intoxicated patients [67, 68]. Flumazenil has been used to identify those patients undergoing treatment with benzodiazepines for alcohol withdrawal who then develop benzodiazepine-induced delirium; administration of flumazenil to this group improved cognition without resulting in major adverse effects [69].

Contraindications

Absolute contraindications to flumazenil administration include allergies to flumazenil or any components of its formulation. Relative contraindications include the use in patients poisoned by proconvulsant agents, use in patients with benzodiazepine tolerance, and use in patients currently treated for seizures or with a seizure history [38].

Administration

Flumazenil is available as an intravenous preparation. It is formulated as a 5- or 10-mL vial containing 0.1 mg of flumazenil per mL of normal saline and small amounts of methylparaben, propylparaben, edetate disodium, and acetic

acid. Sodium hydroxide, hydrochloric acid, or both are used to adjust the pH of the solution to 7.4.

We recommend that in order to avoid any adverse effects, the smallest effective dose of the drug should be given for reversal of sedation (grade III recommendation). The US Food and Drug Administration approved dosing regimen for reversal of benzodiazepine overdose is 0.2 mg flumazenil administered intravenously over 30 s. If the desired level of consciousness is not attained within 1 min, an additional 0.3 mg may be administered intravenously over 30 s. Repeat doses of 0.5 mg intravenously may be given at 1-min intervals up to a maximum total dose of 3.0 mg. If resedation occurs, additional dosing at 20-min intervals may be given up to a maximum dose of 3 mg in 1 h. For reversal of conscious sedation, flumazenil may be administered at a dose of 0.2 mg intravenously over 15 s. If reversal of sedation does not occur, after 1 min an additional 0.2 mg may be given, and repeated each minute, up to a total dose of 1.0 mg [70]. Following administration and effective use, patients should be monitored for resedation, which can occur 20–120 min after flumazenil administration. If needed, a continuous infusion can be given at 0.3–0.5 mg/h [53].

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Folic acid is a water-soluble B-complex vitamin essential for nucleoprotein synthesis, which is necessary for normal growth and development. It traditionally is administered for the treatment of megaloblastic anemias, as for a vitamin supplement or as food fortification due its ability to reduce fetal neural tube defects. Medical toxicologists use folic and folinic acid in the treatment of drug-induced toxicity due to folic acid antagonists and methanol. The focus of this chapter is the use of folic and folinic acids as antidotes.

History of Use

Research in anemias in the early to mid-twentieth century demonstrated that extracts of crude liver had hematopoietic properties and could be used to treat macrocytic anemia [1]. These observations led to the discovery of cyanocobalamin (vitamin B12) and folic acid (vitamin B9), both water-soluble vitamins necessary for the maturation of erythrocytes [2]. Folic acid was first isolated from spinach in the early 1940s and received its name from the word foliage (dark green leaf). Common dietary sources include green leafy vegetables, liver, beans, peas, asparagus, beets, broccoli, and citrus fruits. Subsequent work demonstrated that dietary folate is not metabolically active, but must be converted in vivo to the active tetrahydrofolate (THF) or folinic acid (5-formyl THF) [3].

Folic acid is recognized as a necessary cofactor not only for hematopoiesis but also for normal

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growth and development. Periconceptional treatment with multivitamins containing folic acid has reduced the incidence of babies born with neural tube defects, such as spina bifida, encephalocele, and anencephaly [4, 5]. In the United States, the Food and Drug Administration mandated the fortification of enriched grain products with folic acid by 1998, and birth prevalence of neural tube defects is reduced with food fortification of 140 mcg of folic acid per 100 g of grain (approximately 100 mcg to average daily diet) [6]. Most recent data demonstrates approximately 1,326 births which occur annually in the United States without neural tube defects which would otherwise have been affected without this mandate [7].

Folic acid may indeed have non-dietary benefits. Studies from Bangladesh propose folic acid as a treatment for chronic arsenic toxicity. It is thought folic acid administration increases methylation of arsenic, leading to increased arsenic clearance from solid organs in patients who are folic acid deficient and who have chronic arsenic toxicity [8–10]. In addition, folic acid may have a role in preventing bone growth defects in long-term therapeutic methotrexate treatment in children [11, 12].

The ability of leucovorin (folinic acid) to attenuate the toxicity of high-dose methotrexate therapy was first demonstrated in mice in the 1960s [13]. The concept of “leucovorin rescue” is to take advantage of the cytotoxicity of high-dose methotrexate against malignant cells and spare the normal cells from toxic effects [13, 14]. This is discussed in more detail in ► Chap. 60, “Methotrexate.” Leucovorin is also used for the treatment of toxicity from other folate antagonists (trimethoprim, pyrimethamine), but two trials found no benefit, and possibly worse outcomes, in patients with HIV-associated infections [15, 16]. Case reports showing possible benefit of leucovorin treatment in vincristine toxicity have also been published [17, 18]. However, other studies have shown no benefit [19–21].

Commercially available folic acid (pteroylmonoglutamic acid) is prepared synthetically and is used in vitamin supplements (alone or in multivitamin preparations) and in food fortification. Commercial products containing more than

0.4 mg (or 0.8 mg for prenatal use) require a prescription in the United States, as does the parenteral formulation. Folic acid is used in the treatment of megaloblastic and macrocytic anemias that result from folate deficiency.

Folinic acid is commercially available as the calcium salt (leucovorin), and it is marketed primarily as an antidote for the hematologic toxicity of folic acid antagonists such as methotrexate, trimethoprim, or pyrimethamine.

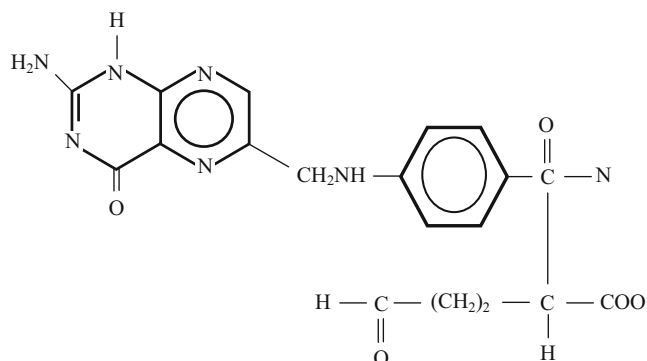
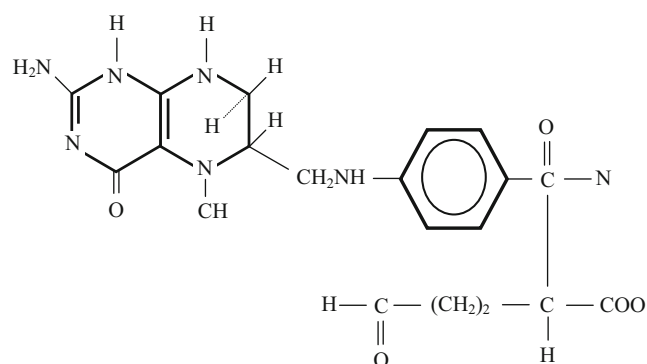
Properties

The term *folic acid* refers to dihydrofolic acid, a B-complex vitamin that in pure form appears as a yellow-orange crystalline powder. It is slightly soluble in water, soluble in dilute alkaline solutions, and insoluble in alcohol. The pharmaceutical folic acid products are prepared synthetically and consist of a central *para*-aminobenzoic acid molecule which is linked to a pteridine ring on one end and a glutamate molecule on the other end (Fig. 1). The molecular formula of folic acid is $C_{18}H_{19}N_7O_6$ (molecular weight, 441.4 g/mol). It is heat sensitive and decomposes rapidly in the presence of light. Dietary folates occur naturally as polyglutamates and must be hydrolyzed (reduced) before absorption [14].

Folinic acid (5-formyltetrahydrofolic acid) is the highly water-soluble product of the reduction of folic acid by the enzyme dihydrofolate reductase (DHFR) (Fig. 2). Its molecular formula is $C_{19}H_{22}N_7O_7$ (molecular weight, 473.4 g/mol). It is commercially available as the calcium salt (leucovorin), a 50% racemic mixture of the *d* and *l* isomers. Only the *l*-isomer (*l*-folinic acid or citrovorum factor) is metabolically active [14].

Pharmacodynamics

Folic acid is an essential vitamin necessary for both nucleoprotein synthesis and the maintenance of normal erythropoiesis (Fig. 3). Folic acid itself is not metabolically active, but rather is activated by reduction and catalyzed by DHFR to 5-methyltetrahydrofolic acid and other

Fig. 1 Chemical structure of folic acid**Fig. 2** Chemical structure of folinic acid

tetrahydrofolate derivatives. Each of the reduced folate congeners can acquire 1-carbon moieties which can be donated in the biosynthesis of nucleic acids, amino acids, proteins, or lipids. Specific reactions (and the specific congener cofactor) in amino acid metabolism which require reduced folic acid coenzymes include the metabolism of homocysteine to methionine (5-methyltetrahydrofolate), the formation of glutamic acid from histidine (tetrahydrofolic acid), and the interconversion of glycine and serine (tetrahydrofolic acid). The methylation of deoxyuridylate to thymidylate, a critical step in the synthesis of DNA, uses 5,10-methylenetetrahydrofolic acid [14]. In folic acid-deficient patients, or patients with inhibited DHFR, a futile cycle of faulty DNA replication occurs leading to clinical effects such as megaloblastic anemias.

Folic acid (as tetrahydrofolate and 10-formyltetrahydrofolate) is also a cofactor necessary for the metabolism of formic acid. Methanol poisoning results in the accumulation of

formic acid in humans. Plasma formic acid concentrations have been shown both in animal models and human case series to correspond closely to the development of metabolic acidosis seen after methanol poisoning [22–26]. The development of metabolic acidosis and depletion of serum bicarbonate, which coincides with the accumulation of formic acid following methanol poisoning, are unique to primates. Other species, such as rats, do not accumulate formic acid and subsequently do not develop metabolic acidosis because of species-specific differences in rates of formic acid oxidation to carbon dioxide, a folate-dependent process [27]. Rats tend to have very high folate stores. The rate of formic acid metabolism and subsequent resolution of metabolic acidosis are decreased during states of folic acid deficiency and increased with folic or folinic acid supplementation in primates [28]. Folic or folinic acid therapy is therefore a component of the treatment of methanol toxicity [29]. This is discussed in greater detail in ► [Chap. 88, “Methanol and Formaldehyde.”](#)

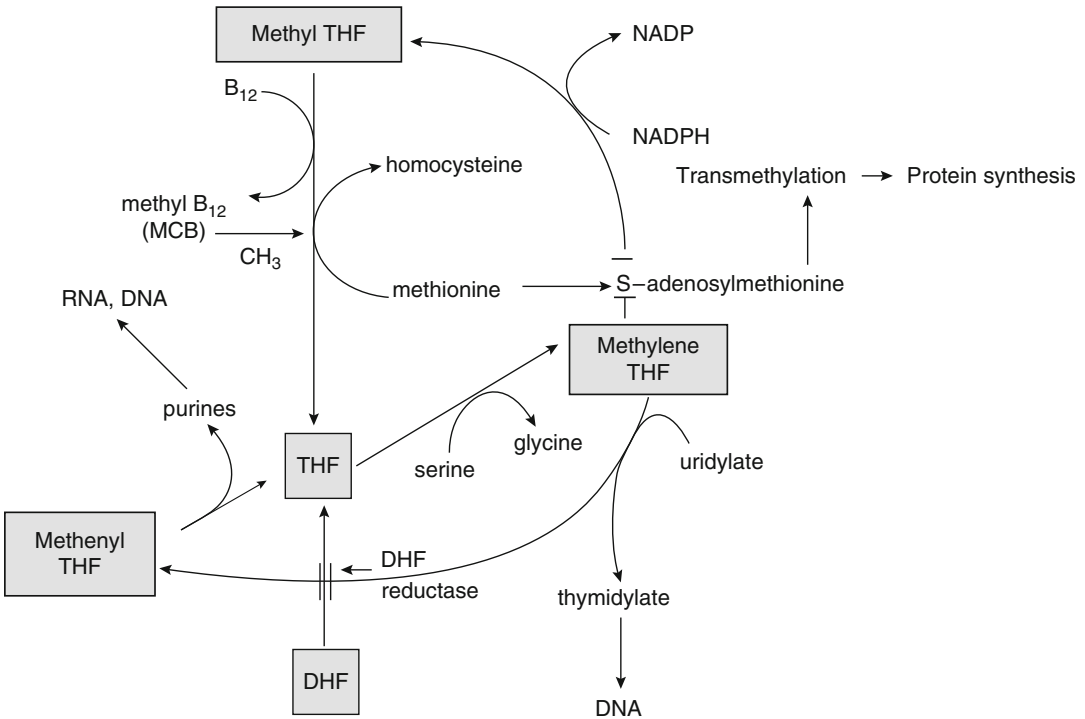


Fig. 3 Folate metabolism. *DHF* folic acid, *NADP* nicotinamide-adenine dinucleotide phosphate, *NADPH* nicotinamide-adenine dinucleotide phosphate, reduced form, *THF* folinic acid (From Ballen KK: Drugs to treat

anemia. In Brody TM, Lamer J, Minneman KP [eds]: Human Pharmacology: Molecular to Clinical, 3rd ed. St. Louis, Mosby, 1998, p 892. – with permission)

Folinic acid is also used in the treatment of methotrexate toxicity [30, 31]. Methotrexate competitively inhibits DHFR and reduces folate formation, which inhibits the biosynthesis of nucleic acids, amino acids, proteins, and lipids (Fig. 4). Clinically, methotrexate toxicity results in a triad of mucositis, renal failure, and myelosuppression [32]. Gastrointestinal signs and symptoms may be pronounced and consist of stomatitis, pharyngitis, anorexia, nausea, emesis, diarrhea, gastrointestinal hemorrhage, and hepatotoxicity. Pancytopenia can develop and may lead to life-threatening bleeding disorders, anemia, and sepsis. Nephrotoxicity can result in oliguria, azotemia, and acute renal failure. This nephrotoxicity may exacerbate systemic toxicity since methotrexate is primarily

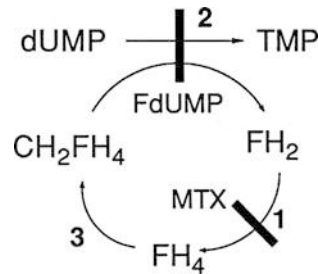


Fig. 4 Sites of action of methotrexate (*MTX*) and the fluoropyrimidine antimetabolite fluorodeoxyuridylate (*FdUMP*): (1) *DHFR* dihydrofolate reductase, (2) *TS* thymidylate synthase, (3) *SHM* serine hydroxymethylase, *FH₂* dihydrofolate, *FH₄* tetrahydrofolate, *CH₂FH₄* *N*⁵,*N*¹⁰-methylenetetrahydrofolate (From Bertino JR: Antineoplastic drugs. In Smith CM, Reynard CM [eds]: Textbook of Pharmacology. Philadelphia, WB Saunders, 1992, p 944. – with permission)

Table 1 Summary of pharmacokinetic parameters

	Folic acid	Folinic acid
Absorption	90–100% (synthetic)	97% of 25 mg; 37% of 100 mg
Time to peak serum concentration	30–60 min	1–2 h
Normal serum concentration (total folate)	5–15 ng/ml	
Normal RBC concentration (total folate)	175–316 ng/ml	
Metabolite(s)	5-methyltetrahydrofolate (active)	5-methyltetrahydrofolate (active) L-formyltetrahydrofolate (active) D-formyltetrahydrofolate (inactive)
Excretion (total folate)	Via urine as metabolites Generally complete by 24 h	

eliminated renally. The management of methotrexate toxicity, which is discussed in detail in ► Chap. 60, “Methotrexate,” focuses on administration of folinic acid (leucovorin). Folinic acid must be administered to allow purine and subsequent DNA synthesis to resume. Folic acid administration is not effective because of the methotrexate-induced inhibition of DHFR. Following methotrexate poisoning, intracellular inhibition of DHFR may persist even after methotrexate concentrations are no longer detectable in blood. Most recommendations call for folinic acid administration until signs of systemic toxicity resolve and methotrexate levels are $<0.1 \mu\text{mol/L}$ if methotrexate is being administered for cancer and $<0.01 \mu\text{mol/L}$ if methotrexate is not being administered for cancer (grade III recommendation) [14, 33]. Theoretically folinic acid rescue can also be employed when toxicity occurs from other weaker DHFR inhibitors such as trimethoprim, trimetrexate, pentamidine, and pyrimethamine.

Pharmacokinetics

Reduced dietary folate and pharmaceutical folic acid are absorbed rapidly from the proximal small intestine, including in cases of preexisting malabsorption syndromes. Absorbed folic acid is methylated rapidly by DHFR to active tetrahydrofolate metabolites, including 5-methyltetrahydrofolate, the primary transport and storage form of folate. The active tetrahydrofolates are distributed throughout the body, with highest concentrations

found in the liver (approximately 50% of body stores) and in the cerebrospinal fluid. Urinary recovery of folate is dose-dependent, with only trace amounts of folate found after low doses ($<1 \text{ mg}$) and 90% of folate found in urine after a dose of 15 mg. Excretion is generally complete within 24 h [34].

In contrast to folic acid, leucovorin does not require reduction (activation) and is converted easily to other tetrahydrofolate derivatives. The absorption of leucovorin administered orally becomes saturated with doses greater than 25 mg, making bioavailability dose limited. The *l*-isomer of leucovorin is converted more rapidly to 5-methyltetrahydrofolate when administered orally than when injected. In addition, oral and parenteral doses of leucovorin result in different kinetic profiles for the various metabolites, but these differences are not known to affect efficacy [14, 35]. The inactive *d*-isomer is excreted renally as unchanged drug. The various reduced serum folate metabolites are removed by hemodialysis [14]. Table 1 summarizes the pharmacokinetics of folic and folinic acids.

Special Populations

Neonatal Patients

Recommended dietary allowances of folate are 65 mcg/day and 80 mcg/day for infants 0–6 months and 6–12 months of age, respectively [36]. Folate is distributed in breast milk, and

infant requirements should be met if the mother is healthy and has adequate folic acid intake [34]. There is no published experience with the use of folate as an antidote in neonates, but there should be no reason not to administer folate if necessary in this population.

Pediatric Patients

Recommended dietary allowances of folate are 150–400 mcg/day for children 1–18 years old [36]. There are no special dosing precautions in children who require emergent leucovorin therapy for methotrexate toxicity.

Pregnant Patients

Dietary requirements of folate are highest in pregnant women, particularly those with a history of previous pregnancies complicated by infants with neural tube defects [4, 6]. The recommended dietary allowance in pregnant women is 600 mcg/day [36]. Theoretically, treatment with folate as an antidote for drug toxicity should be particularly aggressive in these patients.

Alcoholic Patients

Malnourished alcoholic patients may have relative deficiencies of all B vitamins, including folic acid [36, 37].

Contraindications

Folic or folinic acid preparations should not be administered to patients with previous hypersensitivity reactions unless clinical circumstances justify the risk. Folic acid and leucovorin should be administered with extreme caution to patients with undifferentiated anemia as folate alleviates hematologic, but not neurologic complications associated with pernicious anemia due to vitamin B₁₂ deficiency [34, 38].

Precautions

Rare cases of allergic reactions to oral and parenteral folic acid have been reported. Clinical manifestations have included erythema, pruritus, rash, and bronchospasm [34]. No deaths have been reported.

Intravenous leucovorin infusions should not exceed 160 mg/min because of the calcium concentration of the solution [38]. Folic acid for injection contains benzyl alcohol as a preservative and should be administered with caution to neonates because a potentially fatal “gasping syndrome” has been associated with benzyl alcohol administration in this age group [39].

Treatment using high-dose methotrexate with leucovorin rescue therapy is best administered only by physicians who are experienced in cancer chemotherapy. Leucovorin may enhance the toxicity of 5-fluorouracil by causing increased inhibition of thymidylate synthase (Fig. 4). In addition, in patients diagnosed with a high-grade malignancy such as a blast crisis from acute leukemia, the disease process may be accelerated if folic or folinic acid alone is administered without antineoplastic therapy [14]. When administering leucovorin rescue following severe overdose, urinary alkalinization is indicated to prevent accumulation of methotrexate in the kidney [33].

Drug Interactions

Several antiepileptic drugs (AEDs), specifically phenytoin, phenobarbital, primidone, and carbamazepine, may result in a lowering of erythrocyte folic acid concentrations. Phenytoin has been the most extensively studied AED demonstrating this interaction, with reports of abnormally low erythrocyte folic acid concentrations in 25% of patients [40, 41]. Conversely, reports of oral folic acid therapy causing a decrease in serum phenytoin concentrations with subsequent breakthrough seizures have been published [41, 42]. Monitoring of AED drug serum concentrations is indicated in patients who subsequently receive folic or folinic acid supplementation.

Adverse Effects

Folic acid administered orally or parenterally is generally well tolerated. Repeated high oral doses (>15 mg/day) may cause nausea, abdominal pain, anorexia, or flatulence. Central nervous system effects associated with high oral doses include irritability, depression, impaired judgment, difficulty in concentration, and altered sleep [34]. Adverse consequences related to folate therapy have not been reported in patients treated for acute methanol poisoning.

Administration

There are no controlled data evaluating the dose and administration of leucovorin calcium and folic acid for acute poisoning of methotrexate and methanol, respectively; however, the selected doses should be administered intravenously in these patients using the guidelines recommended in the methanol and formaldehyde and the Methotrexate chapters.

Folic acid for injection (5 mg/mL) should be diluted with 49 mL of sterile water for injection to a final concentration of 0.1 mg/mL of folic acid and administered by injection over 30 min. Leucovorin calcium powder, after reconstitution with sterile water for injection, should be infused at a rate not exceeding 160 mg/min due to the calcium content of the leucovorin solution [38]. Intrathecal leucovorin is contraindicated due to the calcium content, and it is a neurosurgical emergency if it occurs [33, 43].

Dosing Recommendations in Toxicity

Clinical guidelines recommend that patients with signs of possible methanol poisoning (lethargy, acidosis, and visual disturbances) should be treated with intravenous leucovorin 1 mg/kg up to a maximum dose of 50 mg as soon as possible over 30–60 min, and then the same dose every 4–6 h for six doses, even if the patient's clinical signs resolve [29]. In patients undergoing

hemodialysis, a dose should be given at the conclusion of each dialysis session.

There are case reports of leucovorin therapy for treatment of acute methotrexate ingestion in children [44–46]. The appropriate pediatric dosing of leucovorin is given in ► Chap. 60, “Methotrexate.” Only leucovorin, not folic acid, is effective for methotrexate toxicity or rescue treatment.

For acute intoxication due to trimethoprim or pyrimethamine, 5–15 mg/day of folic acid may be administered orally or parenterally [16, 38].

Summary

- Folic acid or leucovorin is a potential adjunct in the treatment of methanol toxicity.
- Leucovorin rescue (not folic acid) is used in the treatment of methotrexate toxicity.
- If leucovorin is inadvertently administered intrathecally, it is a neurosurgical emergency due to the calcium content.
- Leucovorin should be administered over 10–15 min because of the calcium content.

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Fomepizole is the generic drug name for the chemical 4-methylpyrazole (4-MP) now widely available in Europe and North America for the treatment of methanol and ethylene glycol poisoning. It is a potent inhibitor of alcohol dehydrogenase (ADH), with an affinity more than 1000 times that of the toxic alcohols [1]. Fomepizole has demonstrated efficacy *in vivo* against the conversion of methanol and ethylene glycol to their toxic metabolites in animal models [2, 3], where it reversed an already-developed metabolite accumulation and severe metabolic acidosis without dialysis. Because of its high safety profile and ease of use in human patients, fomepizole has rapidly replaced ethanol for ADH-inhibitory therapy in methanol and ethylene glycol poisoning [4]. Fomepizole may also have clinical utility in treating similar intoxications, such as those of glycol ethers, diethylene glycol, and propylene glycol [5–7], as well as in ethanol-disulfiram interactions [8].

Fomepizole was originally developed in Sweden in the late 1960s as one of a series of ADH inhibitors with the potential goal of treating alcohol-related pathologies [1, 9, 10]. In a 1969 paper, in which the chemical 4-MP was shown to be a powerful competitive inhibitor of human liver ADH *in vitro* [1], Li et al. suggested that fomepizole might serve as a clinically useful agent for treating methanol and ethylene glycol poisoning. Subsequently, 4-MP was shown to be useful in the treatment of methanol toxicity in monkeys by McMartin et al. [2], by rapidly reversing the formate accumulation and severe metabolic acidosis [11]. It also reversed ocular signs associated with methanol toxicity, such as the decreased b-wave of the electroretinogram [12]. 4-Methylpyrazole was first shown to be effective at reversing the toxicity of lethal doses of ethylene glycol in monkeys in 1977 [3]. In ethylene glycol-poisoned dogs, a comparison of 4-MP and ethanol treatment was conducted [13]. Although both inhibitors decreased the metabolism of ethylene glycol similarly, fomepizole was superior in clinical usefulness in that ethanol produced a greater degree of CNS depression. Additionally, IV fluid therapy was necessary to maintain hydration in the

ethanol-treated animals. Fomepizole was subsequently confirmed to be therapeutically effective as an antidote in veterinary medicine [14].

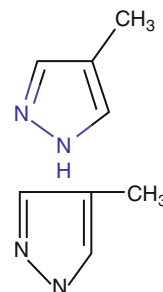
Phase I clinical studies of the safety and metabolism of 4-MP in human volunteers have been published [15–18]. Initial case reports of its use in the treatment of ethylene glycol poisoning appeared in 1987 and 1988 [19, 20] and of its use in methanol poisoning appeared in 1997 [21]. Subsequently, a multicenter prospective clinical trial (Phase II/III) was conducted in the USA for the treatment of ethylene glycol [22] and of methanol [23] poisonings. Based on these trials, fomepizole was approved by the US Food and Drug Administration (FDA) for the treatment of ethylene glycol poisoning in 1997 and treatment of methanol poisoning in 2000. Currently, in most of the developed world fomepizole is available for treatment of methanol or ethylene glycol poisoning. It was accepted on the WHO List of Essential Medicines in September 2013 [24], which will likely increase its availability throughout the world.

Properties

Chemical

In the USA, fomepizole is the parenteral preparation of the free-base 4-methylpyrazole with formula $C_4H_6N_2$ (see Fig. 1) and molecular weight of 82.1 g/mol. The free-base form is soluble in both water and ethanol. Fomepizole exists as the hydrochloride salt formulation in Europe and elsewhere.

Fig. 1 Chemical structure of fomepizole



Physical

4-MP base is stable in light and at 4 °C.

Melting point: 16 °C.

Boiling point: 99 °C.

Density: 0.993 g/mL.

λ max: 219 nm.

The parenteral preparation contains 1.5 g per vial and is a slightly yellow liquid that may solidify at room temperature.

Pharmacodynamics

Mechanism of Action

Fomepizole forms a ternary complex with ADH and its coenzyme NAD^+ , thereby competitively inhibiting formation of the enzyme complex with alcohols. The inhibitory constants for fomepizole in vitro with liver ADH from rat, monkey, and human are reported as 1.0, 7.5, and 0.2 μM , respectively [1, 25, 26]. Fomepizole also inhibits the metabolism of methanol by human ADH in vitro [27]. Its initial metabolite 4-hydroxymethylpyrazole (4-OHMP) is also an inhibitor, but is 66-fold less potent, while its secondary metabolite 4-carboxypyrazole (4-CP) has no ADH-inhibitory activity. The affinity of fomepizole for ADH is about 500–1000 times that of ethanol [1, 25], thus about 5000–10,000 times that of methanol or ethylene glycol [27]. Hence, fomepizole substantially competes with either methanol or ethylene glycol, thereby reducing their metabolism by ADH.

In monkeys, fomepizole at 20–50 mg/kg markedly inhibits methanol metabolism [2, 28], thereby eliminating formate accumulation. Studies with 5–15 mg/kg showed that the minimal plasma fomepizole concentration necessary to prevent formate accumulation was 10 $\mu\text{mol/L}$ [28]. In dogs, doses of 5–20 mg/kg were shown to inhibit ethylene glycol metabolism in vivo [13]. In the clinical trials, fomepizole was confirmed to inhibit ethylene glycol elimination in humans in vivo [29]. Subsequent case reports indicate that fomepizole increases the elimination half-life of methanol and ethylene glycol [30, 31].

Other Effects

Acute administration of fomepizole inhibits rat liver cytochrome P-450 activity, especially the isozyme CYP 2E1 (which metabolizes ethanol, acetaminophen, and nitrosamines), however, at much higher doses (100 mg/kg) than necessary to inhibit ADH [32, 33]. The K_i for this inhibition is about 0.5–1 mM or about 1000 times higher than that for liver ADH. Fomepizole inhibits the clearance of P-450-related substrates such as antipyrine in rats [34]. Repeated administration of fomepizole over several days can induce total hepatic cytochrome P-450 activity in rats [35]. Although not all CYP isozymes have been examined, fomepizole can induce CYP 2E1 as well as CYP 2B1/2B2 in rats [36]. As such, fomepizole can increase the oxidation of several different classes of drugs in rats [37], as well as inducing its own metabolism in humans [17, 38]. Other than the study showing auto-induction in humans [38], there are no published studies on interactions of fomepizole on CYP activity or on drug interactions with specific drugs in humans.

Other actions of fomepizole that may be important include its ability to scavenge hydroxyl free radicals [39], to block the disulfiram-ethanol reactions [8], and to protect against the gastric lesions induced by high concentrations of ethanol, probably due to the ability of fomepizole to decrease lipid peroxidation [40].

Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination

The pharmacokinetic profile of fomepizole is well characterized in animals and humans. Oral fomepizole is rapidly and completely absorbed orally in humans, with doses from 10 to 100 mg/kg producing C_{max} within 2 h and a bioavailability of 1 [16, 38]. Fomepizole is rapidly distributed following IV administration in humans to total body water, with a volume of distribution from 0.59 to 0.74 L/kg. In humans given

equivalent doses of fomepizole either intravenously (IV) or orally [38, 41], plasma fomepizole elimination curves are identical after 30 min, indicating its rapid absorption and distribution. These results suggest that, although fomepizole is marketed as an IV formulation, it should be equally effective if given orally. In dogs, the plasma protein binding of fomepizole is reported to be very low [42]. The renal clearance of unchanged fomepizole is quite low, at about 1 mL/min in human volunteers [16]. Total urinary excretion of fomepizole is only about 3% of the dose in humans and only 1% at similar dose levels in rats [16, 43]. Hence, fomepizole is primarily metabolically eliminated. Fomepizole is metabolized primarily by oxidation to 4-OHMP and then to 4-carboxypyrazole, the latter of which represents > 50% of the dose that is excreted in the urine of humans in 48 h [38]. A minor metabolic pathway appears in rodents to be formation of an N-glucuronide conjugate of fomepizole [44].

Elimination Kinetics

At therapeutic doses (i.e., those producing blood fomepizole concentrations greater than 10 $\mu\text{mol/L}$), fomepizole is eliminated by saturation or nonlinear kinetics. Mayersohn et al. [42] showed that IV doses of 1 and 10 mg/kg in dogs produce a downward curvature of the log-linear plot and an AUC ratio significantly greater than the dose ratio, two indications of saturation kinetics. The apparent zero-order elimination rate at 10 mg/kg was 5 $\mu\text{mol/L/h}$ and an estimate of the Michaelis constant (K_m) was 6 $\mu\text{mol/L}$. In human volunteers, elimination of fomepizole after a single IV dose (5 mg/kg) showed saturation kinetics, with a zero-order rate of 4.2 $\mu\text{mol/L/h}$ and an apparent K_m of about 2.5 $\mu\text{mol/L}$ and V_{max} of 4.2–6.5 $\mu\text{mol/kg/h}$ [18]. Few data exist on fomepizole kinetics in patients being treated for methanol or ethylene glycol poisoning. Nonlinear elimination kinetics have been observed in a methanol-poisoned patient treated with fomepizole (IV, 15 mg/kg) [45] and in an ethylene glycol-poisoned patient (IV, two doses, 8 and 16 mg/kg) [46], with zero-order elimination

rates of 16.9 $\mu\text{mol/kg/h}$ and 7.0 $\mu\text{mol/kg/h}$, respectively, similar to those in the human volunteer studies.

The pharmacokinetic profile of fomepizole after multiple doses such as those used therapeutically has been described in 15 healthy human subjects [38]. Three groups of five subjects were administered oral doses of fomepizole as follows: (1) loading dose of 10 mg/kg, followed by maintenance doses of 3 mg/kg every 12 h up to 96 h, (2) doses of 15 mg/kg plus 5 mg/kg/12 h up to 96 h, and (3) 10 mg/kg plus 5 mg/kg/12 h up to 36 h, then 10 mg/kg/12 h up to 96 h. This multiple-dose study showed that plasma fomepizole concentrations were relatively constant for 36–50 h in groups 1 and 2, after which time the levels markedly decreased. By comparison, the increase in supplemental doses of fomepizole at 36 h in group 3 subjects was sufficient to maintain plasma concentrations of fomepizole within the therapeutic range for 5 days. The elimination rate of fomepizole increased two to threefold within 3 days of multiple dosing, suggesting that plasma levels were unable to be maintained constant in groups 1 and 2 due to the increased fomepizole elimination with repeated dosing. This increase was associated with enhanced urinary excretion of 4-carboxypyrazole, suggesting that elimination of fomepizole increased because of auto-induction of its metabolism. The increase in doses of fomepizole at 36–48 h to overcome the increased elimination and to maintain therapeutic fomepizole concentrations supports the current treatment regimen of increasing the fomepizole dose at 48 h (i.e., typically after the fourth dose).

Some alcohols appear to decrease the elimination of fomepizole, suggesting an interesting mutual inhibition of metabolism. In rats, blood ethanol levels in the range of 350 mg/dL (76 mmol/L) decreased the rate of elimination of fomepizole by 50% [43]. In human volunteers, blood ethanol levels from 50 to 150 mg/dL (11–33 mmol/L) also decreased fomepizole elimination by about 50% [18]. Ethanol did not alter the volume of distribution of fomepizole or the urinary excretion of unchanged fomepizole,

though it did decrease the urinary excretion of 4-CP [18]. These data indicate that ethanol inhibits some step in the conversion of fomepizole to 4-CP. In monkeys, high doses of methanol (2–3 g/kg) increased the rate of fomepizole elimination by 25% [28]. In humans, one could expect that the presence of ethanol or methanol (possibly ethylene glycol, but not studied) will slow the rate of fomepizole elimination because of this interaction.

Dialysis Kinetics

Studies in pigs have demonstrated that fomepizole is readily removed by hemodialysis, with a dialysance of 56 mL/min, similar to that of urea (51 mL/min) [47]. About 20% of the dose was removed during a 4 h dialysis run. Similar dialysis clearance rates have been reported in two ethylene glycol-poisoned patients (52 and 80 mL/min), with somewhat higher rates in two other patients (117 and 127 mL/min) [48, 49]. The extraction rate of fomepizole during intermittent hemodialysis was reported to be 0.78 and 0.71 in two patients [49]. In an unpublished case of ethylene glycol poisoning treated initially with an intermittent, and later with a continuous dialysis modality, the extraction rate of fomepizole was 0.74 during intermittent hemodialysis (HD) and 0.08 during continuous veno-veno HD, indicating that intermittent HD is likely to extract greater amounts of fomepizole than continuous modalities. These studies demonstrate the need to replace the fomepizole that is lost when hemodialysis is conducted on fomepizole-treated patients (see dosing guidelines below).

Clinical Use

We have recently suggested updated treatment criteria for the use of fomepizole for methanol or ethylene glycol poisonings (see Table 1) [50] (Grade III recommendation). The cutoff blood concentrations for the toxic alcohols in the table, which are only for a patient without acidosis or

Table 1 Antidote treatment criteria:^a (Adapted with permission from Ref. [50])

	Recommended criteria
I	Serum ethylene glycol or methanol concentration ≥ 10 mmol/L (62 mg/dL and 32 mg/dL, respectively) ^b
II	Documented/suspected recent history of ingestion with an osmolal gap > 25 mOsm/kg H ₂ O ^c
III	Documented/suspected history of ingestion plus two or more of the following criteria:
	A: Arterial pH < 7.3
	B: Serum bicarbonate < 14 mmol/L or base deficit (BD) > 10 mmol/L
	C: Osmolal gap > 25 mOsm/kg H ₂ O ^c
	D: Presence of urinary oxalate crystals (ethylene glycol only) or visual disturbances (methanol only)

^aAntidote should be given without delay, if toxic alcohol cannot be excluded as the cause. No osmolal gap will be able to exclude toxic alcohol as the cause

^bOnly if there is no significant metabolic acidosis (Base deficit < 10 mmol/L (10 mEq)) or no indications of organ toxicity

^cOG calculated after the ethanol contribution is subtracted

evidence of organ toxicity on admission, reflect the potential *molar levels of toxic metabolite* that could be produced from the alcohol. Hence, the cutoff value of 10 mmol/L (62 mg/dL ethylene glycol, 32 mg/dL methanol) implies 10 mmol/L metabolite maximum, a level that normally does not produce clinical effects [51]. Even so, repeat analysis of acid–base status should be done every 2–4 h to evaluate possible development of acidosis in such patients. Note that patients with blood concentrations < 10 mmol/L, but with clinical signs such as acidosis or organ toxicity, should be treated with fomepizole according to the other criteria in the table.

Use of Fomepizole and Dialysis

Historically, hemodialysis was recommended in fomepizole-treated patients if the plasma methanol or ethylene glycol concentration exceeded 50 mg/dL (16 mmol/L methanol, 8 mmol/L ethylene glycol) or if the patient displayed severe symptoms such as visual loss, severe metabolic

acidosis, or acute kidney injury [4, 52]. However, it has been suggested [52–55], and also shown in a prospective study [56], that fomepizole can postpone or even ameliorate the need for hemodialysis. Also, patients with methanol or ethylene glycol concentrations higher than the above cutoff value have been successfully treated with fomepizole alone, without hemodialysis [30, 31, 56]. In the case of ethylene glycol, dialysis is likely unnecessary in a patient with functional kidneys, because ethylene glycol is renally cleared. Thus, even with ADH inhibition, a substantial portion of the body burden of ethylene glycol can be eliminated by functional kidneys. However, there have been cases with extreme ethylene glycol concentrations (>1000 mg/dL, 161 mmol/L), where dialysis was recommended to avoid any complications related to hyperosmolality [57]. In the case of methanol, initiation of hemodialysis in the presence of fomepizole depends on the condition of the patient and not necessarily on the methanol concentrations per se. Whereas dialysis is an important tool to correct severe metabolic acidosis, a mild or moderate acidosis would easily be corrected by the use of bicarbonate and antidote without providing dialysis. More importantly, a number of hospitals do not have sufficient dialysis capacity available, necessitating antidote therapy as the major treatment approach. Because methanol is primarily cleared by metabolism, such that its half-life during fomepizole therapy is much longer (50–80 h) [30], hemodialysis is often used to eliminate methanol and shorten the duration of fomepizole therapy and number of hospital days [55, 58].

Use of Fomepizole with Diethylene Glycol

Fomepizole has been shown to completely block the acidosis and organ toxicity (liver and kidney) produced by diethylene glycol in rats [59]. Although this suggests that fomepizole is likely efficacious in humans, few cases or outbreaks have utilized fomepizole for treatment. In

one case of diethylene glycol ingestion in a 17-month-old girl, early (6 h) administration of fomepizole, combined with hemodialysis, prevented development of metabolic acidosis and renal dysfunction [60]. A case of combined diethylene glycol and triethylene glycol ingestion by a 15-year-old girl was successfully treated with fomepizole [61]. In contrast, another case of diethylene glycol ingestion was fatal despite treatment with fomepizole [62], likely due to the long delay (>58 h) prior to fomepizole treatment. It is important to note that treatment of diethylene glycol poisoning is not among the FDA-approved uses of fomepizole.

Comparison of Fomepizole and Ethanol

Ethanol also inhibits methanol and ethylene glycol metabolism by competing for ADH activity, making ethanol a suitable alternative to fomepizole under certain circumstances. Both antidotes have a stronger affinity to ADH than the toxic alcohols, with fomepizole binding more strongly (>1000 times that of methanol or ethylene glycol) to the enzyme than ethanol (10–20 times that of methanol or ethylene glycol). Also, fomepizole competitively binds to the enzyme active site, while ethanol itself is metabolized by ADH, thus competing only transiently for the active site. Such characteristics would appear to favor the efficacy of fomepizole; however, there exists no evidence for the superiority of either antidote in terms of the efficacy of the treatment, i.e., in reversal of the toxic alcohol syndromes and survival of patients. The prospective clinical trials of fomepizole [22, 23] did not compare it with ethanol and were not able to distinguish the role of antidote therapy from the role of hemodialysis in producing a favorable outcome. Randomized control trials are lacking. Comparing survival, either prospectively or retrospectively, between different outbreaks is problematic for several methodological reasons: variable reporting of the number of victims and fatalities, uncertain times from ingestion to admission, lack of analytical data, variable toxic alcohol and ethanol concentrations in the ingested substance, and uneven reporting history of ingestion. Despite

Table 2 Ethanol versus fomepizole (Adapted with permission from Ref. [50])

	Ethanol	Fomepizole
Availability	Good (especially orally)	Limited (especially in the developing world)
Cost	Low (in most countries)	High
Practical use	Difficult to keep at therapeutic level, especially during HD	Easy to administer, also during HD
Monitoring of serum concentrations	Necessary	Not necessary
CNS-depressive	Yes	No
Need for HD	Yes	May be avoided or postponed
Need for ICU	Yes	May be avoided

HD hemodialysis, ICU intensive care unit

these caveats, there are two large studies that have attempted to compare the effects of ethanol and fomepizole. Although Paasma and coworkers did not find a significantly better overall outcome with fomepizole, methanol-poisoned patients that could hyperventilate had a significantly better outcome (survival) with fomepizole treatment compared to those treated with ethanol [63]. On the other hand, no difference in outcome between ethanol and fomepizole was found in the study by Zakharov et al. [64], who did a pairwise head-to-head comparison to evaluate the outcome parameters. These patients probably had similar treatment except for the antidote, thus supporting ethanol as an equitable antidote given ideal circumstances. As noted in Table 2 [50], various elements make fomepizole *theoretically* superior to ethanol in terms of *practical* use. A major problem related to ethanol therapy is the difficulty in maintaining recommended plasma concentrations, because ethanol is eliminated more quickly than the methanol or ethylene glycol. There is a huge variability in ethanol elimination rates among humans, and ethanol is rapidly

removed with hemodialysis [65, 66]. To maintain sufficient blood ethanol concentrations, plasma measurements must be frequently performed (every 1–2 h) to make appropriate dosing adjustments.

Another problem associated with ethanol therapy is the potential for adverse effects, most notably, CNS depression. For example, Paasma et al. [67] described a methanol poisoning epidemic in which 40% of the patients who were awake on admission became comatose within 1 h of ethanol treatment. In a retrospective chart review of adverse event reporting in methanol- and ethylene glycol-poisoned cases, CNS symptoms were reported in about half of the cases treated with ethanol, but in only about 2% of those treated with fomepizole [68]. Zakharov et al. reported that 48% of patients treated with ethanol developed severe ethanol intoxication, but did not become comatose, most likely because of the close monitoring of patients receiving ethanol [64].

As noted above, maintaining therapeutic blood ethanol concentrations is difficult and frequently results in overdose, which can lead to CNS depression. In contrast, fomepizole is easy to administer because its pharmacokinetics are predictable with and without dialysis [22, 23, 38, 46]. The dosing schedule (Table 3) is known to maintain therapeutic plasma fomepizole concentrations throughout treatment [16, 52] making monitoring of plasma concentrations unnecessary [69]. Also, in contrast to fomepizole treatment, long-term treatment with ethanol (>24–36 h) may also be complicated by ethanol-induced emotional instability or ill feeling in ethanol-treated patients. These are all elements that would *theoretically* make fomepizole superior to ethanol in terms of treatment.

Combination with Hemodialysis

Fomepizole appears to reduce the need for hemodialysis, particularly in ethylene glycol exposures. Because of the potent ADH binding, well-defined kinetics, and simple dosing scheme of

Table 3 Simplified dosing suggestion for fomepizole treatment for methanol or ethylene glycol poisonings (Adapted with permission from Ref. [50])

		Loading dose	15 mg/kg (Dose 1)	
No dialysis		Maintenance dose	10 mg/kg every 12 h (Dose 2–4)	15 mg/kg every 12 h (Dose 5 onwards)
During dialysis	Intermittent HD	Maintenance dose during IHD	10 mg/kg every 4 h	
		<i>or</i>		
	CVVHD	Maintenance continuous dose during IHD	1 mg/kg/h	
		Maintenance dose during CVVHD	10 mg/kg every 8 h	
		<i>or</i>		
	CVVHD	Maintenance continuous dose during CVVHD	0.5 mg/kg/h	

fomepizole, hemodialysis can be postponed, or even omitted, in some cases if there are limitations in the capacity or availability of dialysis facilities [53, 55, 56, 70]. Due to the difficulty in maintaining therapeutic blood ethanol concentrations, postponing or omitting hemodialysis when the procedure is clinically indicated should be avoided in ethanol-treated patients.

Cost-benefit

The higher acquisition cost has been mentioned as a major disadvantage for fomepizole when compared to ethanol, thus limiting its usefulness in some situations. However, in the USA, the cost of intravenous ethanol and generic fomepizole is now similar [52]. Also for a cost comparison between ethanol and fomepizole, the overall cost-effectiveness must be taken into consideration (including expenses to keep a patient in an ICU, need for nursing care, and need for blood ethanol monitoring with ethanol-treated patients) [71]. The cost of fomepizole acquisition compared to these other expenses largely depends on the country in which the patients are managed and should be taken into consideration with the overall healthcare costs [72]. The cost of fomepizole therapy may be a greater issue with methanol than with ethylene glycol due to the lengthy elimination of methanol during ADH inhibition. However, because of this slow elimination rate of methanol in the ADH-inhibited patient, HD should be performed

if blood methanol concentrations are substantially elevated (see ► Chap. 88, “Methanol and Formaldehyde” for further details).

Special Populations

Children

In the USA, fomepizole has not been officially approved for use in children and no controlled studies in poisoned children have been conducted. Nevertheless, fomepizole has been used in several cases of pediatric toxic alcohol poisoning, with apparently excellent results. In four children, three after ethylene glycol ingestions (from 5 months to 4 years old) and one after methanol ingestion (5 years old), fomepizole treatment was well tolerated and useful therapeutically [73–76]. In two ethylene glycol cases, fomepizole was used successfully without hemodialysis [73, 76].

Pregnant Patients

Fomepizole is considered an FDA Class C drug in the USA, meaning that its effects on reproduction and development have not been adequately determined in animal studies. Studies of fomepizole safety in humans have not been conducted during pregnancy. In pregnant rats, fomepizole readily passes into fetal tissues [77], which would imply significant protection against fetal formation of

toxic alcohol metabolites, thus protecting both mother and fetus. No adverse effects from fomepizole were reported in the dams nor were there any gross abnormalities noticed in the fetuses in this study. Fomepizole has been used to treat one case of methanol poisoning during pregnancy without any reported adverse effects [78]. In a pregnant woman severely poisoned by a metabolically toxic alcohol, an antidote is obligatory – hence, fomepizole should be used, but with care, in pregnant or breast-feeding women.

Contraindications

Fomepizole should not be administered to patients with known hypersensitivity reactions to pyrazole-containing compounds (including celecoxib), although this has yet not been reported to occur in common literature.

Precautions

Fomepizole must be administered IV as a properly diluted formulation (see below) to avoid producing venous irritation. It should also be administered as an IV infusion over 30 min, to allow monitoring for hypersensitivity reactions. Animal studies using high doses (100–200 mg/kg) indicate that acute fomepizole dosing inhibits, while repeated fomepizole dosing (similar to the recommended treatment protocol) induces cytochrome P-450, including CYP 2E1 and possibly 2B1/2B2 [32, 33, 35–37]. Secondly, since fomepizole appears to be metabolized by P-450 [79], other inhibitors of the specific CYP isozyme (currently unknown) may interact with fomepizole metabolism. Hence, physicians should be vigilant of possible drug interactions with fomepizole.

Adverse Effects

The acute LD₅₀ in rodents for fomepizole is 310 mg/kg (IV) and 500–650 mg/kg (oral) [80]. The subacute oral toxicity of fomepizole

has been studied in rats (100 mg/kg for 3 week, then 200 mg/kg for 4th week) and monkeys (100 mg/kg for 5 week, then 200 mg/kg for 6th week) [80, 81]. There was no indication of toxicity in terms of clinical signs, clinical chemical measures, or pathology observed in either species. The plasma fomepizole concentrations in the latter study reached 2000 µmol/L in week six. No visual effects were noted in monkeys treated with fomepizole at 100 mg/kg for 9 days [81]. After a 12-week drinking water exposure in rats, no abnormal liver histology was noted, with plasma fomepizole levels at 85 µmol/L (within the therapeutic range) [82]. At high doses of 400 mg/kg in mice, CNS depression was observed [83].

In the human studies conducted in the 1970s and 1980s, 10 subjects were given oral doses of fomepizole up to 10 mg/kg [10, 84] and 54 subjects were given IV doses of fomepizole at 7 mg/kg [8, 9, 85, 86]. Other than irritation of the peripheral vein in the IV studies, there were no adverse effects reported.

In randomized, blinded, placebo-controlled human volunteer studies, 31 subjects received single oral or intravenous doses in the therapeutic range, with no significant adverse effects reported [15, 17, 18]. During the IV administration, some subjects reported an abnormal smell or taste sensation (the free-base form of fomepizole emits an odor), and venous irritation and transient phlebosclerosis were noted near the site of some injections, but only when the preparation was not suitably diluted. At high single oral doses (50 and 100 mg/kg), six of seven subjects experienced dizziness and nausea, with objective signs (positive Romberg's test) of CNS depression at 100 mg/kg [15]. Despite these effects, vital signs were not affected and clinical chemical and hematologic parameters remained within normal limits in all subjects. In placebo-controlled repeat-dose studies, 15 subjects were treated with oral fomepizole (loading doses of 10–15 mg/kg, maintenance doses of 3–10 mg/kg every 12 h out to 5 days) [17]. Subjective side effects such as nausea, headache, or mild dizziness were reported, but with a similar frequency to those subjects receiving placebo. In some subjects, there was a slight, transient increase in either

serum ALT or AST concentration that resolved by the end of the study and was not dose related, since no subject in the high-dose group was affected.

In the Phase II/III clinical trial, adverse effects of fomepizole were infrequent and minor [22, 23]. Four of 19 patients in the ethylene glycol arm reported effects possibly related to fomepizole, including bradycardia, headache (in two patients), and a seizure after a single dose (but not after subsequent dosing). Six of 11 patients in the methanol arm of the trial reported effects possibly related to fomepizole, including phlebitis, dyspepsia, anxiety, agitation (in two patients), transient tachycardia, and a transient rash in one patient (only after initial doses). Two case summaries have been published from the experience with fomepizole use in treatment of ethylene glycol and methanol poisoning in France [87, 88]. Adverse effects in 11 ethylene glycol-poisoned patients included pain or inflammation at site of injection (two patients), transient eosinophilia (two), and cutaneous eruption, and in 14 methanol patients, fever (two), nausea, headache, and a burning skin sensation.

In a retrospective chart review of 44 patients [68], as well as in a systematic review of published literature up to 2010 [72], the reported adverse effects from the clinical use of fomepizole in methanol- or ethylene glycol-poisoned patients were rare (<2% of patients), consisting of occasional nausea or dizziness and a rare seizure, with uncertain causality.

Administration

The dosing schedule for fomepizole is designed to maintain therapeutic plasma concentrations during the necessary treatment course. Thus, unlike ethanol, no monitoring of plasma fomepizole concentrations is needed to assure efficacy. Fomepizole is available as a parenteral solution that may solidify on storage [89]. It should be slightly warmed to liquefy, then diluted in at least 100 mL of sterile 0.9% sodium chloride or 5% dextrose solution. Dilution and administrations as a 30 min intravenous infusion is important to minimize vessel irritation, as noted above under

Adverse Effects. Diluted solutions remain stable for up to 24 h when stored refrigerated or at room temperature.

Dosing Schedules

The dosing schedule for fomepizole is outlined for patients with and without dialysis in Table 3 [50]. These dosing schedules were used and validated in the two prospective clinical trials of fomepizole in methanol or ethylene glycol poisonings [22, 23]. Fomepizole is cleared readily by hemodialysis as shown in animals [47] and poisoned patients [90]. Therefore, the fomepizole removed by hemodialysis must be replaced. As such, the frequency of maintenance dosing should be increased during intermittent hemodialysis to 4 h intervals; after dialysis, continue the usual 12 h dosing from the time of the last dose during dialysis [91]. Dosing during continuous dialysis modalities can likely be done less frequently, e.g., every 8 h, due to the apparently lower extraction of fomepizole, as noted under **Dialysis Kinetics**. An alternative means to deliver extra fomepizole during dialysis is to give a continuous infusion, with different rates depending on type of dialysis (see table).

Route

An oral preparation of fomepizole is not available in the USA, but is available elsewhere. As described above, Phase I studies indicate that both oral and IV routes of administration produce essentially identical blood concentrations and elimination kinetics.

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This chapter describes the administration of specific immunoglobulin antibodies or antibody fragments (IgG, Fab, F(ab')₂, or sFv) to treat toxic exposures. Binding of the antibody to the target molecules or antigen [1] is intended to result in partial or complete neutralization of the toxic effect of the target, a concentration gradient of free target molecules encouraging efflux into the vascular compartment, and ultimate elimination of the antibody/target complex by renal or reticuloendothelial system routes [2–4].

Specific therapeutic antibodies have been developed for cardiac glycosides [5–9], colchicine [10, 11], and phencyclidine [12–14]; paraquat [15–17]; tricyclic antidepressants [18–22]; amantadine [23, 24]; botulinum toxin [25–27]; verapamil [28]; and snake [29–34], scorpion [35–39], spider [40–42], and bee venoms [43, 44]. In the USA, currently approved therapeutic immunoglobulins are available for Crotalinae snake envenomations (Crotalidae polyvalent immune Fab, an ovine Fab; and Anavip, an equine F(ab')₂ that is scheduled to be available in 2018) [Level of evidence(LoE) I], coral snake envenomations (*Micrurus fulvius* antivenom, an equine IgG) [LOE II-3], cardiac glycosides (digoxin immune fab, an ovine Fab) [LoE I], scorpion envenomations (Anascorp, Centruroides (Scorpion) Immune F(ab)₂ (Equine) Injection) [LoE I], and black widow spider envenomations

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(*Latrodectus mactans* antivenom, an equine IgG) [LoE II-3]. Antivenoms to nonnative venomous animals often are kept at zoos. In the USA, these are under US Food and Drug Administration (FDA) Investigational New Drug licenses [45], and information regarding these envenomations and antivenoms are available through the online “Antivenom Index” which is accessible by zoos to update contact information and antivenom stocks and poison centers to help coordinate and guide management: (<https://avi.pharmacy.arizona.edu/a/index#top>)

The use of immunotherapies offers the promise of a family of therapeutic immunoglobulins with the ability to bind, neutralize, and eliminate molecules that produce toxic effects without having to devise specific, metabolically based antidotal therapies. The significant pharmacologic, physiologic, and economic challenges of developing heterologous and homologous proteins as antidotes can be seen by the general failure to bring a larger number of these agents to market.

History

One of the first immunoglobulin antivenoms in clinical practice was anti-Crotalidae polyvalent (ACP), an equine IgG, in widespread use in the USA from 1954 until the early 2000s. Based on decades of compelling case experience and experimental data, ACP was effective at stopping the progression of local effects and reversing the systemic effects of Crotalinae envenomations. The occurrences of sometimes severe immediate and delayed hypersensitivity reactions to heterologous whole IgG [37, 46, 47] led to a search for safer alternatives, including F(ab) and F(ab')₂ fragments of IgG, which have largely replaced IgG antivenoms worldwide. In the 1970s and 1980s, it was shown that F(ab')₂ and Fab fragments (Fig. 1) could be produced by enzymatic treatment of IgG, resulting in immunoglobulin fragments that retained binding specificity [48–50]. Because of the removal of the Fc chain and immunoglobulin and other non-target specific proteins by affinity

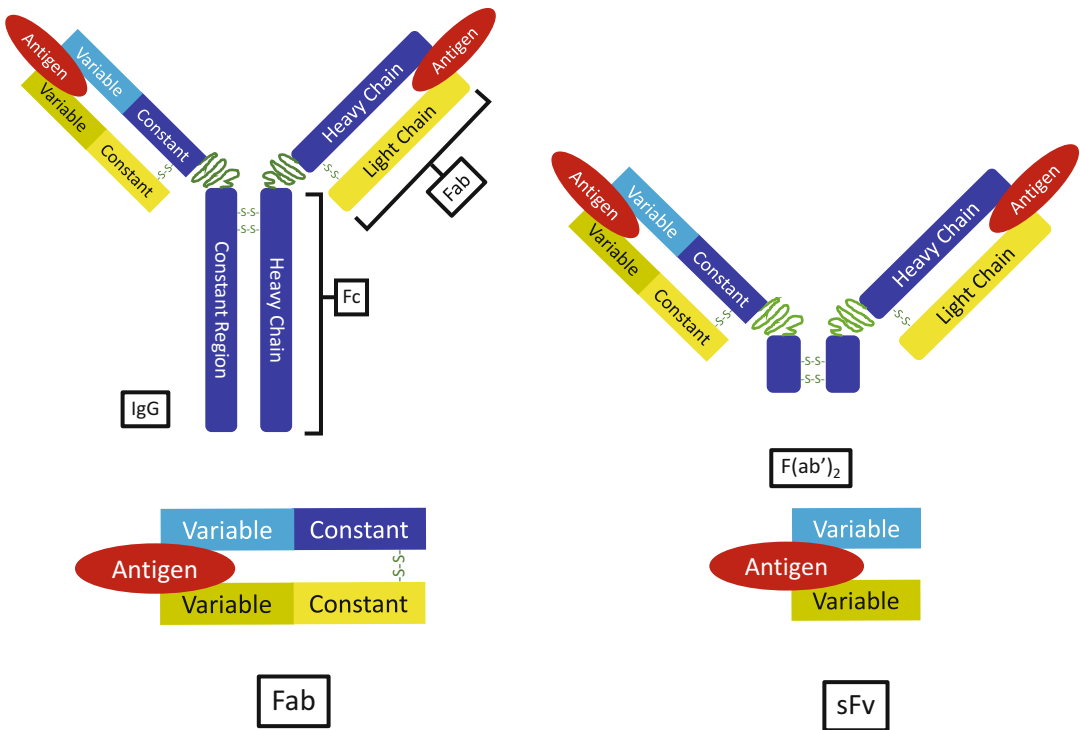


Fig. 1 Chemical structure of immunoglobulin

purification and other techniques [51], $F(ab')_2$ and Fab fragments were shown generally to have fewer immediate and delayed hypersensitivity reactions than whole IgG [32, 52–55], and it was shown that ovine-derived sera were less likely to result in immediate hypersensitivity reactions than equine-derived sera [32, 33, 54, 56, 57]. $F(ab')_2$ and Fab antivenoms from a variety of source animals have been developed to venoms from snakes, scorpions, and spiders in many countries. Target-specific, single-chain Fv fragments (sFv) (see Fig. 1) have been developed to a variety of agents and have been produced in a variety of host cell lines [6, 16, 58–65]. None of the sFv products are currently used in toxicology and, to our knowledge, there are no commercial products being used as antidotal agents anywhere [66].

Properties

Chemical

IgG is one of a family of structurally-related antibodies. In response to an immunologically recognizable antigen, IgM and ultimately, antigen-specific IgG is produced. IgG has a Y-shape and a molecular weight of approximately 150 kDa. IgG can be subdivided into a Fc and a $F(ab')_2$ regions (see Fig. 1). The Fc chain of amino acids is approximately 50 kDa and the $F(ab')_2$ is 100 kDa. The $F(ab')_2$ regions are responsible for antigen binding [47, 50]. Once the $F(ab')_2$ is bound to an antigen, the Fc chain undergoes a conformational change and is activated [67, 68]. The amino acid sequences in the Fc chain are species specific. Consequently, whole IgG is relatively immunogenic. Depending on the source animal and other factors, it may be complement fixing (the binding of serum complement to the union of an antibody and its target-specific antigen) in humans and cause activations of B-cells [67, 69, 70].

IgG may be cleaved between the Fc chain and the $F(ab')_2$ region, and the Fc component may be eliminated leaving $F(ab')_2$ (Fig. 1). $F(ab')_2$ without Fc chain retains excellent antigen-binding specificity while being less immunogenic. The $F(ab')_2$ fragment may be cleaved further at the

hinge, resulting in two Fab fragments of about 50 kDa each, also retaining antigen-binding specificity [31, 50]. Fab itself comprises three portions, a constant, proximal portion and two variable distal chains covalently linked; the conformational relationships of the portions are responsible for the binding specificity. Elimination of the proximal portion of the Fab results in a single variable-chain Fv fragment of about 25 kDa, which contains the target-specific binding region. In addition, there are associated oligosaccharide moieties that contribute to the conformational structure and binding of immunoglobulins and may vary based on the cell type in which the immunoglobulin is produced, on the culture methods, and on nutrient depletion states; these moieties may be responsible for variability not predicted from studies of protein or DNA sequences alone [68].

Physical

In general, immunoglobulins are concentrated or otherwise purified from the source animal's serum or from a cell line culture. Antivenin polyvalent Crotalidae, *Micrurus* antivenin, CroFab, Digibind, and others are lyophilized, resulting in an off-white pellet that retains binding specificity for years. *Micrurus fulvius* antivenom expiration dates have been extended multiple times by the FDA based on stability testing. Heat may result in denaturation, as do shear forces and polymerization from shaking, foaming, and bubbling that may occur in the process of reconstitution, and lyophilized drug product may also become trapped in foam generated by shaking [71–73]. Reconstitution of lyophilized materials may be optimized by using larger volumes of diluent and manual inversion, which will result in faster mixing times and without loss of purity, protein content, homogeneity, or potency [73].

Pharmacokinetics

Immunoglobulin kinetics is source, recipient, and target dependent, making extrapolation from animal studies difficult and giving each therapeutic

immunoglobulin a relatively unique kinetic and dynamic profile. Kinetics are stable over a wide dose range but may be affected by factors such as source animal, valence (monovalent or polyvalent), route of administration, ionic charge, nonspecific binding, analytical methods, and study design. Individuals display varying kinetics based on renal function and other physiologic parameters (See Table 1). Interaction with the target molecule also can alter the kinetics of the immunoglobulin.

Immunoglobulin kinetic profiles usually fit a two-compartment model with a biexponential curve on a log-linear plot [85]. Generally, the larger the immunoglobulin molecule, the smaller the volume of distribution and the longer the elimination half-life. IgG is distributed to a volume roughly equivalent to the vascular space with a volume of distribution (V_d) < 100 mL/Kg. IgG is eliminated predominantly by the reticuloendothelial system, with a relatively long half-life (approximately 60–194 h) [74, 86]. $F(ab')_2$, Fab, and sFv are distributed to volumes closer to the extracellular volume and are eliminated more rapidly: $F(ab')_2$, 18–133 h; Fab, 15–25 h; sFv, 1.5 h. As their size decreases, proportionate renal elimination increases [74, 86, 87]. Elimination ultimately depends on the size and charge of the unbound immunoglobulin and immunoglobulin/target molecule complex, affecting renal or reticuloendothelial system clearance or both [5, 82, 87]. Interaction between the target molecule and immunoglobulin may affect the target molecule's kinetics, resulting in altered tissue and vascular compartment concentrations [12, 15, 23].

Pharmacodynamics

Clinical efficacy depends on many factors. In general, the immunoglobulin locates and binds to its target and neutralizes its physiologic interaction. Target specificity and binding affinities of immunoglobulins are high (10^8 [8] to 10^{10} [10] M^{-1}) [88, 89] and usually greater than tissue affinities for most drugs. Specific IgG, $F(ab')_2$, Fab, and sFv with similar target specificity and affinity or given in equivalent neutralizing doses should display

similar acute neutralization of a target molecule that is localized in the central circulation or must pass through the central circulation to exert its toxicity [90, 91], excluding half-life differences. Compared with IgG, the larger volumes of distribution of $F(ab')_2$, Fab, and sFv should allow increasing tissue penetration and target binding and neutralization. Mean tissue residence time still may be greater, for IgG than for smaller immunoglobulin fragments, because of its long half-life [87]. In the case of destructive tissue effects from snake envenomation, some venom remains unneutralized, likely in tissue interstices and in the lymphatic system [80, 92, 93]. Unneutralized antivenom may be present likely because immunoglobulin access to the site is limited [94, 95] and appears unrelated to immunoglobulin fraction size or neutralization profiles [70, 96, 97]. Because low-molecular-weight toxins and toxicants may assume the kinetic profiles of their specific antibodies and are redistributed to the vascular compartment or other tissues, if there is only partial neutralization of the target molecules or if immunoglobulin/target dissociation occurs, it may result in increased tissue toxin/toxicant concentrations, variable efficacy, and potentially increased toxicity [12, 15, 17, 23, 24].

Disparity may exist between the half-life of the antigen and specific immunoglobulin, resulting in clearance of unbound immunoglobulin while there still is a body depot of unneutralized target [80, 92, 93]. This situation may result in recurrence of toxicities after most of the unbound immunoglobulin has been eliminated [57, 98]. Degradation of the immunoglobulin may occur, with some $F(ab')_2$ having instability at the hinge region. Conversion of a $F(ab')_2$ to a Fab alters distribution and elimination kinetics, although immunoglobulins seem to retain the ability to bind their targets as long as they are in circulation [5]. Manipulation of cross-linking of sulfhydryl bonds between cysteine residues can increase resistance to degradation of $F(ab')_2$ [99]. Theoretically, the target/immunoglobulin complex may dissociate if it remains in circulation for prolonged periods. A rebound rise of unneutralized digoxin has been reported

Table 1 Human pharmacokinetic parameters of specific IgG, F(ab')₂, and Fab antibodies by IV route^a

Ig type	Valence	Target	Source	Dose	Vdss (Vdb) mL/kg	T1/2a (h)	T1/2b (h)	Clearance (mL/min)	Special notes
IgG	M	<i>C. rhodostoma</i>	Horse	1081 µL/kg	90	0.46	82	0.525	7 patients; unpurified horse serum [74]
IgG	M	<i>C. rhodostoma</i>	Goat	216 mL/kg	92.5	1.96	45.5	1.118	6 patients. Processing to minimize aggregate formation [74]
IgG	P	<i>Crotalus</i> , <i>Agkistrodon</i>	Horse	100 mL			158.4		Antivenin polyvalent Crotalidae (Wyeth) [®] ; 1 patient with <i>Crotalus atrox</i> envenomation [75]
IgG		<i>Clostridium botulinum A and B</i>	Human	50 mg/kg			Type A 593–744 Type B 670		Half-life of antitype A is 24.7–31.0 days and B 27.9 days [76].
F(ab') ₂	P	<i>Crotalus</i> , <i>Agkistrodon</i>	Horse	10 vials	3,300		133	0.367	Anavip [®] ; Healthy volunteers, n = 15 [77]
F(ab') ₂	M	<i>C. rhodostoma</i>	Horse	1087 µL/kg	233	0.3	96	1.279	5 patients; pepsin-digested serum [74]
F(ab') ₂	P	<i>Echis</i>	Horse				18		17 patients with <i>Echis ocellatus</i> envenomation [54]
F(ab)2	P	<i>Centruroides sculpturatus</i>	Horse	47.5 mg	1540	0.25	161.3	5.8	Anascorp [®] . 8 healthy volunteers [78]
F(ab)2		<i>Clostridium botulinum A</i> , B, C, D, E, F, and, G	Horse	1 vial adults Peds based on Salisbury Rule	1465–14172	7.51–34.2		2.28–20.83	Heptavalent botulism, the variation in PK is result of 7 different fragments [79]
Fab	P	<i>Crotalus</i> , <i>Agkistrodon</i>	Sheep	3 k – 6 k mg	110	2.7	18	5.7	CroFab [™] ; 4 patients with <i>Crotalus</i> snakebite [80]
Fab	M	Digoxin	Sheep	800 mg	1080		12.1	23.4	Digibind; 1 patient with digoxin toxicity [81]
Fab	M	Digoxin	Sheep		369 (Vdβ)	9.3		0.389	Digibind; 4 patients with digoxin toxicity and impaired renal function – CrCl = 38 mL/min [82]
Fab	M	Digoxin	Sheep	121 mg	669 (Vdβ)		23.9	7.1	Digibind; treatment of digoxin toxicity in a patient with serum creatinine = 1.4 mg/dL [83]
Fab	M	Digoxin	Sheep	80 mg	2751 (Vdβ)		56.3	6.3	Digibind; treatment of digoxin toxicity in a patient with serum creatinine = 1.8 mg/dL [83]

(continued)

Table 1 (continued)

Ig type	Valence	Target	Source	Dose	V _{dss} (V _{db}) mL/kg	T ₁ /2 _a (h)	T ₁ /2 _b (h)	Clearance (mL/min)	Special notes
Fab	M	Digoxin	Sheep	160 mg	95 (V _{dβ})		71.8	2.6	Digibind; treatment of digoxin toxicity in a patient with serum creatinine = 4 mg/dL [83]
Fab	M	Digoxin	Sheep	120 mg	163 (V _{dβ})		45.6	2.3	Digibind; treatment of digoxin toxicity in a patient on hemodialysis [83]
Fab	M	Digoxin	Sheep		290		82	0.049	Digibind; 4 patients with digoxin toxicity, ESRD, and hemodialysis [5]
Fab	M	Digoxin	Sheep	80 mg	3620	49.9	138.6	3.02	Digibind; 1 patient with digoxin toxicity, ESRD (CrCl = 8 mL/min), and peritoneal dialysis [84]
Fab		Digoxin	Sheep					13.6	DigFab; 17 patients with digoxin toxicity, ESRD, [82]
Fab		Dabigatran	Human	5 g	8900	0.78	10.3	47	Idarucizumab [130]

^aSignificant variability in kinetic parameters can be seen within and between classes depending on source animal, target antigen, renal function, immunoglobulin structure, route, and other factors

CrCl creatinine clearance, *ESRD* end-stage renal disease

Valence abbreviation *M* monovalent, *P* polyvalent

V_{dβ} volume of distribution in the beta phase

posttreatment with digoxin immune Fab, with possible explanations including redistribution of peripheral stores of unneutralized drug and drug-antibody dissociation [5, 100]. Host antibodies targeting the target-specific immunoglobulin (antiidiotypic antibodies) may develop one to several weeks after exposure and may decrease therapeutic immunoglobulin efficacy in subsequent treatments [52, 101]. Because IgG and F(ab')₂ antibodies bind to their targets in a 1:2 M ratio and Fab and sFv bind in a 1:1 ratio, the quantity of target molecules in certain overdoses (e.g., tricyclic antidepressants) may exceed the amount of immunoglobulin that can be given safely or practicably. Clinical efficacy in these circumstances still may be shown if the life-threatening toxicities are abated by partial neutralization of toxin body burdens [22, 34].

In the USA, decades of experience have shown clinical efficacy for immunoglobulin treatment of snake (*Crotalus* and *Micrurus*), scorpion (*Centruroides*), and spider (*Latrodectus*) envenomations and cardiac glycoside poisonings. Because of similarities of venom components across genera, specific antibodies raised to one venomous species often show clinical efficacy against the same genus [40, 47, 102]. Similarly, antidigoxin antibodies show efficacy against other plant and animal cardiac glycosides [7–9] [LoE II-3].

Clinical efficacy of this immunotherapy in humans has yet to be shown convincingly for bee envenomation, colchicine, tricyclic antidepressants, phencyclidine, paraquat, and diquat. Future developments include possibly complexing immunoglobulin fragments with molecules that alter their kinetics and dynamics as well as the use of recombinant DNA technology [66–68, 103–105].

Special Populations

Neonatal and Pediatric Patients

Generally, the dose of immunoglobulin is related to the quantity of target molecules to be neutralized. Children usually receive more

immunoglobulin per body weight than adults, especially for antivenoms [106]. The dose adjustment for body size generally made for pharmaceuticals is not appropriate for immunotherapeutic agents. Attention also should be paid to fluid volumes. Snake antivenom should be reconstituted in a fluid volume of 20 mL/kg with a total to be infused of ≤ 250 mL [LoE I] [45].

Elderly Patients

Unbound sFv and Fab, some F(ab')₂, and immunoglobulin/target complexes of less than 70 kDa are eliminated in part by renal excretion [2, 87, 107]. Impaired renal function results in prolonged half-lives of unbound immunoglobulin and immunoglobulin/target complexes [5, 83, 84]. This situation may prevent or delay recurrence of toxicity by delaying the elimination of unbound immunoglobulin when there is a large disparity between its half-life and that of the target.

Pregnant Patients

Immunoglobulins generally have not been tested in pregnant patients. F(ab')₂ and smaller fragments may cross the placental barrier. The effects of the immunoglobulin and immunoglobulin/target complex on the developing fetus are unknown.

All of the FDA-approved immunoglobulin antibodies are FDA pregnancy category C, which is defined as follows: “Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women [LoE II-3]” [108]. These immunoglobulin antibodies in the USA include antivenin (*Crotalidae*) polyvalent (equine; Wyeth-Ayerst, Philadelphia, PA), antivenin *Latrodectus mactans* (equine; Merck & Co, West Point, PA), CroFab (ovine; BTG International, London, UK), and *M. fulvius* antivenin (equine; Wyeth-Ayerst).

Contraindications

Contraindications to the use of therapeutic immunoglobulins include a perceived risk-to-benefit ratio that does not favor treatment. This determination must be made on a case-by-case basis. Because type I (anaphylactic) reactions are common, particularly with whole immunoglobulin preparations, and may be fatal [47, 109–111], indications and contraindications for use have varied [33]. Because of the improved safety profiles of F(ab')₂ and Fab antivenoms, indications for treatment have broadened in recent years [112]. In some cases, because of the rapidity of onset of respiratory paralysis with eastern coral snake envenomations, for example, it has been recommended that antivenom be given before signs and symptoms appear [47, 113]. Special caution should be used when administering immunoglobulin treatment to patients with a history of prior immediate hypersensitivity reactions to that antivenom or to the serum of the source animal, although such patients have been treated successfully with antivenom [114–116]. Multiple doses of immunoglobulin antibodies have been given without the development of type 1 hypersensitivity reactions [LoE II-3] [117].

Precautions

Type I hypersensitivity reactions are immediately occurring reactions to an antigenic stimulus, usually because specific immunoglobulins to that antigen were produced during a previous exposure. Anaphylactic reactions can occur with immunoglobulins, particularly as they involve nonhuman source animals. IgE-mediated hypersensitivity reactions may be fatal [109, 111]. Anaphylactoid (non-IgE-mediated type I hypersensitivity) reactions often are related to the infusion rate. ► Chapter 26, “Toxicant-Induced Immunological Reactions” reviews management of type 1 hypersensitivity reactions. These are discussed in greater detail in the chapter on immunologic reactions.

Skin tests are recommended by the manufacturers of ACP, *Micrurus*, and *Latrodectus* antivenoms as a way to test for the patient's risk of developing a type I hypersensitivity reaction. Skin testing is controversial but for most modern antivenoms, the sensitivity and specificity of skin tests to predict subsequent hypersensitivity reactions are insufficiently sensitive and insufficiently specific to rely on for clinical decision-making [LoE II-2] [33, 47]. The initial dose of antivenom given in a location has the capability to manage allergic reactions [LoE III]. Pretreatment with H₁- and H₂-receptor blockers may be considered in patients considered at high risk (e.g., a history of allergy or atopy) [LoE II-3] [47]. In general, smaller immunoglobulin fragments have fewer and milder reports of type I reactions. Reports of the incidence of type I reactions to various IgGs have ranged from 8% to 87% and to various Fab and F(ab')₂ immunoglobulins from 6.3% to 20% [47, 118]. In one large study, type I reactions to ACP in Crotalinae envenomations were reported in 23% of cases, with half of them severe reactions [109]. In contrast, type I reactions to CroFab, a Crotalinae ovine Fab, were reported in 19% of cases, with two thirds of them mild, one third moderate, and none severe [57]. Because venom and other toxins can cause type I hypersensitivity reaction, the trigger may not be clear [119]. When the trigger is unclear, timing of onset of symptoms versus timing of administration may be helpful.

Type III (delayed) hypersensitivity reactions (serum sickness) may occur 1 day to 3 weeks after treatment with an immunoglobulin. Type III reactions result from the formation of circulating immunoglobulin/target complexes, usually in the context of antigen excess and associated with complement activation [120]. These complexes are deposited in endothelial cells in vessels, where they produce widespread vascular injury and complement activation. Clinical effects of type III reactions are persistent urticaria, arthralgias, myalgias, angioedema, swollen lymph nodes, vomiting, and fever [47, 109]. Type III reactions typically are seen much more frequently and are more severe with IgG snake antivenoms than with other antivenoms [47]; this is thought to

reflect the higher doses associated with treatment of snakebites and the relatively greater immunogenic reactivity of whole IgG preparations, which may predispose to vascular injury. The incidence of type III reactions after equine IgG has been reported to be 15–86% with ACP [33, 47] and 61% with *Centruroides* antivenom [37]. CroFab had an incidence of type III reactions of 13% [57, 121].

Recurrence Phenomena

A phenomenon of recurrent toxicity (recurrence of toxicity after initial reversal or stabilization) has been reported in patients treated with therapeutic immunoglobulins and is believed to be the result of disparities in the pharmacokinetics and pharmacodynamics between the target and its specific immunoglobulin [93]. In the treatment of Crotalinae envenomations with a Fab antivenom, local symptoms may recur in 50% of patients after initial control with antivenom. Coagulopathy (abnormal platelet counts, fibrinogen, prothrombin time, and activated thromboplastin time) may recur in 69% of patients after initial control with the antivenom [57, 122]. The mechanisms of recurrence are believed to be a kinetic disparity between the half-life of venom components and unbound immunoglobulin and a dynamic disparity in which not all venom is neutralized initially. This situation allows local injury to recur when protective serum levels are lost at the interface between normal tissue and the local venom depot and likewise allows coagulopathy to recur when unneutralized venom from a depot reenters the vascular compartment after protective Fab concentrations have been lost [57]. Coagulopathy recurrence with ACP, an equine IgG, usually mild and subclinical but occasionally severe, also has been reported and is likely due to the same mechanism [98, 122, 123]. Local recurrence with Fab antivenom, consistent with the time course of local injury [124], typically occurs within the first 24 h [57, 124]. Because coagulopathy recurrence likely results from recurrence of venom antigenemia from a depot of unneutralized

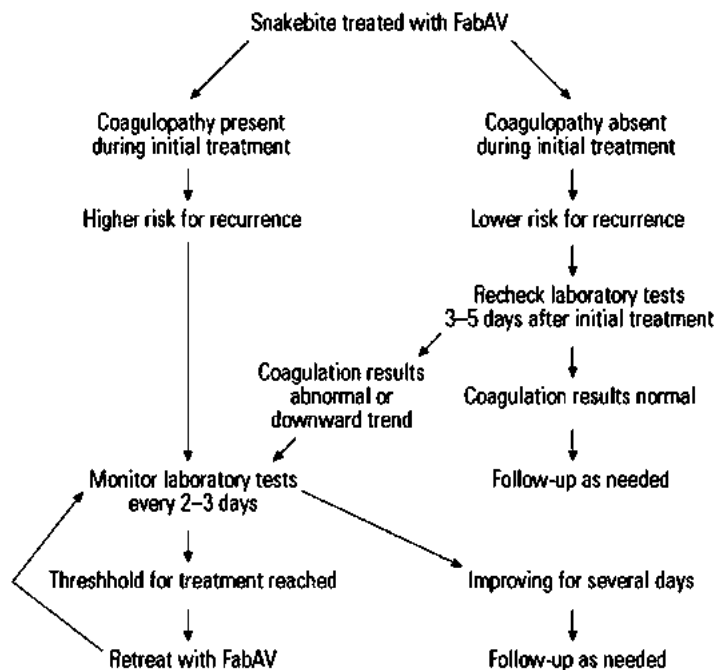
venom, it is similar in kind and degree to the presenting coagulopathy, is typically seen 2–4 days after treatment, and may persist for more than 2 weeks [57, 92, 123]. Predictors of either recurrent or late, new-onset hematologic effects include early hematologic abnormalities or indicators such as elevated d-dimers indicating fibrinogenolysis and an increase in platelets following antivenom administration indicating platelet-active venom factors [125].

A similar recurrence phenomenon has been reported with digoxin toxicity treated with an ovine Fab. Recurrence of free digoxin concentrations usually occurs 12–24 h after initial treatment and may be due to redistribution of unneutralized, peripheral stores of the drug or possibly to drug-antibody dissociation. In patients with renal failure, this recurrence may occur within a few hours of treatment [100] or be delayed 12–130 h [5]. Other kinetic and dynamic mismatches between targets and target-specific immunoglobulins may result in decreased therapeutic benefit or other adverse effects.

Treatment of Adverse Effects

Anaphylactic and anaphylactoid reactions should be treated in the standard manner. If an immunoglobulin is being given intravenously and is suspected of being the cause of the reaction, the infusion should be stopped. Epinephrine, H₁- and H₂-blockers, and corticosteroids should be given as indicated. The treatment of anaphylaxis is discussed in detail in the chapter on immunologic reactions. The decision to restart the infusion in severe reactions should be made on the basis of the risk-to-benefit ratio to the patient. If the infusion is restarted, consideration should be given to diluting the infusion further and restarting it slowly to avoid an anaphylactoid reaction. It is uncertain, however, whether the incidence of severe type I reactions can be reduced by slower infusion (LoE II-3) [45, 126]. Simultaneous infusion of antivenom along with intravenous epinephrine may be instituted and maintained cautiously if the patient is showing signs of an

Fig. 2 Monitoring for coagulopathy in patients treated with Crotalidae polyvalent immune Fab (ovine) (From Boyer et al. [131])



anaphylactic reaction, but it still is deemed clinically essential that the patient receive the antivenom [LoE III-3] [114, 115, 119, 127].

Late hypersensitivity reactions (serum sickness) usually produce pruritic and sometimes painful urticaria or purpuric skin rashes. Mild reactions may be treated with H₁- and H₂-blockers and nonsteroidal antiinflammatory agents. For moderate-to-severe symptoms, corticosteroids have been recommended [LoE II-3] [37, 128]. Although patients have been reported to improve after these medications [109, 128], no controlled studies have firmly established their utility. Some patients may require readmission for symptomatic care [109].

Prevention of recurrence of local effects in ovine Fab-treated Crotalinae envenomation can be accomplished by following the initial control of local symptoms with additional scheduled doses of antivenom (two vials of antivenom every 6 h for three additional doses) [LoE II-1] [57]. Although it is theoretically possible to

prevent coagulopathy recurrences by maintaining a constant protective level of antivenom [80], no such studies have been performed. The need for and efficacy of late use of antivenom in these cases are uncertain [122]. Although the risk of spontaneous bleeding from recurrent coagulopathy is considered small, there almost certainly is an increased risk with surgery or trauma in patients with low platelet counts or fibrinogen [122]. Recommendations for posttreatment monitoring of Fab-treated patients and for consideration of retreatment with antivenom are presented in Fig. 2 and Table 2. [LoE II-2] [122]. Continuous IV infusion of antivenom has been used for severe recurrent or late, new-onset hematologic effects and better matches antivenom and venom kinetics, although it requires in-hospital management [LoE II-3] [129]. Similarly, significant recurrence of toxic effects from digoxin toxicity after treatment with ovine Fab may be retreated with additional digoxin-specific Fab [LoE II-2] [5], Table 2.

Table 2 Recommendations for indications for retreatment of recurrent coagulopathy with FabAV

Fibrinogen <50 µg/mL
Platelet count <25,000/mm
INR >3.0
APTT >50 s
Multicomponent coagulopathy
Worsening trend in patient with prior severe coagulopathy
High-risk behavior for trauma
Comorbid conditions that increase hemorrhagic risk

From Boyer et al. [131]

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The phrase lipid resuscitation therapy (LRT) refers to the intravenous administration of an emulsion, typically containing approximately 20% lipid, for the management of poisonings. Originally developed for the treatment of local anesthetic cardiovascular toxicity, the use of LRT has extended to the management, or attempt at management, of a multitude of other poisonings.

In 1974 Kriegelstein et al. demonstrated that lipid administration acts as a large reservoir for the drug chlorpromazine [1]. However, the concept of LRT for local anesthetic toxicity has its roots in a study by Weinberg et al. (1998) [2] in which it was demonstrated that rats can be resuscitated from bupivacaine-induced cardiac arrest by the administration of a large of dose lipid emulsion. In this study 7.5 cc/kg of a 30% lipid emulsion was given as a bolus post-arrest, followed by 3 cc/kg/min for 2 min. The LD₅₀ for bupivacaine if treated with lipid emulsion was 18.5 mg/kg. In contrast, in rats treated with an equivalent volume of saline, it was statistically significantly lower at 12.5 mg/kg [2].

Further impetus for the use of LRT for local anesthetic poisoning came from a very dramatic finding [3] in a canine model of bupivacaine-induced cardiac arrest. In this study dogs in cardiac arrest were given 10 min of open chest cardiopulmonary resuscitation at which time they were randomized to a 20% lipid emulsion or an equivalent volume of normal saline, given as a 4 cc/kg bolus followed by 0.5 cc/kg/min for

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10 min. Reportedly, 100% (6/6) dogs were successfully resuscitated in the LRT group; none of the six dogs in the saline group survived the arrest.

The first published use of LRT in human toxicity described a 58-year-old male with a known history of exertional angina and an electrocardiogram (ECG) showing a right bundle branch block, a left anterior hemiblock, and an old anterior myocardial infarction, undergoing arthroscopic rotator cuff repair. Described as awake and alert during the bupivacaine infusion, 30 s later he had the first of two generalized clonic tonic seizures followed by an asystolic cardiac arrest. Advanced cardiac life support (ACLS) consisting of intubation, chest compressions, epinephrine, atropine, amiodarone, and arginine vasopressin failed to provide return of spontaneous circulation (ROSC). Consequently, after 20 min of unsuccessful resuscitation using standard medications, the patient received 100 mL of 10% ILE followed by an infusion of 0.5 cc/kg/min through a peripheral IV line. Fifteen seconds after the bolus, he achieved ROSC with normal sinus rhythm and was ultimately discharged neurologically intact [4].

Also in 2006, Litz et al. [5] reported a case of an 84-year-old female with a left bundle branch block and mitral and tricuspid regurgitation who accidentally received 50 cc of 1%, instead of the intended 0.5%, ropivacaine for the repair of a Dupuytren's contracture. The ropivacaine administration was followed by an asystolic cardiac arrest which was managed with 10 min of ACLS, including three 1 mg epinephrine boluses. Because of a lack of response, 100 mL of 20% lipid emulsion was administered, followed by a 10 cc/min infusion (0.2 cc/kg/min). After a total of approximately 200 cc, she achieved ROSC and had a complete recovery and no evidence of myocardial injury.

Following these, and other sometimes less dramatic, reports, considerable enthusiasm has emerged about the potential utility of LRT in the treatment of cardiovascular and, to a lesser extent, neurological toxicity from a variety of poisonings. Most of the published subsequent literature has been in the form of anecdotal case reports and controlled animal studies, the latter done with

various degrees of rigor. Although some case reports continue to describe sometimes dramatic feats of survival following LRT, their significance is limited by certain publication bias, given that only successfully resuscitated patients are likely to be the subjects of reports deemed publishable by journal editors. Lipid resuscitation therapy is currently widely attempted, even if still non-validated under real-world clinical conditions. While its role, if any, is still being elucidated, many medical toxicologists view it as a reasonable measure for patients *in extremis*, or in actual cardiac arrest, given the possibility of benefit. Current American Heart Association ACLS recommendations are [6]:

1. "It may be reasonable to administer ILE (Intravenous lipid emulsion), concomitant with standard resuscitative care, to patients with local anesthetic toxicity and particularly to patients who have premonitory neurotoxicity or cardiac arrest due to bupivacaine toxicity"; and,
2. "It may be reasonable to administer ILE to patients with other forms of drug toxicity who are failing standard resuscitative measures."

A systematic review sponsored by six major clinical toxicology societies worldwide (three from the USA and one each from Canada, the Asia-Pacific region, and Europe) concluded that the quality of evidence for the use of LRT in nonlocal anesthetic poisoning is low to very low [7].

Given the widespread use of LRT, the impressive anecdotes describing its victories, particularly in cases of local anesthetic toxicity, and the possible benefit that may accrue from its use, this chapter on the clinical pharmacology of LRT is included in this text. A discussion of the potential, role, if any, for LRT in the treatment of specific poisonings is discussed in the various toxicant-specific chapters. Table 1 lists drugs for which LRT has been utilized.

Properties

Lipid emulsions designed for pharmaceutical use are formulated as a source of calories and lipids for patients receiving parenteral nutrition. These preparations vary between countries. For

Table 1 List of xenobiotics for which ILE has been utilized as a treatment modality

Acebutolol (h)	Dabigatran (a)	Hydroxychloroquine (h)	Phenytoin (a + h)
Ajmaline (h)	Desipramine (a)	Ibuprofen (a)	Praziquantel (a)
Alprazolam (h)	Desvenlafaxine (h)	Imipramine (h)	Propafenone (h)
Amlodipine (h)	Detomidine (h)	Ivermectin (a)	Propofol (a)
Amitriptyline (a + h)	Dexmedetomidine (h)	Labetalol (h)	Prilocaine (h)
Atenolol (a + h)	Diazepam (h)	Lamotrigine (h)	Propranolol (a + h)
Avermectin (a)	Diazinon (a)	Levobupivacaine (a + h)	Quetiapine (h)
Baclofen (a + h)	Dichlorvos (a)	Lidocaine (a + h)	Romifidine (h)
Bisoprolol (h)	Digoxin (a)	Liraglutide (h)	Ropivacaine (a + h)
Bupivacaine (a + h)	Diphenhydramine (h)	Malathion (a)	Sertraline (h)
Bupropion (h)	Diltiazem (a + h)	Metformin (h)	Thiopental (a)
Caffeine (h)	Diphenhydramine (a)	Mepivacaine (h)	Tramadol (a)
Carbamazepine (h)	Dothiepin (h)	Metoprolol (a + h)	Trandolapril (h)
Carvedilol (h)	Endosulfan (h)	Moxidectin (a)	Valsartan (h)
Chloroquine (h)	Escitalopram (h)	Nebivolol (h)	Verapamil (a + h)
Chlorpyrifos (a)	Etomidate (a)	Nifedipine (a)	Venlafaxine (h)
Citalopram (h)	Felodipine (h)	Olanzapine (h)	Zolpidem (h)
Clomipramine (a)	Flecainide (a + h)	Parathion (a + h)	Zopiclone (h)
Clonazepam (h)	Glyphosate (h)	Pentobarbital (h)	
Clonidine (a)	Haloperidol (a + h)	Permethrin (a)	
Cocaine	“Hydrocarbons” (h)	Phenobarbital (a)	

a animal only, h human only, A + H animal and human

example, in the USA the most frequent product used is Intralipid^R a 20% emulsion composed of 10% soybean oil, 1.2% egg yolk phospholipids, and 2.25% glycerin and other bioactive substances such as vitamin K and phytoestrogens [8]. There are other products in various countries, such as Liposyn III^R, Nutrilipid^R, SMOFlipid^R, ClinOleic^R, and Lipoven^R. Most of these preparations contain 10 or 20% soybean oil.

Pharmacodynamics

The actual mechanism by which LRT may act is illusive. The two main mechanisms that have been postulated are partitioning of lipid-soluble drugs into an iatrogenically lipophilic serum fraction, hence causing an efflux from peripheral targets (the “lipid sink” theory), and enhancing cardiac fatty acid metabolism and mitochondrial respiration. The latter is predicated on the fact that the heart preferentially utilizes fatty acids for approximately 70% of its energy generation, the balance from glucose and pyruvate oxidation [9].

The lipid sink model is supported by several reports that serum drug concentrations increase after LRT [7]. However, this is not universally the case, suggesting that this is either not the mechanism of action of LRT or that it exerts more than one mechanism [7, 10]. In an in vitro model, Weinberg et al. (2006) [11] demonstrated that a lipid infusion accelerates removal of bupivacaine from the rat heart and that this is correlated with recovery of markers of cardiotoxicity. The degree of induced serum lipophilicity necessary to produce a partitioning effect is a matter of controversy. Clearly, this will vary with the partition coefficient of the drug (or other chemical substances) under physiological conditions, its degree of protein binding, and its volume of distribution. However, at the present state of our understanding of LRT, there are few data that can be relied on to tailor the specific LRT infusion to a specific drug or other target molecules. Fettiplace and Weinberg [12] have argued that a 1% serum lipid concentration is sufficient to generate a partitioning effect for molecules likely to be influenced by lipophilicity. Their rationale

for this is the calculated lipid fraction of serum necessary to produce a partitioning effect in two human volunteer studies [10, 13] and porcine models demonstrating partitioning of amiodarone and amitriptyline [12].

Further support for the lipid sink mechanism comes from a study on isolated verapamil-poisoned cardiomyocytes, in which verapamil binding to the L-type calcium channel inhibited the inward calcium current and myocyte shortening [14]. Incubation with ILE in serum caused a flux of verapamil into the serum compartment and restored both the calcium current and myocyte shortening. The sequestration of verapamil into the serum increased in a dose-dependent manner between 0.03 and 2.5 vol.%. Visual inspection of their data suggests that any further increase in serum lipid concentration did not appear to have a significant effect. One percent lipid in serum sequestered 70% of the added verapamil. The concentration of lipid at the completion of an ILE infusion has been estimated at 1.6 volume percent [14].

The cardiostimulatory theory finds considerable support in both in vivo [10] and in vitro models where direct effects on cardiac function can be assessed in the absence of any lipid sink effect [15, 16]. It has shown that a 1% plasma lipid concentration in crystalloid produced a cardiostimulatory effect in a Langendorff model of a perfused rat heart. A similar computerized physiologically based pharmacokinetic model predicted that the major effect of ILE on the bupivacaine toxic rat heart Langendorff model was primarily cardiostimulatory [17]. However, an in vivo porcine model of bupivacaine toxicity failed to find any significant enhancement of myocardial respiration from LRT. This is in marked contrast to in vitro studies with isolated bupivacaine-poisoned mitochondria [10]. However, the difference between in vitro and in vivo studies likely derives from the non-physiological conditions in the former. The in vitro study by Kryshtal et al. (2015) [14] described above found no increase in cardiomyocyte calcium currents when incubated with serum containing lipid emulsion in the absence of verapamil.

A third proposed mechanism for LRT is that it raises blood pressure due to vasoconstriction in

the absence of enhancing cardiac function. A porcine study showed substantial increases in mean arterial pressure when ILE was administered either alone or after a bupivacaine infusion without a concomitant effect on myocardial bioenergetics [10]. This vasotonic effect may be secondary to enhancing α_1 -adrenoreceptor tone. An effect on the α_1 -receptor, or its downstream mechanism, is supported by both human volunteer [18–20] and in vitro studies [10]. The α_1 -receptor is G-protein linked, with further stimulation of phospholipase C leading to activation of protein kinase C and subsequent vasoconstriction. Protein kinase C is stimulated by unsaturated fatty acids such as oleic acid, a constituent of Intralipid^R. Similarly, an ILE infusion of only 40 cc/h in human volunteers has been shown to modestly increase blood pressure [10, 21, 22]. However, a study on nonpoisoned rats found that ILE administration increases blood pressure and aortic flow in the absence of a significant effect on peripheral vascular resistance [15].

A fourth postulated mechanism of action of LRT derives from the observation that ILE may inhibit endothelial nitric oxide synthase (e-NOS), thus decreasing nitric oxide-induced vasodilatation [23]. Unsaturated fatty acids are direct inhibitors of e-NOS [24, 25]. However, support for this mechanism, based on current knowledge, is weak. Lastly, some advocate that ILE may work via altering calcium levels in the heart. In vitro studies have demonstrated free fatty acids can open voltage-gated calcium channels in myocardial cells. Those who believe the change in calcium theory argue the associated increase in intracellular calcium after ILE may be desirable in drug-induced myocardial depression [26].

Pharmacokinetics

The pharmacokinetics of ILE is only partially understood. In human volunteers administered lipid emulsion lipid clearance from serum was a first-order process [27]. In a case of verapamil poisoning successfully treated with LRT, the serum triglyceride concentration fell with an approximately 3 h half-life [28].

Contraindications

Lipid resuscitation therapy is obviously contraindicated in patients with an allergy to soybean oil, unless it is felt that the patient was in extremis and unlikely to survive without it. In patients that have active pancreatitis, a history of chronic pancreatitis or severe hypertriglyceridemia there is a theoretical risk of causing or exacerbating pancreatitis (Grade III evidence).

Administration

The American College of Medical Toxicology (ACMT) has recommended an ILE infusion protocol [29] that is a minor modification of that initially put forth by the UK Resuscitation Council. The Association of Anesthetists of Great Britain and Ireland and the web site LipidRescue.org have also suggested similar infusion regimens. The ACMT recommended regimen (Grade II-3 evidence) calls for the initial infusion of 20% ILE as a 1.5 cc/kg bolus over 2–3 min. This can be administered by drawing the desired volume of 20% lipid emulsion into 50 cc syringes. The bolus can be followed by an infusion of 0.25 cc/kg/min. For asystolic patients, or those with pulseless electrical activity, the dose can be repeated. Unless absolutely necessary, the infusion should be stopped after an hour (Grade III recommendation). This amounts to 1,890 ccs for a 70 kg patient. Fettiplace et al. has warned that exceeding this amount may predispose to potential adverse effects [12] and has suggested a more conservative protocol of a 1.5 cc/kg loading dose and 0.225 cc/kg (or roughly 150 cc in a 70 kg person) over 3 min, followed by an infusion of 0.025 cc/kg/min (or approximately 100 cc/h in a 70 kg person) for up to 6.5 h (Grade III recommendation). None of these infusion regimens have been empirically tested or compared. Based on our current state of knowledge, for the patient in extremis or in cardiac arrest, it seems more sensible to use the more aggressive regimen such as that proposed by the ACMT (Grade III recommendation). For more stable patients, the Fettiplace protocol may be preferred; however,

there is no clear rationale for using LRT in relatively stable patients.

Adverse Effects

Theoretically, the potential complications of LRT relate to lipid overload, which could manifest as acute pancreatitis and the acute respiratory distress syndrome. Other obvious theoretical concerns are lipid interference with extracorporeal circuits used for cardiorespiratory support on substance removal and laboratory studies. The extent to which these complications occur with LRT is unknown.

A recent systematic review of adverse effects associated with LRT assessed cardiovascular, hematological, renal, metabolic, pulmonary, allergic, vascular, pancreatic, and inflammatory effects as well as effects on extracorporeal circuits [30]. That review considered 114 publications, 24% of which were controlled animal studies. Assessment of study quality was by the GRADE criteria [31]. Most publications were found to be of low quality. Potential adverse effects of lipid therapy identified were acute kidney injury, cardiac arrest, ventilation/perfusion mismatch, acute respiratory distress syndrome, venous thromboembolism, hypersensitivity, fat embolism, fat overload syndrome, pancreatitis, extracorporeal circuit obstruction, and allergic reactions (Grade III evidence). With the exception of allergic reactions, these adverse effects appeared to be dose dependent. Nevertheless, the degree to which any of these obtain cannot be determined from the available data, and it is likely that some are conflated with the actual condition being treated.

Interference with laboratory testing by hypertriglyceridemia is well known and can occur in patients treated with ILE [32]. Serum lipid concentrations that are sufficiently high to cause separation of the serum into a lipid-rich supernatant and an aqueous infranatant can cause partitioning of analytes such that the results may not accurately reflect their concentration in the patient's circulation. Even in the absence of such partitioning, light scattering by high lipid concentrations can cause an analytical error. The

degree to which these errors occur will vary with the lipid concentration and technique used, so are effectively unpredictable.

Analytical errors caused by hyperlipidemia may be remedied by centrifugation [33] after which the lipemic supernatant can be removed by gentle aspiration. It has been suggested that approximately two thirds of the remaining infranatant serum can be transferred to a clean tube using a glass pipette prior to analysis in order to achieve a more valid assay [33]. This extra processing can be time consuming and can result in substantial delays before analytical results are available [32]. Nonetheless, despite performing such a process, laboratory interference can persist.

Lipid emulsions may contain a variety of ingredients, depending on the manufacturer and formulation. Potential adverse events may depend on the specific formulation used. For example, for soybean oil and egg yolk phospholipid-based ILE, such as Intralipid^R, it is possible that individuals with either soybean or egg allergy may have immunological reactions to lipid emulsion administration. However, if these allergies are to soy or egg proteins, it seems unlikely that an allergic reaction will ensue. Nevertheless, before administering ILE to a patient with one of these allergies, appropriate precautions, such as an established epinephrine infusion, are warranted (Grade III recommendation). Given that many patients are in extremis when they receive their lipid therapy, they may already have such an infusion established.

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Methylene blue was one of the first antimalarial agents to be used clinically. It was also used as an intestinal and urinary antiseptic since the nineteenth century [1]. Since that time, methylene blue has mostly been abandoned for these clinical indications owing to the discovery of much more effective agents. Today, however, methylene blue continues to be a component of certain medications, used to treat urinary tract infections, including Atrosept, Dolsed, UAA, Uridon modified, Urised, Uritin, and Prosed/DS. (Trade names given here are examples from those used in the USA. They may vary between countries.) Methylene blue also has many nontoxicologic medical uses. A major use of methylene blue by clinical toxicologists is in the treatment of methemoglobinemia, a condition discussed in detail in ► Chap. 30, “Toxicant-Induced Hematologic Syndromes.” Methylene blue was reported to have been administered as an antidote in the USA 149 times in 2013 (116 in patients over 20 years old) by US poison centers [2]. Its use has been increasing; methylene blue was reported to be administered 105 and 85 times in the USA in 1999 and 2000, respectively. It is likely that these data represented a fraction of its total antidotal use.

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Nontoxicologic Medical Uses for Methylene Blue

Urinary tract infections, antiseptic [1], antimalarial agent [1]

Nasolacrimal duct patency [3]

Topical ophthalmic medication [4]

Detection of cerebrospinal fluid leaks after intrathecal administration [5]

Detection of enteroperitoneal fistulas [6]

Evaluation of fallopian tube patency after cervical administration [7, 8]

Component of cancer chemotherapeutic regimens [9–15]

Histochemical staining reagent [16]

Priapism treatment [17]

Viral inactivation [18–25]

Treatment for septic shock [26]

Management of condylomata acuminata [27]

Reduction of intraperitoneal surgical adhesions [28]

Treatment of hepatopulmonary syndrome [29]

Inhibition of postintervention restenosis of vessels [30]

Use in multiple indicator dilution studies of in situ pulmonary endothelium [31]

Multidrug-resistant reverser in cells [32]

Component of protein solder for vascular anastomoses [33]

Intraoperative parathyroid gland identification [34]

Targeting of melanomas [35]

Supravital stain [36]

Detection of parturient leakage in the presence of twins after intra-amniotic infusion (rarely used) [37–50]

Treatment of distributive shock [51–56]

Antimicrobial photosensitizers (photodynamic therapy) [57]

Distributive shock [58]

Recurrent laryngeal nerve identification during thyroidectomy [59]

Intravital staining in parotidectomies [60]

Reduction of pain following lumbar open discectomies [61]

Improved lymph node harvest in rectal CA specimens [62]

History

Before its use in the treatment of methemoglobinemia, methylene blue was used as an antidote for cyanide and carbon monoxide poisoning. After the studies of Sahlin in 1926 and Eddy in the early 1930s as reported by Hanzlik [63], Geiger [64] was the first to use methylene blue clinically as an antidote for cyanide poisoning. Geiger, the director of public health in San Francisco, reported the demise of three patients from cyanide poisoning treated with supportive care only. A fourth patient, following an attempted suicide by potassium cyanide ingestion, was resuscitated successfully, however, using 50 mL of 1% methylene blue solution. At the same time, numerous cases of the successful treatment of patients with carbon monoxide poisoning with methylene blue were reported [65–67]. Today, more effective and appropriate therapies are available for carbon monoxide and cyanide poisoning.

The first reported case showing the use of methylene blue to treat methemoglobinemia was by Williams and Challis [68], who described their treatment of a male university student exposed to *para*-bromoaniline who presented with a skin color of “mauve lavender.” Spectrophotometric evaluation confirmed the disappearance of methemoglobin from the blood after treatment with methylene blue. Animal experimentation with two rabbits by these authors, published in conjunction with this case report, showed that 5–6 mg/kg of a 1% methylene blue solution was effective in treating methemoglobinemia. The reported patient was treated with 1000 mg of methylene blue as an intravenous 1% solution. Williams and Challis [68] chose to use methylene blue in their reported case and animal studies because of the previous literature suggesting the utility of this dye in cyanide and carbon monoxide poisoning. Steele and Spink [69] reported a similar reversal of methemoglobinemia in two cases, one aniline induced and the other caused by acetanilide intoxication, after the administration of methylene blue at a dose of approximately 4 mg/kg. The reversal of methemoglobinemia by methylene blue reported by these authors did not elicit enthusiasm because it was thought of as the

antidote for cyanide toxicity. In addition, there were reports that warned of the potential problem of methylene blue paradoxically inducing methemoglobinemia [70–72].

Nadler and colleagues [73] examined the possible induction of methemoglobinemia by intravenous methylene blue (50 mL of 1% solution) administered to 18 healthy adult volunteers. This was the same dose reported by Geiger to be effective in the treatment of his cyanide-poisoned patient. Assuming that the volunteers weighed 50–70 kg, this would constitute a 5–7 mg/kg dose of methylene blue. Neither Geiger nor Nadler provided the actual weights of the patient or volunteers treated; however, a letter to the editor of the *Journal of the American Medical Association* by Bodansky [74] in 1950 stated that the dose was approximately 7 mg/kg. Nadler and colleagues [73] showed that in their volunteers methemoglobin concentrations never exceeded 1.3 g/dL and that the side effects, including electrocardiogram changes, “a sense of oppression in the chest,” dysuria, nausea, and blue discoloration of the skin and mucous membranes, were due not to the presence of methemoglobin, but rather to the direct effects of the dye itself.

Wendel [75], who had shown that methylene blue’s mode of action in cyanide toxicity derived from its ability to form methemoglobin, initially expressed disbelief in the ability of methylene blue to reduce the concentrations of methemoglobin in the blood. However, his own later studies in dogs with sulfanilamide-induced methemoglobinemia showed that intravenous administration of methylene blue at 5 mg/kg would increase the normal conversion rate of methemoglobin to hemoglobin by eight- to tenfold, and a dose of only 1 mg/kg intravenously would increase this rate three- to fourfold [76]. Gutmann and coworkers [77] later elucidated the mechanism by which methylene blue reduces methemoglobin levels.

Further refinement of the dosage of methylene blue required for the treatment of methemoglobinemia arose from the work of Hartmann and colleagues [78]. This was a case series of six patients, ranging from 3.5–11 years of age, admitted to the hospital with an infection and treated with

sulfanilamide. Four patients developed methemoglobinemia, which was treated successfully with methylene blue at doses of 1–2 mg/kg intravenously or 65–130 mg/day orally (3.8–4.7 mg/kg/dose; 18.9–23.9 mg/kg/day). Two of the six children were given methylene blue orally concomitant with the sulfanilamide administration and had no methemoglobinemia. This series suggested that elevated methemoglobin concentrations could be treated successfully with a methylene blue dose of 1–2 mg/kg and that the higher doses administered in earlier studies were unnecessary. Additional reported cases of methemoglobinemia confirmed the safety and efficacy of intravenous methylene blue administered at 1–2 mg/kg [79–81].

Etteldorf [82] reported eight premature infants, ages 6–26 days, all of whom developed methemoglobinemia after being placed in new cloth diapers with the name of the hospital recently stamped on them with an aniline-containing ink. Seven of the eight infants were discovered to be neurologically depressed, with cyanosis of the nail beds and mucous membranes and with methemoglobin concentrations ranging from 10% to 60%. These infants received methylene blue intravenously at a dose of 1.5 mg/kg (0.1% via a scalp vein). All had clinical responses within 15–30 min, simultaneous with the resolution of the methemoglobinemia. Strauch and colleagues [83] published a report of the development of methemoglobinemia in a 2-year-old girl with burns over 50% of her body after treatment with topical 0.5% silver nitrate. Her methemoglobin concentration of 59% and clinical findings resolved 15–30 min after the initiation of intravenous methylene blue at a dose of 2 mg/kg. Wendel [75] reported that dogs with sodium nitrite-induced methemoglobinemia responded rapidly to the intravenous administration of 2 mg/kg of methylene blue, which also reportedly increased the rate of conversion of methemoglobin to hemoglobin by four to fivefold. This report also described 100 cyanotic patients receiving sulfanilamide; 90 of these had methemoglobin concentrations of greater than 3%, and 35 had methemoglobin levels of 15–40%. The administration of 1–2 mg/kg of intravenous methylene

blue to these patients was associated with rapid clinical improvement and resolution of methemoglobinemia [84].

Based on the above, the generally recommended dose of methylene blue for the treatment of methemoglobinemia is 1–2 mg/kg intravenously. Continuous intravenous administration of methylene blue, in doses ranging from 0.1 mg/kg/h for 96 h to 3–7 mg/kg/h for 7 days, has been reported in the treatment of dapsone intoxication. Acute Heinz body hemolytic anemia, as a result of either the dapsone or the methylene blue treatment, was reported in both patients. Until further evidence of its safety and efficacy can be attained, methylene blue therapy via continuous intravenous administration is not recommended [85, 86].

Properties

Chemical

Methylene blue (Fig. 1), with its polycyclic, planar ring structure, is a chromophore possessing the ability to absorb photons (λ_{max} 665 nm) with consequent transformation to a short-lived excited state. The chromophore character of methylene blue is essential for the important role this cationic dye assumes in the treatment of methemoglobinemia because it allows the molecule to accept electrons from the nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH-dependent methemoglobin reductase) and subsequently donate them to methemoglobin with the resultant reduction back to hemoglobin. This same characteristic is also the basis of the methylene blue-associated phototoxicity reactions that have been noted in neonates having been exposed to it

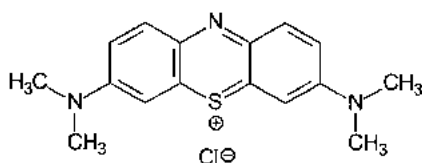


Fig. 1 Chemical structure of methylene blue (tetramethyl thionine chloride)

intra-amniotically and who then were placed under phototherapy lights for hyperbilirubinemia [37, 38].

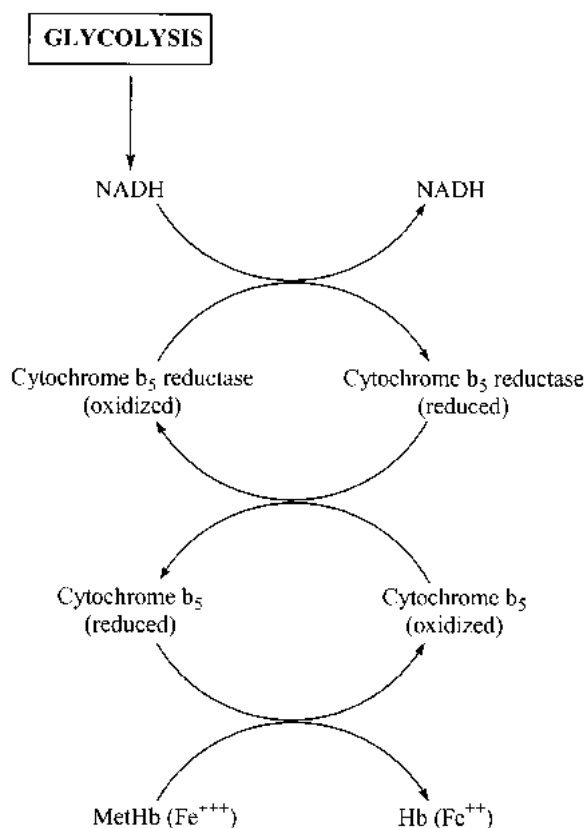
Physical

Methylene blue, tetramethyl thionine chloride (anhydrous form, CAS (Chemical Abstracts Service number) no. 61-73-4; trihydrate form, CAS no. 7220-79-3), is a water-soluble and alcohol-soluble compound with a molecular weight of 373.90 g/mol and a maximum absorption at wavelength of 665 nm. First prepared by Caro in 1876, this compound now is usually prepared from dimethylaniline and thiosulfuric acid. The trihydrate form usually is found as dark green crystals with a bronze-like luster and a slight odor or as a crystalline powder.

Pharmacodynamics

Methylene blue's role in the treatment of methemoglobinemia arises from its ability to interact with methemoglobin and specific enzyme systems within the erythrocyte. Even in the absence of any additional chemically induced oxidative stress, the hemoglobin within the red blood cells (RBCs) slowly tends to oxidize in the presence of normal concentrations of oxygen. The enzyme system responsible for the endogenous reduction of methemoglobin to hemoglobin is NADH-dependent cytochrome-*b*₅ reductase, which actually consists of the cytochrome *b*₅ and the flavin-containing cytochrome-*b*₅ reductase (Fig. 2) [87, 88]. This is a first-order process that occurs at a rate of approximately 15% of total methemoglobin per hour. Under normal circumstances, this enzyme system is capable of maintaining the methemoglobin concentration at less than 1% of the total hemoglobin [89]. The reducing agent NADH is a normal product of glycolysis (see Fig. 2) and acts as an electron source to reduce cytochrome-*b*₅ reductase. This reduced enzyme acts as an electron donor for oxidized cytochrome *b*₅. The now-reduced cytochrome *b*₅ reduces the ferric (Fe^{3+}) iron of methemoglobin to the ferrous (Fe^{2+})

Fig. 2 Predominant pathway for endogenous methemoglobin (*MetHb*) reduction. *NADH* nicotinamide adenine dinucleotide (reduced form)



form, generating hemoglobin. In the presence of a sufficient exogenous oxidative stress, the amount of methemoglobin formed may exceed the reducing capacity of this cytochrome-*b*₅ reductase system, resulting in methemoglobinemia.

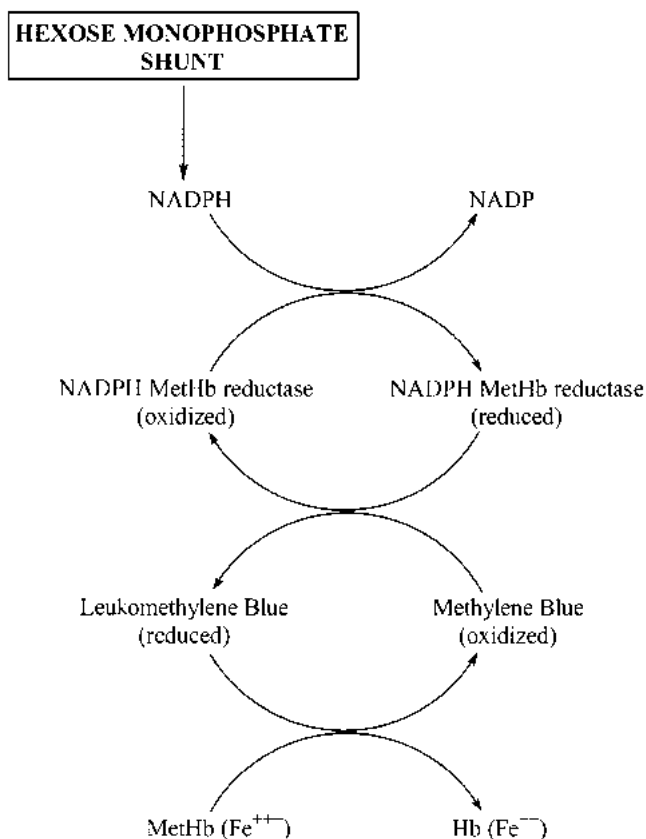
A second enzyme system within the RBC, the NADPH-dependent methemoglobin reductase, normally has a minimal role in the reduction of methemoglobin (Fig. 3). Under usual conditions, the absence of this system or its activity does not result in clinical methemoglobinemia [88, 90]. This enzyme system, which apparently usually functions to reduce exogenous substances other than methemoglobin, in the presence of methylene blue can enhance the reduction of methemoglobin to hemoglobin [77, 91, 92]. NADPH, produced by the hexose monophosphate shunt, reduces NADPH-dependent methemoglobin reductase, an enzyme that has an affinity for methylene blue, among other dyes, and reduces methylene blue to the form leukomethylene blue,

which has a high affinity for methemoglobin (see Fig. 3). The leukomethylene blue reduces the ferric (Fe^{3+}) iron of methemoglobin, forming hemoglobin. The NADPH-dependent methemoglobin reductase, which under usual conditions is responsible for less than 5% of the reduction of methemoglobin to hemoglobin, assumes a major role in the pharmacotherapy of methemoglobinemia. Oxidation of hemoglobin to methemoglobin can occur at high doses of methylene blue due to a reversal of the NADPH-dependent methemoglobin reductase pathway.

Pharmacokinetics

After developing a spectrophotometric assay to measure methylene blue and leukomethylene blue in blood, urine, and tissues, DiSanto and Wagner [93–95] examined the pharmacokinetics of methylene blue in humans, dogs, and rats. In a

Fig. 3 Minor pathway for methemoglobin (*MetHb*) reduction, which is increased in the presence of methylene blue. *NADP* nicotinamide adenine dinucleotide phosphate, *NADPH* nicotinamide adenine dinucleotide phosphate (reduced form)



study of seven adult male volunteers who received 10 mg of methylene blue orally, with subsequent urinary methylene blue determinations for 120 h, 74% (range 53–97%) of the administered material was recovered; 78% (range 65–85%) in the leukomethylene blue form was recovered, showing that methylene blue is well absorbed orally in humans. In the same study, two dogs (one female and one male) received methylene blue orally, with blood concentrations assayed in both animals and urine concentrations assayed in one animal. After receiving 15 mg/kg of methylene blue orally, the male dog had undetectable blood methylene blue 6.9 h after administration. No urine was sampled from this animal. The female dog received 15 mg/kg of methylene blue orally, with urine sampled every hour for 10 h. Only 2.4% of the methylene blue was excreted in the urine over 10 h. This same female dog also received a total of 10 mg of methylene blue orally

followed by methylene blue measurements in the blood at 2.5 and 3.5 h and in the urine every hour for 14 h after the administration. Only 3.8% of the methylene blue was recovered in the urine, and essentially undetectable levels of methylene blue were reported in the blood. The authors concluded that in contrast to humans, dogs have poor gastrointestinal absorption of methylene blue.

Pharmacokinetics of Methylene Blue

Volume of distribution (Vd): 0.222–0.876 L/kg

pKa: 0 to –1

Clearance (CL): 1.98–2.65 L/kg/h

Half-life (T_{1/2}): 5–6.5 h

Time of maximal concentration (T_{max}): 1–2 h

In a second study by the same authors, one dog was administered each of five doses of methylene blue (2–15 mg/kg) at least 2–3 weeks apart

followed by measurement of the compound in the blood. A semilog plot revealed a biexponential relationship between blood concentration of methylene blue and time after administration, which was consistent with a linear two-compartment open model. The data also were well fitted to the nonlinear single-compartment model, however, with even less variability noted in the volumes of distribution, elimination rate constants, and clearance rates. Using the linear two-compartment model, the average volume of distribution was found to be 0.876 L/kg, with a plasma clearance rate of 2.65 L/kg/h. The nonlinear one-compartment model yielded an average volume of distribution of 0.222 L/kg, with a plasma clearance rate of 1.98 L/kg/h.

In rat studies of intravenous administration of methylene blue, six doses ranging from 2 to 25 mg/kg were given, and methylene blue was measured spectrophotometrically in the blood, lungs, liver, kidney, and heart after the rats were killed 3 min after the injection. An average of 29.8% (range 25.3–35.8%) of the administered dose of methylene blue was present in the four tissues 3 min after intravenous administration. This finding provided support to the nonlinear one-compartment model. The pharmacokinetics of methylene blue after oral and intravenous administration also has been studied in humans [96]. After the administration of 100 mg of methylene blue via either the oral or the parenteral route in seven human volunteers, the time course of methylene blue in the blood was measured by high-performance liquid chromatography, and the urinary excretion was determined spectrophotometrically. After oral administration, the maximal methylene blue blood concentration was reached at 1–2 h, with the levels being an order of magnitude lower than that attained after intravenous administration of the same dose. The time course displayed by methylene blue blood concentrations after intravenous administration was multiphasic, requiring an equation containing three exponential terms to fit the data. The urinary excretion of methylene blue at 24 h was approximately 28% and 18% after intravenous and oral

administration, respectively, with one third excreted as leukomethylene blue. The half-life of methylene blue was calculated to be 5–6.5 h.

These same authors studied the organ distribution of methylene blue after oral and intravenous administration in eight rats. One hour after the administration of 10 mg/kg of methylene blue intravenously or intraduodenally, the animals were killed, and the distribution of methylene blue into the blood, brain, intestinal wall, liver, and bile was measured by high-performance liquid chromatography. These studies revealed that greater than 97% of the dose administered intraduodenally was absorbed in this period. Little methylene blue could be detected in the blood 1 h after intraduodenal administration compared with the significantly higher level after intravenous administration; however, there was a 50-fold greater concentration of methylene blue in the intestinal wall after intraduodenal administration than that measured after intravenous administration. The authors offer this “first pass distribution” as the explanation for the order-of-magnitude difference in the methylene blue blood concentrations and area under the concentration curve found after intravenous and intraduodenal administration. As a result of the experimental differences noted between species and within the same species, as attested to by previous studies in humans, dogs, and rats, the pharmacokinetic profile of methylene blue requires further elucidation.

Special Populations

Neonatal Patients

Neonates, especially premature ones, are expected to be more vulnerable to the formation of methemoglobin and to the development of side effects from methylene blue therapy if appropriate doses are not used. Neonates may be more vulnerable to the oxidative stresses of the environment for the following reasons: (1) NADH-dependent methemoglobin reductase activity or levels or both are not fully acquired until age 3–6 months (perhaps longer in premature infants) [97–100];

(2) although this idea is controversial, the fetal hemoglobin may be oxidized more readily into methemoglobin than the adult type [101, 102]; and (3) the skin of infants (especially premature infants) is much more permeable to some external toxicants than the skin of children or adults. Heinz body hemolytic anemia has been noted in premature infants in whom methylene blue was instilled to ensure proper placement of a nasojunal tube [103].

Exposure of an infant during intra-amniotic infusion of methylene blue to determine prepartum leakage or the presence of twins may result in methemoglobinemia, acute hemolytic anemia with Heinz body formation, hyperbilirubinemia, photosensitization of the skin with subsequent desquamation in the newborn, and possibly intestinal obstruction [37–50]. Goluboff and Wheaton first reported methylene blue-induced hemolytic anemia in the treatment of methemoglobinemia in an infant [104]. The doses used were excessive, however, a total of > 26 mg/kg in one infant and > 35 mg/kg in the second infant. Many reports showed that newborn infants, including premature ones, with methemoglobinemia from an intoxicant may be treated safely with intravenous methylene blue at a dose of 1–2 mg/kg without adverse effects (level of evidence [LoE]III) [79–82]. The 1–2 mg/kg dose may not be required, however. Hjelt and colleagues [105] treated 13 infants with a mean gestational age of 28 weeks and birth weight average of 895 g with methylene blue for methemoglobinemia. In these neonates, intoxicated via the skin and respiratory tract by parachloraniline produced by the heating of chlorhexidine, the mean methemoglobin concentration was 19% (range 6.5–45.5%). Intravenous methylene blue administered at a dose of 0.3–0.9 mg/kg was found to be as effective as the 1–1.6 mg/kg initially used in this group. In the treatment of neonates with methemoglobinemia, a lower dose of intravenous methylene blue may be effective. A problem commonly encountered in small infants is intravenous access. Methylene blue at a dose of 1 mg/kg administered by the intraosseous route over 3–5 min has been shown to be effective in the

treatment of methemoglobinemia in a 6-week-old infant without adverse effects [106].

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disorder that results in an altered primary structure of G6PD with a subsequent reduction in the enzyme's functional activity [90, 107]. A male with the disorder or a female homozygous for the mutant gene would be expected to express the defect fully. Numerous variants of this enzyme deficiency exist. The African type, the G6PD A variant, is estimated to be present in approximately 11% of African Americans. The G6PD activity level within the erythrocyte of unaffected individuals normally decreases as the RBCs age. An accelerated rate of activity loss is seen in the African type of G6PD, with only 10% residual activity present mostly in the younger RBCs. An even greater rate of loss is found in the Mediterranean type of the deficiency, which may be present in 2.5–25% of that population [108, 109]. Heinz body hemolytic anemias and methemoglobinemias may be produced by the administration of methylene blue to patients with G6PD deficiency [7, 110, 111]. An absence of G6PD, the first enzyme in the hexose monophosphate shunt pathway, results in the absence of NADPH production within the RBCs. Without NADPH, the RBC is unable to reduce methylene blue to leukomethylene blue. The resultant proportionately higher levels of the electron acceptor (oxidizing agent) methylene blue may produce hemolysis and, paradoxically, methemoglobinemia in the G6PD-deficient patient.

Methylene blue administered to a G6PD-deficient patient with methemoglobinemia would not be expected to be effective because of the absence of sufficient NADPH. However, a G6PD-deficient patient may possess only a partial deficiency of the enzyme. This is true especially in a heterozygous female, who may possess nearly normal activity levels and display some lowering

of methemoglobin levels after methylene blue therapy [112, 113]. Methylene blue administration remains the first-line therapy for methemoglobinemia, even in G6PD-deficient individuals. If the recommended dose of 1–2 mg/kg of intravenous methylene blue does not produce a response in these individuals, additional doses of methylene blue should be avoided owing to the possibility of escalating further the already elevated levels of methemoglobin and inducing a hemolytic anemia.

Other Patients

Patients not expected to respond to methylene blue include those with sulfhemoglobinemia, fully expressed G6PD deficiency (X-linked), NADPH-dependent methemoglobin reductase deficiency [114], NADH-dependent cytochrome-*b*₅ reductase deficiency (autosomal recessive) [115], cytochrome-*b*₅ deficiency (autosomal recessive) [116], and hemoglobin M (autosomal dominant) [117]. Patients already treated with excessive doses of methylene blue who have developed methemoglobinemia may experience an escalation of methemoglobin concentration with further methylene blue administration. Lastly, patients poisoned with an overwhelming amount of intoxicants or poisons characterized by continual gastrointestinal absorption or metabolite formation may seem not to respond to methylene blue.

Methylene blue has been used as adjunctive therapy in toxicities and overdoses other than methemoglobin producers. Through its ability to inhibit nitric oxide synthase (along with scavenging nitric oxide), it has been reported to have been used successfully in treating refractory distributive shock due to atenolol/amlodipine overdose along with mixed valproate, carbamazepine, quetiapine, and fluoxetine overdose (LoE III) [52–56, 118]. In the latter case, a loading dose of 1.5 mg/kg and continuous infusion of 1.5 mg/kg for 12 h followed by 0.75 mg/kg for 12 h resulted in rapid improvement in blood pressure [53].

Methylene blue has also been used to treat refractory shock from anaphylaxis with most

case reports involving protamine or radiocontrast as the offending agent [54].

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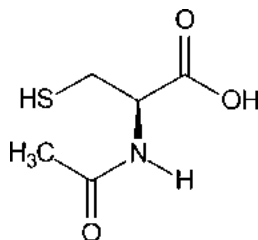
N-Acetylcysteine (NAC) was originally marketed in 1963 as Mucomyst[®] [1] for inhalation use as a mucolytic due to its ability to break disulfide bonds in mucoprotein complexes in chronic bronchopulmonary disease [2]. It was then studied as an antidote for acetaminophen (paracetamol; APAP) poisoning in the 1970s and since then has been the standard of care for treatment of APAP toxicity. NAC has also been investigated as an antidote for many other toxicants [3–13].

In 1973, Mitchell and coworkers described the metabolism of acetaminophen (see Fig. 2 of ► Chap. 59, “Acetaminophen/Paracetamol”) and postulated that acute toxicity of this drug was related to the bioactivation of acetaminophen to a chemically reactive arylating agent [14]. With therapeutic doses of acetaminophen, this highly reactive intermediate (later discovered to be *N*-acetyl-*p*-benzoquinone imine [15]) is conjugated by glutathione, which prevents tissue damage. When hepatic glutathione stores are depleted to 10–30% of normal stores, the reactive intermediate binds to hepatocyte proteins, initiating a cascade of events leading to hepatocellular necrosis [16]. Recent studies question the role of this binding in the pathogenesis of the hepatic necrosis and postulate a large role for the downstream mechanism of oxidative stress [17, 18]. Nevertheless, this earlier discovery led to a search for agents that could modify the metabolism of acetaminophen or interrupt the binding of the toxic metabolite to liver cells. Agents such as cysteamine and methionine were tried with varying

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Fig. 1 Chemical Structure of N-Acetylcysteine



degrees of success [19–21]. While screening potential antidotes in mice, Piperno and Berssenbruegge showed that doses of NAC of up to 1,200 mg provided protection from hepatotoxicity against a fatal dose of 1,500 mg/kg of acetaminophen [22].

Before this experiment, NAC, sold in the United States and elsewhere under the brand name of Mucomyst[®], had been used by inhalation as an adjunct in the removal of abnormally thick, excessive mucus secretions from the lungs. Rumack and Peterson obtained a New Drug Application from the US Food and Drug Administration (FDA) in 1976 to study the effectiveness of the oral administration of NAC in the management of acetaminophen poisoning and in 1978 reported the successful treatment of the first 416 patients [23]. At the same time, the efficacy of intravenous NAC was under investigation by Prescott in the United Kingdom, with the results reported in 1977 [24]. In 1985, NAC received FDA approval for the 72-h oral treatment of acetaminophen poisoning supported by the results of the US National Multicenter Study [25]. Extensive use of NAC in the treatment of acetaminophen poisoning worldwide since the publication of these studies resulted in it being the standard of care in the treatment of APAP poisoning. In 2004, NAC received FDA approval for intravenous use under the brand name of Acetadote[®] [26].

Although not as well studied as in the treatment of acetaminophen poisoning, NAC also has been advocated in the treatment of mercury toxicity [3, 4], carbon tetrachloride hepatotoxicity [5, 6], gold toxicity [7], arsenic toxicity [8], zinc chloride smoke inhalation [9], and *Amanita phalloides* mushroom poisoning [10, 11] as well as to reduce the adverse effects of many cancer chemotherapy drugs [12, 13]. The enthusiasm for the free

radical-scavenging properties of NAC has extended into the treatment of non-toxicology-related critical illnesses, such as septic shock [27], coronary artery disease [28], hepatic failure of any cause [29–31], respiratory distress syndrome [32], abdominal aortic aneurysm repair [33], necrotizing enterocolitis [34], and sickle cell disease [35]. Oral NAC administration has also been studied in the prevention of contrast-induced nephropathy, but several studies failed to show superiority to hydration or other treatments, such as sodium bicarbonate or ascorbic acid [36–42]. In addition, NAC has been promoted as a dietary supplement; it is marketed as a free radical scavenger capable of enhancing immune function, specifically for prevention of colds and influenza and as an adjunct to mainstream therapy for patients with human immunodeficiency virus infection and chronic lung disease [43]. Recent studies also report better recovery following NAC administration after intensive exercise training [44].

Chemical Properties

The chemical structure of NAC is shown in Fig. 1. Other chemical names synonymous with NAC are *N*-acetyl-L-cysteine, L- α -acetamido- β -mercaptopropionic acid, and *N*-acetyl-3-mercaptoalanine.

Physical Properties

The molecular weight of NAC is 163.2 g/mol. It is a crystalline solid at room temperature with a melting point of 110 °F (43 °C). It has a strong, disagreeable, sulfur-esque “rotten egg” odor [45].

Pharmacodynamics

The precise mechanism through which NAC protects from acute acetaminophen toxicity is not entirely known. However, several possible mechanisms have been proposed. First, NAC is deacetylated to cysteine, which can be incorporated into the synthesis of glutathione, raising the intracellular concentration of reduced glutathione

[46]. Second, the availability of cysteine seems to be the rate-limiting step in the synthesis of glutathione, and NAC administration replenishes depleted supplies. Alternatively, NAC may act as a glutathione substitute, providing thiol groups to bind *N*-acetyl-*p*-benzoquinone imine, or encourage the reduction of this metabolite back to acetaminophen, thus sparing hepatocytes [47]. However, animal experiments failed to show that NAC formed significant amounts of conjugate with the reactive metabolite of acetaminophen [48, 49]. In one model, NAC provided a source of sulfate, reduced *N*-acetyl-*p*-benzoquinone imine back to acetaminophen, and increased the synthesis of glutathione [48]. Lastly, new animal findings suggest that the role of NAC in acetaminophen overdose might be more than related to its metabolism itself and could also involve recovery of mitochondrial glutathione levels and support of the mitochondrial bioenergetics [50].

In acute acetaminophen poisoning, NAC, if given within 8 h of ingestion, is highly effective [25, 51] (Grade II-2). Beyond 8 h, efficacy declines with the amount of time during which NAPQI can be produced and subsequently cause hepatotoxicity [25]. However, as demonstrated in randomized clinical trials in selected patients who developed fulminant hepatic failure admitted to a liver unit, the rate of survival was significantly higher in the NAC-treated group even with a delay from ingestion to treatment of more than 50 h [52, 53] (Grade I). NAC may be effective at modulating the cascade of inflammation that occurs in hepatic necrosis, limiting further injury to unaffected liver cells. It also has been postulated that NAC increases hepatic and cerebral microvascular blood flow in patients with liver failure [29]. The efficacy of NAC in acetaminophen poisoning is discussed in more depth in ► Chap. 59, “Acetaminophen/Paracetamol.”

Pharmacokinetics

The pharmacokinetic profile of NAC is difficult to study because the drug exists in the plasma in a multitude of forms – oxidized, reduced, and protein bound. Analytical techniques may detect some but not all of the forms, making comparisons between studies impossible [54].

Oral absorption of NAC seems to be rapid, with peak blood concentrations occurring at 30–90 min after ingestion [55, 56]. The bioavailability of oral NAC may be as little as 10% because of significant first-pass extraction or metabolism by the liver [57]. With such a large first-pass effect with a possible enhancement of portal circulation by direct delivery to the liver and the fact that the target organ of acetaminophen is the liver, the clinical relevance of this low bioavailability explains the manyfold safety margins that were calculated when the dosing schedule for the PO regimen to treat APAP toxicity was proposed. The volume of distribution of unchanged NAC has been estimated to be 0.3–0.5 L/kg [56, 57]. Metabolism of NAC is extensive, with the following oxidized metabolic products found in the plasma: *N,N'*-diacetylcysteine, *N*-acetylcysteine cysteine, *N*-acetylcysteine protein, and *N*-acetylcysteine glutathione. The major metabolic products after complete metabolism are cysteine, cystine, inorganic sulfate, and glutathione [57].

After an intravenous loading dose of 150 mg/kg administered over 15 min, peak plasma NAC concentrations averaged 554 mg/L. Using the 20-h intravenous NAC protocol described by Prescott (150 mg/kg loading dose, followed by 50 mg/kg for 4 h, followed by 100 mg/kg for 16 h), a mean steady-state concentration of 35 mg/L (range 10–90 mg/L) was achieved at 12 h [58]. North and colleagues reported peak NAC plasma levels of 9.3–16.2 µg/mL after the oral administration of 140 mg/kg of NAC [55].

Controversy exists over the effect of concurrently administered oral activated charcoal on the bioavailability of oral NAC. Ekins and coworkers, using 19 healthy volunteers, reported a 39% reduction in the oral absorption of NAC when immediately followed by a 100-g dose of activated charcoal [59]. North et al. reported no decrease in peak plasma NAC concentrations or area under the curve and a slight delay in time to peak when 50 g of oral activated charcoal was given 15 min before a 140-mg/kg oral dose of NAC in three healthy volunteers [55]. Renzi et al. found similar results in six volunteers given activated charcoal and NAC in the same fashion as in the other study [60]. None of these

three studies considered the total amount of NAC that must be supplied to prevent acetaminophen-induced cell injury effectively [55, 59, 60]. Because the oral dose of NAC used (140 mg/kg loading dose followed by 17 doses of 70 mg/kg every 4 h) seems to be effective for even large acetaminophen overdoses, there is an apparent “margin of safety” built into the total dose.

There is preliminary evidence that the pharmacokinetics of NAC may be altered in patients with severe hepatic injury. The pharmacokinetic profile of NAC was compared in nine biopsy-proven cirrhotic patients and compared with six controls [61]. In the patients with cirrhosis, the area under the serum concentration versus time curve was nearly double (152.3 vs. 93.9 mg/L/h) following administration of 600 mg intravenously compared with controls given the same dose. This was mainly due to decreased clearance. NAC has not been formally studied for potential teratogenic effects in humans and is listed as FDA pregnancy category B (animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester). There is greater risk associated with withholding NAC treatment in pregnant women with acute acetaminophen poisoning (Grade III). Although few cases have been reported, deaths of the mother and fetus have occurred when NAC treatment was either withheld or delayed [62, 63]. NAC concentrations in the cord blood of infants whose mothers are being treated with NAC were shown to be equal to concentrations seen in adults being treated with NAC [64]. When 300 pregnant women with acetaminophen overdose were studied, in which 33 were treated with *N*-acetylcysteine, only 17 patients had acetaminophen concentrations greater than or equal to 100 mg/L at 4 h (661 μ mol/L). Twelve pregnancies ended with normal infants, three were electively terminated, and two were spontaneously aborted [65].

Adverse Effects and Contraindications

Oral NAC is generally well tolerated and considered an extremely safe treatment. As a result of the strong rotten egg odor and the gastrointestinal upset commonly seen after acetaminophen overdose, vomiting is the most common side effect observed with oral NAC. In fact, in one study, 51% of 515 acetaminophen overdose patients experienced vomiting while receiving oral NAC [66]. Administration of NAC through an enteral tube in patients that can protect their airways minimizes the nausea caused by the unpleasant odor (Grade III). If vomiting remains a problem, antiemetics may be helpful (Grade III). Scharman reported in a retrospective review of 78 patients with vomiting due to acute acetaminophen poisoning that the vomiting could not be controlled with antiemetic agents in only three patients who finally were treated with IV NAC [67]. Allergic skin reactions were reported in 13 of 515 acetaminophen overdose patients while receiving oral NAC [66]. Anaphylactoid reactions to oral administration of NAC have not been reported, outside of a single case of angioedema [68]. A serum sickness-like disorder with fever, arthritis, adenopathy, rash, and thrombocytopenia occurred in a young man 3 days after starting oral NAC treatment [69].

Intravenous NAC is associated with more adverse events. Anaphylactoid reactions characterized by sudden onset of respiratory distress with dizziness, rash, nausea, bronchospasm, angioedema, and apnea have been reported with intravenous infusion and are thought to be due to high plasma concentrations resulting from overdose or rapid infusion [58, 70–72]. In two instances, these reactions were associated with hypotension and death [73, 74]. The mechanism of this anaphylactoid reaction is believed to be NAC-induced histamine release, and although the role of histamine in these reactions is unclear, some clinicians advocate administration of H_1 -receptor antagonists [75]. Mild anaphylactoid reactions to NAC can be managed by slowing or discontinuing the infusion (Grade III). In many

patients, if it is determined that intravenous therapy is required to prevent acetaminophen-induced hepatic injury, the infusion may be restarted at a slower rate, or oral therapy may be substituted [76] (Grade III). However, given that this reaction is short-lived, and most often mild, many would recommend administration of H₁-receptor antagonists and continue the infusion at the same rate to avoid lowering NAC concentrations below the efficacy threshold (Grade III).

Following the publication of a randomized controlled trial which evaluated the difference in reactions with different infusion rates, some authors recommend routine administration of the initial infusion over 1 h rather than over 15 min. This likely results in reduction of the peak plasma concentration of NAC and may thereby decrease the risk of anaphylactoid reactions, even though the incidence of drug-related adverse events was not shown to be statistically different [77] (Grade II-2). Moreover, the incidence of anaphylactoid reactions seems to be lower in patients with high acetaminophen concentration after an overdose [78].

Vomiting, flushing, rash, pruritus, chest pain, cough, bronchospasm, headaches, dizziness, and convulsions have also been reported with intravenous NAC [79]. Others reported a decrease in prothrombin time at the beginning of NAC infusion in patients without liver impairment [80]. An increase in the international normalized ratio (INR) attributed to an inhibition of factor VII by NAC has also been reported [81–83].

Adverse effects have been reported with intravenous NAC overdose. One author reported a fivefold NAC overdose resulting in hemolysis and hemolytic uremic syndrome [84]. Others discussed a patient who developed cerebral edema and seizures after receiving 100 mg/kg/h for several hours instead of 100 mg/kg over 16 h [85].

The only absolute contraindication to the use of NAC is a well-documented history of a prior severe allergic reaction. In these cases, the benefits of treatment must be weighed against the potential severity of anaphylaxis. True allergic

reactions to NAC are rare because most individuals do not have prior exposure and are therefore not sensitized. With the use of NAC as a dietary supplement, the number of people with prior exposure and the possibility of sensitization may increase (Grade III).

Treatment and Administration

The traditional US dosing protocol (see below) for oral NAC was based on the amount needed to protect experimental animals from acetaminophen toxicity extrapolated to humans with an added safety factor [86]. At the time when NAC's first use was being studied, it was thought that the drug acted primarily as a glutathione surrogate. From the early animal work, it was known that liver injury occurred after the depletion of hepatic glutathione by 70%. Extrapolating from animals, it was estimated that the typical 70-kg human had approximately 6 mmol of glutathione in the liver. The dose of NAC necessary to compensate for a 70% level of depletion was calculated and multiplied by a threefold safety factor to produce the dose that currently is in use. The duration of treatment was determined by taking the worst-case scenario half-life of 12 h, multiplying it by 5 to account for total disappearance. The FDA requested the inclusion of an additional safety factor of 12 h, resulting in the 72-h treatment protocol. This was the best information available at the time that could be used to develop an acceptable protocol for the FDA. With time and experience, the dose and duration have proved effective [87]. The lowest effective dose of NAC for most acetaminophen overdose situations and the optimal duration of treatment are unknown. It is likely in most cases that far more NAC is being given for longer than actually needed.

In the United States, the traditional, although rarely used, oral dosing schedule for NAC is technically an oral loading dose of 140 mg/kg followed by a 70-mg/kg dose every 4 h for 17 doses [23] (Grade II-2). The solution of NAC

should be diluted to a 5% concentration with juice or a soft drink to attempt to enhance palatability [23, 66] (Grade III). It can also be administered via an enteral tube in patients with a protected airway to avoid the risk of aspiration, if vomiting occurs. If vomiting occurs within 1 h of administration, the vomited dose should be repeated (Grade III). As stated previously, the duration of treatment is probably longer than necessary in the great majority of cases, and shorter protocols are almost always used in patients treated orally. A retrospective study of 305 hospital cases of acetaminophen poisoning reported that, in patients who do not show evidence of hepatotoxicity within 36 h of an acetaminophen overdose, treatment with oral NAC may be stopped when the serum acetaminophen is no longer detectable [88] (Grade III). Although, not formally validated, most medical toxicologists empirically stop NAC treatment, APAP concentrations are less than 10 $\mu\text{g/mL}$ (66 $\mu\text{mol/L}$), which is the detectable threshold in most laboratories. If hepatic transaminases or INR were initially abnormal, therapy is generally continued until these are improving.

Prescott and colleagues' intravenous protocol is preferred in most countries and in the United States since the FDA approval of an intravenous formulation in 2004 [89]. Prescott's protocol is 150 mg/kg given intravenously over 15 min followed by 50 mg/kg over 4 h and then 100 mg/kg over 16 h (Grade II-2). This regimen has been shown to be almost universally effective if started within 10 h of ingestion [89]. The other intravenous protocol uses a 140-mg/kg loading dose followed by 70 mg/kg every 4 h for 48 h [51]. Both oral and intravenous protocols have similar efficacy [87].

The administration time of Prescott protocol's first bolus was changed from 15 to 60 min following a 2005 Australian study examining these two durations, even though the study conclusion states that the adverse event profiles were not statistically different between the two infusion periods [77] (Grade II-2).

In children and adult patients weighing less than 40 kg, the 21-h protocol remains the same but the volume of diluent varies. There are no

official recommendations for patients weighing more than 100 kg. A secondary analysis of a retrospective cohort study looked at dosing of NAC in patients weighing more than 100 kg and found that clinicians often use actual body weight [90]. The severity of obesity could not be evaluated because the body mass index was not reported. It is believed that the volume of the functional liver remains constant even in obese patient and that lean weight may be more appropriate to estimate liver size and NAC requirements.

In a 2012 commentary, Rumack questioned the preferred protocol duration and pointed out that extending the third infusion beyond 16 h when the acetaminophen concentration is still detectable (10 $\mu\text{g/mL}$ or 66 $\mu\text{mol/L}$) or when transaminases are still rising is now considered standard of practice [86] (Grade III). Many speculate that the dose administered should be based on the acetaminophen body burden and the duration of five half-lives for acetaminophen removal (Grade III). This theory has not yet been formally studied, but has been translated in practice in many ways, one of which includes doubling the infusion rate of the third bag in the presence of a very high acetaminophen concentration (Grade III). What is considered a very high concentration seems to vary significantly among experts. A recent international survey showed that one-third of the respondents considered doubling the third infusion if the acetaminophen concentration was greater than 453 $\mu\text{g/mL}$ (3,000 $\mu\text{mol/L}$) [91]. The same survey showed that two-thirds believed that doubling the NAC rate of infusion would be appropriate in patients receiving continuous renal replacement therapy or hemodialysis. The EXTRIP group, in their acetaminophen poisoning publication, made a strong recommendation based on a very low level of evidence that NAC should be continued at an increased rate during extracorporeal treatments due to its significant extraction with hemodialysis [92] (Grade III).

The 21-h Prescott protocol is complicated due to three different infusion rates. A retrospective chart review of 227 patients in a regional poison center showed that one-third of the patients had medication errors [93]. Eighteen percent of the patients had an interruption of the infusion of

more than 1 h. When NAC is interrupted, factors such as the amount of acetaminophen still estimated to be present in the blood and the presence or risk of hepatotoxicity need to be considered to know at what rate to restart the infusion. Although there is no guidance from the manufacturer or published recommendation, it is advised that if more than 2–3 h have elapsed, the entire protocol, including the loading dose, should be restarted. Others recommend restarting at the second infusion. In circumstance where the NAC infusion is stopped for longer than 30 min, advice from the local medical toxicology service or poison center is recommended (Grade III).

The amount of fluid to dilute NAC with cerebral edema accompanying liver failure is debated. It might be safe to prepare more concentrated solution of NAC for the second and third infusion using 100-mL and 250-mL bags instead of 500 mL and 1,000 mL. The final concentration would still be smaller than the first infusion and also smaller than the 40 mg/mL suggested to decrease the risk of hyponatremia in the pediatric population [94]. Even though NAC is hyperosmolar, the osmolality of the more concentrated solution would still be lower than the maximum osmolality recommended for peripheral administration.

The future of acetaminophen overdose treatment may become patient-tailored therapy [95]. The NAC dose could be based on the acetaminophen concentration and time from ingestion considering the difficulty in measuring NAPQI directly [86]. Research is ongoing to identify a more specific marker for evolving toxicity like the 3-*para*-cysteinyl acetaminophen and acetaminophen protein adducts. However, these approaches have not yet been proven to be of added value compared to other markers [96, 97].

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Nitrites have been used in a variety of food packaging, manufacturing, and medical settings for more than 150 years. The therapeutic benefit of nitrites was first investigated in the mid-1800s, when nitroglycerin was used as a treatment for angina [1]. Antidotal use of nitrites currently is reserved as a secondary treatment for cyanide poisoning and for consideration in the treatment of severe hydrogen sulfide poisoning. There are no human studies that are available to demonstrate benefits of nitrites in hydrogen sulfide overdoses. Animal studies of nitrites for hydrogen sulfide are equivocal. In the USA, two nitrite agents were packaged together in the cyanide antidote kit (originally manufactured by Eli Lilly and Company); the current cyanide antidote kit contains sodium nitrite (NaNO_2) injection and sodium thiosulfate injection (Nithiodote[®], Hope Pharmaceuticals, Scottsdale, AZ). These agents have been used for the treatment of cyanide toxicity since the 1930s. However, since its approval by the US Food and Drug Administration in 2006, hydroxocobalamin is considered the preferred cyanide antidote in the USA, Europe, and Australia [2].

History

Amyl nitrite was first investigated by Guthrie in 1859 for the treatment of angina [3]. Initial descriptions of the actions of amyl nitrite

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inhalation included profound vasodilatory effects: “When inhaled in doses of from 5 to 10 drops, nitrite of amyl produces in man violent flushing of the face, associated with a feeling as though the head would burst, and a very excessive action on the heart” [2]. At the time, inhaled amyl nitrite was recommended for a variety of conditions, including angina, asthma, tetanus, seizures, strychnine poisoning, and hysterical convulsions. The earliest described use of amyl nitrite as a potential cyanide antagonist was in 1888 by Pedigo [4].

These findings were followed by Mladoveanu and Gheorhiu [5] in 1929 with sodium nitrite being used to block lethal doses of cyanide in dogs. In 1932, Geiger [6] used methylene blue as a methemoglobin former in experimental cyanide poisoning. In 1933, Mota [7] published the first human case of cyanide poisoning successfully managed with sodium nitrite alone. That same year, Chen and colleagues [8, 9] showed dramatic improvements in survival when nitrites were paired with sodium thiosulfate in a canine model of cyanide poisoning. These studies led to the development of the original cyanide antidote kit, which contained sodium thiosulfate plus amyl and sodium nitrites.

Properties

Amyl Nitrite

The molecular weight of amyl nitrite (Fig. 1) is 110 g/mol. It is a clear, yellow, volatile, flammable liquid with an unpleasant, fruity odor. It is nearly insoluble in water but miscible with alcohol and ether [10].

Sodium Nitrite

Sodium nitrite (NaNO_2) has a molecular weight of 69 g/mol. It exists as white or slightly yellow, hygroscopic granules, rods, or powder with a mild saline taste. In aqueous solution, sodium nitrite has a pH of 9 [11].

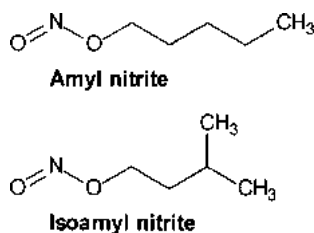


Fig. 1 Chemical structure of the two primary constituents of amyl nitrite

Pharmacokinetics

Absorption

Amyl nitrite is absorbed rapidly via inhalation. Its clinical effects may be seen within seconds and typically continue for 5–10 min.

Sodium nitrite is rapidly absorbed following intravenous (IV) administration with rapid onset of vasodilation.

Metabolism

Nitrite is converted almost completely to nitrate within 1 h and is largely excreted in urine; 33% of the dose is excreted as unchanged nitrate. Urinary nitrite and nitrate concentrations in normal healthy volunteers average 0.2 mg/L and 61 mg/L, respectively [12, 13].

In unexposed persons, plasma nitrite and nitrate concentrations average 0.19 mg/L and 1.22 mg/L, respectively [13]. Serum nitrite concentrations have not been assessed during treatment for cyanide poisoning. As nitrites induce methemoglobinemia, measurement of methemoglobin concentration is frequently used as a marker of nitrite activity.

Pharmacodynamics

The original cyanide antidote kit and the mechanism of action of nitrites in cyanide poisoning were originally described by Chen in 1933 [9]. Cyanide blocks the activity of cytochrome

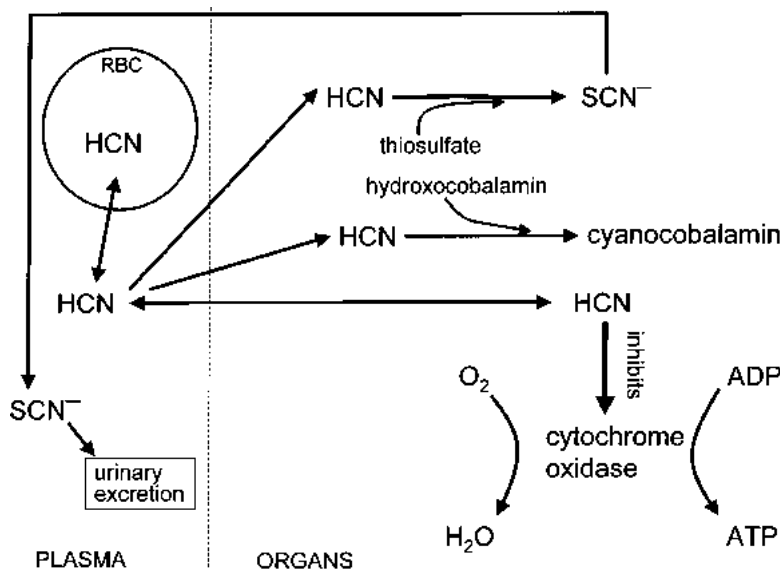


Fig. 2 Schematic diagram of cyanide's distribution and elimination. At physiologic pH, virtually all cyanide is present as hydrogen cyanide (HCN). HCN that has entered plasma after absorption is concentrated within red blood cells, at least in part by binding to the normally small amount of methemoglobin, which contains ferric (Fe^{3+}) iron. HCN also easily diffuses across cell membranes into various organs, where it binds to and inhibits many

enzymes, the most important being cytochrome oxidase. HCN binds to the binuclear center (copper and iron) of cytochrome oxidase to inhibit electron transport through this complex. This produces a decrease in oxygen consumption and, indirectly, a decrease in adenosine triphosphate formation. HCN is detoxified by transsulfuration to thiocyanate (SCN^-), which is excreted in the urine

oxidase, preventing the use of oxygen for cellular respiration (Fig. 2). Nitrites oxidize hemoglobin to form methemoglobin. Because of its high affinity for methemoglobin, cyanide preferentially binds to methemoglobin, forming cyanmethemoglobin (Fig. 3). Further elimination of cyanide occurs through the conversion of cyanide to thiocyanate (SCN^-) via rhodanese. Sodium thiosulfate serves as a substrate for rhodanese, enhancing cyanide clearance.

Despite these findings and the demonstrated clinical benefit of nitrite administration in cases of cyanide poisoning, other pathways for cyanide detoxification have been investigated [14, 15]. In clinical settings, methemoglobin formation lags behind the clinical response to nitrite treatment [15–17]. In experimental animal studies of cyanide exposure in which methemoglobin formation is blocked by administration of methylene blue, the antidotal response to nitrite administration is retained [18].

These observations, plus the enhanced understanding of mitochondrial nitric oxide synthase, led to the discovery of the role of nitric oxide (NO) in electron transport and its importance in the treatment of cyanide poisoning. Nitric oxide alters intracellular binding of cyanide to cytochrome c oxidase in mitochondria, actually displacing cyanide from its binding site [19, 20]. Pearce et al. found that nitric oxide not only functions as a competitive inhibitor of cytochrome c oxidase but is also a substrate which is metabolically converted to nitrite. The displaced cyanide may then be directly converted to thiocyanate or bound to methemoglobin.

Similar to many poisonings, cyanide-exposed patients experience a broad continuum of effects. Wurzburg [21] described a series of patients with acute occupational cyanide exposure who were managed successfully with amyl nitrite and supplemental oxygen alone. In this setting, some workers underwent treatment and were able to return to work and complete their shifts. Other cases describe the

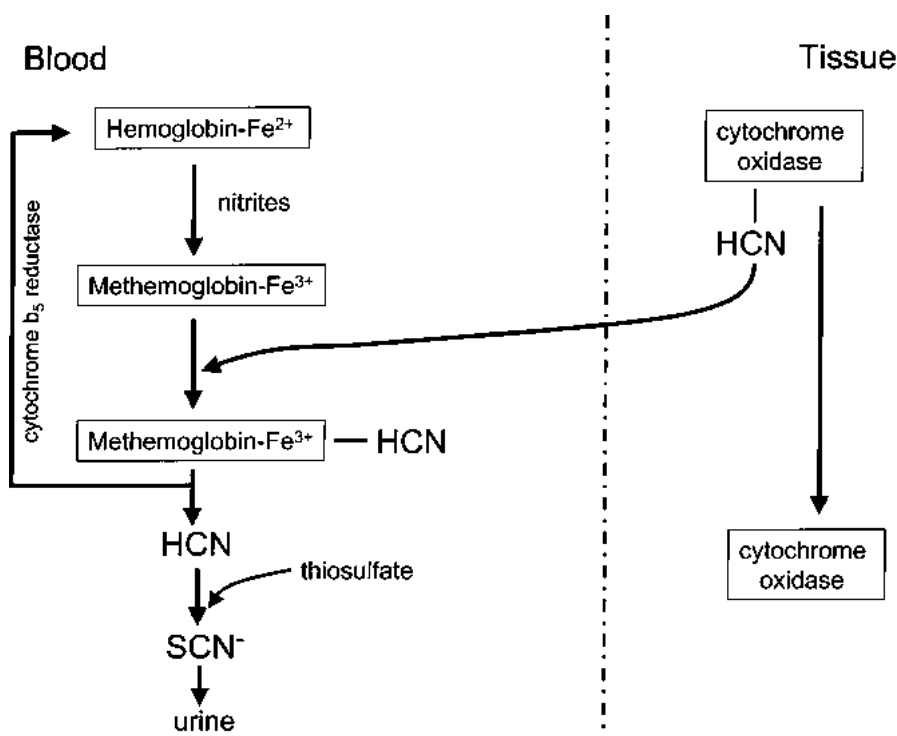


Fig. 3 Antidotal strategies in the treatment of cyanide toxicity with nitrites and thiosulfate. Hydrogen cyanide (HCN) binds to tissue cytochrome oxidase to inhibit oxidative phosphorylation. Nitrite (sodium nitrite or amyl nitrite) converts some ferrous hemoglobin (Fe²⁺) to methemoglobin (Fe³⁺), creating a large circulating sink of ferric iron. HCN quickly

dissociates from cytochrome oxidase and moves from tissue to bind to methemoglobin, forming cyanmethemoglobin and reversing inhibition of cytochrome oxidase. As cyanmethemoglobin is reduced back to Fe²⁺, HCN is released. Sodium thiosulfate markedly enhances transsulfuration of HCN to thiocyanate (SCN⁻)

survival of cyanide-poisoned patients managed simply with aggressive supportive therapy [22, 23]. Survival of patients with even higher whole-blood cyanide concentrations has been reported following treatment with the combination of antidotal and supportive therapies [15, 16, 24].

Overaggressive nitrite use is associated with hypotension, reflex tachycardia, syncope, and cyanosis. One death has been reported secondary to excessive nitrite use [25]. Nitrites are considered secondary treatments for cyanide poisoning and should not be given indiscriminately.

Special Populations

Amyl nitrite and sodium nitrite are listed as US Food and Drug Administration pregnancy risk category C (evidence of teratogenicity in animals but not in

humans) [26]. Patients who are anemic should have the nitrite dose adjusted based on blood hemoglobin concentration (Table 1) [25]. The formation of any amount of methemoglobin in these patients causes a proportionally higher percentage of methemoglobin. Concerns over the administration of nitrites to victims of smoke inhalation exist as nitrite-induced methemoglobin formation may further limit the oxygen-carrying capacity of blood in the presence of carbon monoxide [27]. However, this limitation needs to be understood and managed in the clinical setting of severe and potentially fatal poisoning [28].

Contraindications

Cyanide poisoning is potentially life-threatening. Although some conditions (e.g., severe anemia, methemoglobinemia) may have been at

Table 1 Adjustment of sodium nitrite dose with hemoglobin concentration

Hemoglobin (G/DL)	Initial dose of sodium nitrite (Mg/Kg)
7	5.8
8	6.6
9	7.5
10	8.3
11	9.1
12	10.0
13	10.8
14	11.6

Adapted from Berlin [25]

heightened risk for nitrite toxicity, there are no absolute contraindications to nitrite therapy in the management of cyanide poisoning.

Precautions

Patients with Profound Hypotension

Despite the ability of nitrite therapy to produce vasodilation with resultant hypotension, their use in cyanide poisoning is not contraindicated. The rationale for this is that because cyanide poisoning causes life-threatening hemodynamic compromise, therapy – including with nitrites – is expected to improve overall hemodynamic status. However, treatment with hydroxocobalamin is preferred over nitrite treatment for cyanide overdose in part because of its safety and tolerability.

Patients Taking Phosphodiesterase Inhibitors

There is no specific clinical experience with patients using phosphodiesterase inhibitors being treated with amyl nitrite or sodium nitrite for cyanide poisoning. However, a pronounced hypotensive effect is expected based on the interaction between phosphodiesterase inhibitors and other nitrites [11].

Other Patients

Amyl nitrite is extremely flammable. It should be kept away from any source of open flame or spark.

Adverse Effects

Signs and symptoms of hypotension (dizziness, fainting, mental status changes) are common with cyanide exposures and with nitrite administration. Headache is a commonly encountered side effect, especially following amyl nitrite use. This effect generally is short-lived.

Administration

Amyl Nitrite

Nitrites are now considered part of a secondary treatment for cyanide overdose. The primary treatment is hydroxocobalamin. However, in the setting where hydroxocobalamin is not available but nitrites are, amyl nitrite pearls may be broken in gauze, cloth, or a sponge and then held close to the nose and mouth of a spontaneously breathing patient. In patients requiring assisted ventilation, the broken pearls may be placed into the lip of the face mask, inside the resuscitation bag, or in a port access of an endotracheal tube. Directions for administration of amyl nitrite from the previous version of the cyanide antidote kit were glass pearls should be crushed in gauze and inhaled for 30 s out of each minute. The pearls could be replaced with a fresh one every 2–4 min, and the use of amyl nitrite should be considered, at best, a temporary measure until sodium nitrite can be administered [29].

Sodium Nitrite

If the determination is made to use nitrite therapy after IV access is established, sodium nitrite may be considered a part of the secondary antidote for cyanide poisoning (along with sodium thiosulfate) when hydroxocobalamin is unavailable (level III recommendation). It is possible in patients with a positive clinical response to amyl nitrite and supportive care that sodium nitrite therapy may not be needed. In patients with

significant cyanide poisoning and when hydroxocobalamin is unavailable, sodium nitrite and thiosulfate should be administered as soon as possible (level III recommendation).

The usual adult intravenous dose of sodium nitrite is 300 mg (one 10-mL vial of a 3% solution); the pediatric dose is 0.12–0.33 mL/kg to a maximum of 300 mg (10 mL) (level III recommendation) [22]. The dose can be given intravenously over at least 5 min or diluted in 50–100 mL of intravenous fluid and infused slowly (level III recommendation). Blood pressure monitoring is essential during nitrite administration [25].

Early animal studies showed the superiority of the combination of nitrite and thiosulfate over either agent alone in the treatment of cyanide poisoning [8, 9]. The use of sodium nitrite plus sodium thiosulfate was shown to be protective to 18 times the median lethal dose of cyanide in dogs. If sodium nitrite is given for cyanide poisoning, it should be followed by an appropriate dose of sodium thiosulfate (level III recommendation).

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Octreotide (Sandostatin) is a synthetic analogue of somatostatin that has similar, if not identical, pharmacologic activity to this endogenous hormone but is longer acting and more potent [1–11]. Somatostatin was first isolated from the hypothalamus and characterized as an inhibitor of pituitary growth hormone secretion in 1973 [12]. It is synthesized and widely distributed throughout the body (particularly in neurons, pancreas, and gastrointestinal tract but also in immune and inflammatory cells), modulates neurotransmission (primarily in the central nervous system), and has generalized inhibitory effects on paracrine function. With respect to the last-mentioned, somatostatin inhibits the release of the following:

Thyrotropin
Prolactin
Gastrin
Motilin
Vasoactive intestinal peptide
Pancreatic polypeptide
Glicentin
Glucagon
Insulin
Insulin-like growth factors (somatomedins)
Parathyroid hormone
Luteinizing hormone
Calcitonin
Renin
Adrenocorticotrophic hormone
Growth hormone

This is an update of the chapter written by Christopher H. Linden for the first edition of this text.

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Somatostatin is involved in the regulation of many physiologic processes and also inhibits exocrine secretions from the pancreas, gut, gallbladder, and salivary glands. It consists of two main peptides, SST-14 and SST-28, which bind to and activate five related G-protein coupled receptors [1–5]. Octreotide, lanreotide, and pasireotide are the only three somatostatin analogs currently in widespread clinical use and approved for use in the USA. Octreotide and lanreotide are cyclic octapeptides, while pasireotide is a cyclohexapeptide. They display the greatest affinity for somatostatin type 2 and type 5 receptors found in the pituitary gland and the pancreas [6–12].

Indications for the use of octreotide currently approved by the US Food and Drug Administration are limited to the treatment of acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors [11]. Clinical experience also supports its use in the treatment of nonsecretory, corticotropin-secreting, and thyrotropin-secreting pituitary adenomas; pancreatic islet cell tumors; congenital and acquired hyperinsulinism; nesidioblastosis; acute pancreatitis; pancreatic fistulas and pseudocysts; bleeding from esophageal varices and peptic ulcers; and diarrhea associated with ileostomies, short bowel syndrome, intestinal graft-versus-host disease, radiation colitis, intestinal fistulas, and acquired immunodeficiency syndrome [6–10, 13, 14]. Its effects on other endocrine disorders, nonendocrine tumors, hematologic function, immunologic function, neurologic function, vascular disease, and a host of other processes, including aging, are under investigation. Lanreotide is a longer-acting depot preparation used for acromegaly and gastroenteropancreatic neuroendocrine tumors. Pasireotide is used to treat acromegaly and Cushing's syndrome.

The ability of octreotide to inhibit the secretion of insulin, glucagon, and other insulin counterregulatory hormones makes it a rational choice for the treatment of poisoning due to sulfonylureas and other drugs causing hyperinsulinemia (see ► Chap. 70, "Antidiabetic Agents"). With proven efficacy, low cost, ease of administration, and a highly favorable safety profile, it has virtually all the properties characterizing an ideal antidote.

Although much more is known about the pharmacology of octreotide (and somatostatin), the remainder of this chapter focuses only on the actions relevant to the understanding and treatment of drug-induced hyperinsulinemic hypoglycemia.

Pharmacodynamics

Physiologically, somatostatin acts as a gastrointestinal and pancreatic counter-regulatory hormone [1, 3, 15]. It is secreted from pancreatic islets of Langerhans delta cells in response to increases in blood glucose, amino acids, fatty acids, and gastrointestinal hormones that occur after the ingestion of food. Systemic effects include decreased gastrointestinal and gallbladder motility and secretory activity with consequent slowing of the digestion and absorption of food. Locally, somatostatin inhibits the pancreatic secretion of insulin from islet beta cells and of glucagon from islet alpha and intestinal alpha-like or L cells, decreasing the uptake and use of absorbed nutrients. Although pancreatic alpha cells are about 50 times more sensitive to somatostatin than beta cells, their effect on insulin secretion is more prolonged than that on glucagon secretion. Teleologically, by preventing the rapid assimilation and consequent exhaustion of ingested food, somatostatin lessens inequalities between the intermittent supply and continuous demand for nutrients, increasing the overall efficiency of food processing.

Sulfonylurea drugs counteract hyperglycemia by enhancing the release of insulin from pancreatic islet beta cells in response to glucose, the principal stimulus and an essential permissive factor for insulin secretion [3, 16, 17]. Their mechanism of action is similar to that of high plasma glucose concentrations: inhibition of the pancreatic islet beta cell membrane adenosine triphosphate (ATP)-sensitive potassium (K^+) channels leading to membrane depolarization with consequent calcium (Ca^{2+}) influx through voltage-sensitive Ca^{2+} channels, mobilization of Ca^{2+} from the endoplasmic reticulum, increased intracellular Ca^{2+} , and insulin secretion.

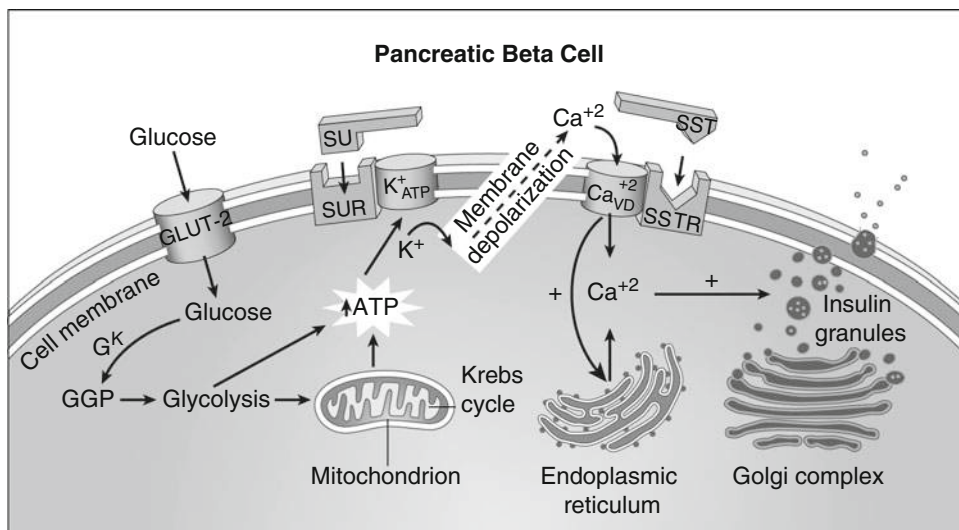


Fig. 1 Schematic diagram of a pancreatic beta cell showing the regulation of insulin secretion. Glucose is transported into the beta cell by a glucose-transporter protein (GLUT-2). The enzyme glucokinase (GK) initiates glycolysis by catalyzing the transfer of phosphate from adenosine triphosphate (ATP) to glucose, resulting in the formation of glucose-6-phosphate (G-6-P). ATP generated by subsequent steps in the glycolytic pathway and by the Krebs (citric or tricarboxylic acid) cycle leads to closure of ATP-sensitive potassium channels (K^+_{ATP}) and membrane depolarization. Membrane depolarization results in opening of voltage-dependent calcium channels (Ca^{2+}_{VD}), influx of extracellular calcium, and subsequent release of calcium from intracellular (endoplasmic reticulum) stores. Increased intracellular calcium promotes the exocytosis

of insulin granules (Golgi vesicles) with release of insulin into extracellular fluid and the systemic circulation. Although the phosphorylation of glucose is a rate-limiting step, beta cell GK has a high Michaelis constant (K_M , the substrate concentration at which the reaction rate is half of the maximal value) for glucose. Glucose metabolism and ATP production, potassium and calcium channel activity, intracellular calcium concentration, and insulin release are controlled primarily by the intracellular glucose concentration. Sulfonylureas (SU) inhibit potassium efflux by binding to specific receptors (SUR) associated with K^+_{ATP} channels and enhance the release of insulin. Somatostatin (SST) and its analogues, such as octreotide, inhibit calcium influx by binding to receptors (SSTR) associated with Ca^{2+}_{VD} channels, inhibiting the release of insulin

Sulfonylureas bind to specific receptors associated with K^+ channels on the beta cell membrane, whereas glucose generates ATP through its oxidative metabolism within beta cells. Intracellular Ca^{2+} is the ultimate insulin secretagogue, with increases in intracellular calcium promoting the synthesis and release of insulin (Fig. 1).

The action of octreotide (and of somatostatin and other analogues) on beta cell Ca^{2+} disposition is diametrically opposite to that of the sulfonylureas, and the mechanism is slightly different [3, 18, 19]. Octreotide binds to specific somatostatin membrane receptors (SST receptors or SSTRs) associated with Ca^{2+} channels, resulting in decreased calcium conductance, decreased intracellular Ca^{2+} , and inhibition of insulin secretion. Opening of potassium channels with subsequent

membrane hyperpolarization also may be involved. Somatostatin receptors are coupled to G proteins. To date, five SSTR subtypes have been identified. Receptor affinity and selectivity differ from one somatostatin analogue to another. Subtypes 2 and 5 mediate insulin secretion. Octreotide's action does not seem to be mediated by increased potassium efflux through K^+ channels [20]. Suppression of insulin secretion by octreotide has been documented in experimental [21–24] and human sulfonylurea poisoning [25, 26] (see Fig. 1).

The antidotal effects of octreotide in sulfonylurea poisoning also may be due to its antagonism of glucagon and possibly other counterregulatory hormones. Octreotide not only inhibits the secretion of glucagon in response to hypoglycemia but

also inhibits the actions of glucagon [1, 3]. Glucagon activates adenylyl cyclase, which catalyzes the synthesis of cyclic adenosine monophosphate (AMP), whereas octreotide inhibits this enzyme. In the absence of octreotide, this action of glucagon increases cyclic AMP levels, and this stimulates glycogen phosphorylase (the rate-limiting enzyme in glycogenolysis), inhibits glycogen synthase, and increases intracellular Ca^{2+} , effects that may lead to hyperglycemia, rebound hyperinsulinemia, and recurrent hypoglycemia after glucose administration (see Fig. 1 and see ► Chap. 70, “Antidiabetic Agents”). As with insulin, SSTR subtypes 2 and 5 mediate glucagon secretion [18, 19]. Octreotide has been shown to decrease epinephrine, norepinephrine, and glucagon levels in experimental models of glipizide overdose [21].

Octreotide also is likely to be effective in treating hyperinsulinemic hypoglycemia due to other drugs, including insulin itself (see ► Chap. 70, “Antidiabetic Agents”). One report described improvement in glucose concentrations after octreotide was administered to a 56-year-old male who overdosed on insulin glargine [27]. The meglitinides (repaglinide and nateglinide) act similarly to sulfonylureas to increase insulin secretion by blocking ATP-dependent potassium channels. This leads to depolarization of the membrane and facilitates calcium entry through calcium channels, thereby stimulating insulin release from the pancreatic beta cells. At least one report described successful treatment of repaglinide-induced hypoglycemia with octreotide [28]. Its use has also been reported in a case of quinine-induced hypoglycemia [29]. Octreotide is relatively inexpensive, costing less than \$10 US for a 100- μg dose.

Pharmacokinetics

Octreotide is well-absorbed after subcutaneous administration, with peak plasma concentrations averaging 5.2 ng/mL 0.4 h after a 100- μg dose in healthy volunteers [11]. It is about 65% bound to plasma lipoproteins, has a small volume of distribution (approximately 0.2 L/kg), and a half-life of

about 1.7 h, which is much longer than that of somatostatin (1–3 min). About one third of the dose is excreted unchanged in the urine, and the half-life is doubled in renal dialysis patients and the elderly. The metabolic fate of the remaining fraction has not been determined.

Octreotide is also absorbed after oral administration, though bioavailability is low. A 2-mg oral dose results in peak plasma drug levels similar to a 50- μg subcutaneous dose, with the time to peak level delayed about 1.5 h.

Contraindications and Adverse Effects

Except for hypersensitivity, there are no contraindications to octreotide use [1, 3, 5–11]. Overall, octreotide is well tolerated. As with most subcutaneously administered medications, burning pain at the injection site can occur. In the three largest studies and case series evaluating octreotide for sulfonylurea poisoning in adults, no adverse effects were reported among almost 40 patients [30–32]. Similarly, a larger retrospective study in pediatric patients reported no adverse effects in 121 patients [33]. There are a few scattered reports of adverse effects temporally related to octreotide administration for sulfonylurea poisoning, but a cause-and-effect association is unclear. A pediatric patient developed hypertension and apnea 30 min after administration of octreotide; the dose was not reported [34]. Hyperkalemia and worsening heart failure have each been reported once, both in adult patients [35, 36]. When used for congenital diseases such as acromegaly and hyperinsulinism, octreotide has been associated with cases of drug-induced hepatitis [37–40]. However, there may have been other contributing factors and the hepatitis occurred after prolonged use in each case. Hepatitis has not been reported with the short-term therapeutic use of octreotide for sulfonylurea overdose.

Octreotide has been used in all age groups, including neonates and pregnant women. Although no adverse effects on fertility or fetal development have been noted in experimental animals, because octreotide has not been studied extensively in pregnant women, it has a Food and Drug

Administration category B use-in-pregnancy rating (no evidence of risk in humans; the chance of fetal harm is remote but remains a possibility).

Treatment

There have been numerous case reports, case series, retrospective studies, and even randomized controlled trials examining octreotide for sulfonylurea poisoning. Both pediatric and adult populations have been studied. One of the earliest studies demonstrated that a continuous octreotide infusion (30 ng/kg/min or 126 µg/h for a 70-kg person) was effective in lessening the severity of hypoglycemia in nondiabetic human volunteers ($n = 8$) who ingested a large dose of glipizide (1.45 mg/kg) [21]. This therapy reduced the need for exogenous glucose in all subjects and entirely eliminated it in half. It was also found that without octreotide, some patients experienced recurrent hypoglycemia up to 30 h following glipizide ingestion.

Pediatric Patients

There are at least 10 published reports of octreotide use in pediatric patients [33, 34, 43–50]. Fifteen children are discussed in nine small studies [34, 43–50]. Ages ranged from 1 to 17 years with most under age 6 years. Fourteen of the 15 children ingested second-generation sulfonylureas (eight glipizide and six glyburide or glibenclamide); the drug was not reported in the remaining case. Octreotide was generally administered after intravenous (IV) 10–50% dextrose boluses and infusions failed to correct hypoglycemia or maintain euglycemia. The dose range of octreotide was 0.51–2.5 µg/kg IV or SC; most patients received octreotide 1–1.5 µg/kg IV. Octreotide resulted in correction of the serum glucose concentration in all 15 patients and recurrent hypoglycemia was observed in eight. Seven patients received additional octreotide doses as IV boluses or infusion. Time to recurrent hypoglycemia after octreotide administration ranged from 6 to 17 h.

One group retrospectively examined 9 years of the American Association of Poison Control Centers' National Poison Data System to evaluate octreotide as an antidote for sulfonylurea overdose in children younger than 6 years of age [33]. One hundred twenty one cases were identified in which a child ingested a sulfonylurea and experienced at least one episode of hypoglycemia (median age 22 months). Prior to octreotide administration, the median glucose concentration was 44 mg/dL (range 2–62 mg/dL). Glipizide was the most frequently ingested sulfonylurea accounting for 70% of cases. Though octreotide doses were not recorded, the number of hypoglycemic episodes before octreotide (median, 2) was significantly higher than after octreotide (median, 0; $P < 0.0001$). After octreotide, 99 of 121 had no further hypoglycemic episodes. Twenty-two children experienced a hypoglycemic episode after the first dose of octreotide, occurring at a median time of 5 h (range, 1–25 h) after administration. Further details about these cases were not reported.

Adult Patients

At least 16 published reports describe octreotide use for sulfonylurea poisoning in adults [25, 30–32, 35, 36, 41, 42, 51–58]. Thirteen case reports (16 patients) described exposures to first and second generation sulfonylureas, with 10 identified as glyburide/glibenclamide or glipizide [25, 35, 36, 41, 42, 51–58]. The most common dose of octreotide was 50 µg subcutaneously, followed by 50 µg subcutaneously every 6–12 h for 2–3 doses. A 100 µg subcutaneous dose was also used in a few cases, followed by 50–100 µg subsequent doses. Two patients were treated with octreotide by continuous IV infusion (30 ng/kg/min for 13 h, and 50 µg/h). Five patients developed recurrent hypoglycemia 2–9 h after octreotide was administered. Six patients had serum insulin or C-peptide levels measured during hypoglycemia; all were elevated. Three of the six had repeat levels drawn after octreotide administration; all had decreased.

Six adult patients were reported in a case series, all of which experienced hypoglycemia after therapeutic doses of sulfonylureas (4 glimepiride, 1 glyburide, and 1 glipizide) [32]. Intermittent IV administration of 50% dextrose did not result in a sustained and adequate blood glucose response. The patients were treated with octreotide 50 µg subcutaneously every 8 h, receiving 2–4 doses. Half experienced recurrent hypoglycemia after initial octreotide administration. Three patients had serum insulin and C-peptide levels measured during hypoglycemia; all were elevated and decreased after octreotide. Nine adult patients were retrospectively reviewed after ingestion of a sulfonylurea (6 glyburide and 3 glipizide) [30]. The initial octreotide dose was 40–100 µg subcutaneously, followed by 40–100 µg subcutaneously every 6–12 h, 2–3 doses in six patients and 125 µg/h IV for 9 h in one patient. There were 3.2 hypoglycemic events per patient recorded before octreotide compared to 0.2 per patient after octreotide ($p = 0.008$). There were 72.5 g of 50% dextrose administered before octreotide compared to 5 g after octreotide ($p = 0.004$). Two patients had recurrent hypoglycemia, one 14 h after octreotide and the other 36 h after octreotide. In the first patient, hypoglycemia occurred more than 30 h after the ingestion of glyburide. The second patient experienced recurrent hypoglycemia 40 h after ingestion of extended-release glipizide. Both were beyond the duration of effect of octreotide.

One randomized, double-blind, placebo controlled trial exists evaluating the efficacy of octreotide in sulfonylurea poisoning [31]. In addition to standard dextrose therapy, 22 patients received octreotide 75 µg subcutaneously after sulfonylurea-induced hypoglycemia. Eighteen patients served as controls and received placebo in addition to standard dextrose therapy. The mean glucose values for octreotide patients compared with placebo were consistently higher during the first 8 h but showed no difference in subsequent hours. The mean glucose difference in the octreotide group versus placebo was 56 mg/dL in hours 1–3 after administration and 127 mg/dL in hours 4–8. Ten octreotide-treated patients experienced recurrent hypoglycemia

compared with six patients in the control group. Only one dose of octreotide was administered. All patients were admitted to the hospital and monitored for recurrent hypoglycemia for at least 24 h.

Indications for octreotide treatment are not well defined. Although it is generally agreed that octreotide is indicated for recurrent hypoglycemia due to sulfonylurea poisoning, whether it should be given after the first episode of hypoglycemia is unclear. Doing so is reasonable in patients who are likely to develop further episodes (e.g., patients with large or intentional overdoses or children with an unsupervised ingestion of an unknown amount), but it may prolong unnecessarily the period of observation for patients who are not (e.g., patients with therapeutic misadventures). As always, the reliability of the history must be assessed when making such decisions. Given that the overdose history is often inaccurate, incomplete, or unobtainable, we prefer to reserve treatment for patients with a documented second episode of hypoglycemia (Grade III recommendation). Treatment recommendations for these patients are discussed in detail in ► [Chap. 70, “Antidiabetic Agents.”](#)

Administration

Based on clinical experience and the available data, a subcutaneous dose of 1–2 µg/kg (50–100 µg in adults) every 6–8 h can be expected to be effective for the treatment of sulfonylurea-induced hypoglycemia (Grade II-2 recommendation). A continuous IV infusion of the same dose on an hourly basis also is likely to be effective. IV administration is more expensive and more difficult to prepare and administer (and more susceptible to dosing errors). Because there is no evidence that this route and method of dosing are superior or necessary, we recommend intermittent subcutaneous dosing as the preferred treatment regimen. For adult patients, we recommend 100 µg subcutaneously every 6 h (GRADE I recommendation). For pediatric patients, we recommend 1.5 µg/kg subcutaneously every 6 h (Level of Evidence II-3) (Table 1).

Table 1 Octreotide dose recommendations with associated GRADE ratings

Population	Dose	Supporting studies	GRADE rating
Pediatric	1–1.5 mcg/kg subcut	Case reports, case series, and one large retrospective review of national poison center data [33, 34, 43–50]	II-3
Adult	50–100 mcg subcut	13 case reports, 2 case series, and one randomized, placebo, controlled trial [25, 30–32, 35, 36, 41, 42, 51–58]	I

Octreotide is administered parenterally for the treatment of hyperinsulinemic hypoglycemia due to drug overdose. Solutions containing 50 µg/mL, 100 µg/mL, 200 µg/mL, 500 µg/mL, or 1000 µg/mL are available for subcutaneous injection or intravenous infusion. Long-acting, sustained-release preparations containing 10 mg/2 mL, 20 mg/2 mL, or 30 mg/2 mL for intramuscular (intragluteal) injection at monthly intervals (e.g., Sandostatin LAR Depot) are used for the treatment of chronic conditions. No oral formulations of octreotide are commercially available. Similar doses to the above are likely effective for the treatment of other drug-induced states of hyperinsulinism (see ► [Chap. 70, “Antidiabetic Agents”](#)), but there is little experience with its use in this setting.

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Despite the long history of opioid use, opioid receptor antagonists were not developed until the twentieth century. The impetus for their development was, at least in part, the increasing incidence of abuse and overdose, coinciding with the understanding that minor structural alterations to certain opioid receptor agonists impart receptor antagonist activity. In the 1940s, *N*-allylnormorphine (nalorphine) was widely used to reverse the adverse effects of opioid receptor agonists, but its mixed receptor agonist-antagonist profile was not defined until 1954 [1]. Further refinements in opioid structure-activity relationships led to the development of naloxone and naltrexone (Fig. 1), the opioid receptor antagonists currently in routine clinical use. Oxymorphone is an opioid receptor agonist with structural similarity to morphine; replacement of the N-17 methyl group on oxymorphone with a larger functional group results in the formation of naloxone and naltrexone [2]. Nalmefene, an opioid receptor antagonist that was discontinued from the US market in 2008, is a 6-methylene derivative of naltrexone.

Pharmacodynamics

Opioid receptor antagonists are structural analogues of opioid receptor agonists and bind effectively at the μ , κ , and δ receptors. These agents exert receptor antagonist activity predominantly at the μ receptor; higher doses are required

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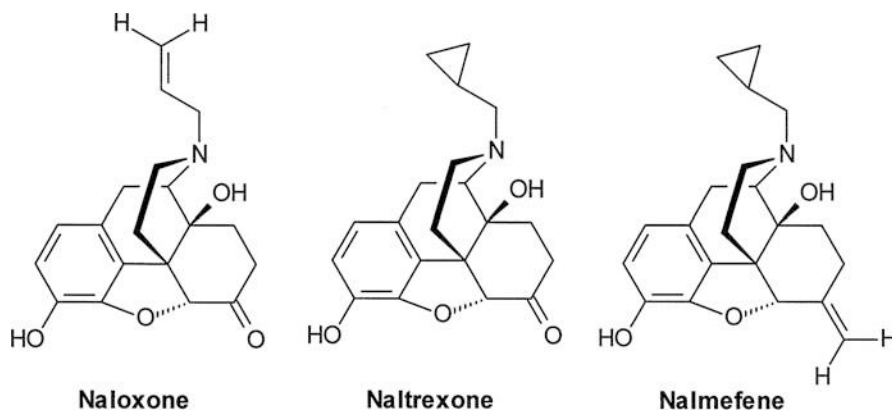


Fig. 1 Chemical structures of morphine, nalmefene, naloxone, and naltrexone

to affect the κ and δ receptors. As competitive receptor antagonists, they have no significant effect in the absence of opioid receptor agonists, in opioid naïve, or in non-opioid-dependent patients.

With adequate dosing, opioid receptor antagonists reverse the pharmacologic effects of both endogenous and exogenous opioid receptor agonists at the μ , κ , and δ receptors, as well as prevent opioid agonism if given as a pretreatment. Reversal of opioid agonism corrects most signs of opioid poisoning including: respiratory and CNS depression, analgesia, miosis, inhibition of baroreceptors, vasodilation, and gastrointestinal immobility. Opioid receptor antagonists do not reverse effects that are not mediated through opioid receptor interactions, including opioid-associated histamine release (e.g., morphine and codeine) [3, 4] or the sodium channel receptor antagonist effects of propoxyphene.

The goal of opioid receptor antagonist administration is alleviation of respiratory depression and avoidance of withdrawal precipitation. Rarely it is necessary to administer higher doses (≥ 0.04 mg) of naloxone *initially* because the primary desired effect of naloxone, the reversal of respiratory depression, may be temporized by exogenous ventilation using a bag-valve-mask apparatus. Experimental studies demonstrate that catecholamine surge associated with naloxone administration in hypercapnic animals may be ameliorated by establishment of normocapnia or hypocapnia prior to its administration [5]. The use

of careful naloxone titration to allow slow reversal and spontaneous normalization of hypercapnia may prevent the effect of precipitation of opioid withdrawal yet allow a larger dose ultimately to be administered in the rare instances in which it is required (evidence level II-3) [5]. The most consequential effects of opioid receptor antagonists are at the μ receptor subtype, where they may precipitate the opioid withdrawal syndrome in opioid-dependent patients, characterized by yawning, rhinorrhea, lacrimation, nausea, vomiting, diaphoresis, piloerection, mydriasis, abdominal cramping, diarrhea, and insomnia. Abstinence-related opioid withdrawal is not generally considered life threatening. However, rapid opioid withdrawal, often iatrogenic or precipitated, carries significant morbidity and mortality as profound catecholamine surge can lead to cardiac dysrhythmias and acute lung injury [6]. In addition, precipitating withdrawal-associated emesis in a patient whose mental status is altered concomitantly by another substance (e.g., ethanol) or another condition (e.g., head injury) may lead to catastrophic effects. Specifically, pulmonary aspiration and its sequelae may occur owing to the inability to clear or protect the airway. To that end, the lowest dose necessary to reverse the patient's respiratory depression should be administered initially (e.g., 0.04 or 0.05 mg, depending on the starting concentration of the naloxone preparation) and titrated upward as indicated to 0.4 mg, 2 mg, and possibly up to 10 mg until desired clinical effect is achieved (evidence

level II-3) [7, 8]. However, if no effect is achieved following administration of a total of 2 mg within minutes, the respiratory depression is unlikely to be caused by an opioid receptor agonist. Exceptions to this include toxicity from certain fentanyl derivatives, including acetylfentanyl, α -methylfentanyl (“China White”), and 3-methylfentanyl (“Tango and Cash”), which have increased potency and may require naloxone doses of 2–10 mg to achieve reversal [9, 10].

Certain opioids, primarily buprenorphine, will respond to naloxone less predictably and in a nonlinear fashion compared to other opioid receptor agonists [11, 12]. Studies in healthy human volunteers showed the failure of reversal of buprenorphine-induced respiratory depression with 0.8 mg intravenous naloxone [11]. Reversal of buprenorphine toxicity occurs along a bell-shaped dose–response curve, with doses of 2–4 mg intravenous naloxone being effective. Doses exceeding 5 mg may have decreased reversal potential and may paradoxically increase respiratory depression [11]. Reversal of buprenorphine toxicity with naloxone should be undertaken in a similar manner described above, but with the starting dose of naloxone being slightly higher. For example, initial intravenous naloxone dosing should be 1–2 mg with titration of dosing to reversal of respiratory depression, not to exceed 5 mg in an adult (evidence level II-3) [11].

Pharmacokinetics

Although opioid receptor antagonists are remarkably similar in clinical effects, they differ markedly in their pharmacokinetic profiles. The duration of action of naltrexone (approximately 24 h) is substantially longer than that of naloxone (20–90 min). The practical implication of their pharmacokinetic differences is that opioid effect may recur, particularly if a short-acting opioid receptor antagonist (e.g., naloxone) is administered to a patient exposed to a long-acting receptor agonist (e.g., methadone). For this reason, continuous cardiorespiratory monitoring, including end-tidal capnography (EtCO₂), for recrudescence is required following naloxone

administration. Use of continuous EtCO₂ monitoring may provide the earliest indicator of ventilatory compromise, including rising EtCO₂ levels or loss of waveform, prior to changes in oxygen saturation (SpO₂) [13]. This is particularly important for patients receiving exogenous oxygen. Recurrent sedation and respiratory depression should be treated with an additional naloxone bolus, followed by continuous infusion if additional naloxone dosing is expected. Continuous infusion dosing should be started at two-thirds the dose at which reversal was achieved, administered hourly (evidence level II-3) [14]. Patients receiving continuous naloxone infusions should be monitored closely because of the possible increase in opioid absorption associated with normalization of intestinal mobility, resulting in increased naloxone requirements. Although an agent with a longer duration of action is preferable to promote abstinence and prevent resedation, the risk of inadvertent withdrawal precipitation in an opioid-dependent patient favors initial titration with a short-acting agent.

Contraindications

Opioid receptor antagonists should not be used in certain populations, specifically opioid-dependent neonates, and cautiously used in patients using cocaine (or another stimulant) in combination with opioids, colloquially known as a *speedball*. Naloxone at doses of 0.04 mg titrated to resolution of respiratory depression, as described above, may be administered. Excessive or rapid reversal of a patient with a heroin-cocaine overdose with naloxone may result in the unopposed effects of cocaine and lead to cardiac dysrhythmias or seizures [15]. Opioid-dependent neonates who develop withdrawal may develop life-threatening seizures (see ► Chap. 27, “Withdrawal Syndromes”).

Treatment

In the event that naloxone is administered in excess to a patient presenting with an opioid overdose, the treatment recommended during the

Pharmacokinetics of Opioid Receptor Antagonists

Drug	Route	Dose	Elimination half-life	Duration of effect
Naloxone ^a	IM, IV, ET, SC, IN, IO, PO	Neonate, 0.01 mg/kg	60–90 min	20–90 min
		Adult with opioid dependence, start 0.04 mg and titrate as necessary to avoid withdrawal symptoms and to preserve ventilation	—	—
		Adult without opioid dependence, start at 0.4 mg	—	—
		Continuous infusion, two-thirds of reversal dose, given hourly		
Naltrexone ^b	PO	PO not well absorbed and only used for local GI effects		
		50 mg PO daily	10 h	24 h

ET endotracheal, IM intramuscular, IV intravenous, PO oral, SC subcutaneous, IN inhalational, IO intraosseous

^aFrom Yaksh and Wallace [24]

^bFrom Nelson and Howland [25]

period of mild-to-moderate withdrawal is supportive, including reassurance that the withdrawal syndrome is not usually life threatening and will wane rapidly. Symptomatic care, such as antiemetic therapy for severe nausea and vomiting, should be provided. Care should be taken to avoid antiemetic drugs with sedating properties, such as antihistamines or promethazine. We do not recommend treating iatrogenically induced withdrawal syndrome from naloxone with an opioid receptor agonist because it is difficult to titrate an individual’s opioid needs, and naloxone’s short effects wane rapidly without any intervention (evidence level III). However, opioid withdrawal precipitated by naltrexone may last for hours, and attempts to overcome the competitive antagonism with the use of a high-potency, short-acting opioid receptor agonist, such as fentanyl, in titrated doses with continuous monitoring are often successful. Alternatively, in this situation, symptomatic care may suffice, often with the addition of clonidine, a sympatholytic with opio-mimetic effects (evidence level II-3) [16].

Administration

Naloxone must be given by a parenteral route owing to its extensive first-pass hepatic elimination. Naltrexone may be administered orally and typically is used for detoxification and

maintenance of opioid abstinence secondary to its long duration of action.

Although opioid receptor antagonist administration is predominantly done by trained health-care providers, its administration by laypersons is becoming increasingly advocated by proponents of harm reduction and community-based opioid overdose death prevention programs [17]. Providing overdose education and naloxone to opioid users and persons who may be present during or proximate to an opioid overdose (e.g., family, friends, homeless shelter workers, substance abuse treatment program staff) may help to decrease opioid overdose morbidity and mortality. Layperson naloxone administration may be intramuscular or intranasal, based largely on the jurisdictional regulations and availability. Though potentially beneficial in opioid intoxication, reversal following naloxone administration may lead to opioid withdrawal (evidence level II-1) [18].

Other Uses of Opioid Receptor Antagonists

Opioid-induced constipation is a common side effect of opioid receptor agonists due to reduced gastrointestinal motility. Certain opioid receptor antagonists, including methylnaltrexone,

alvimopan, and naloxegol, may be used specifically for reversing opioid-induced bowel dysmotility (evidence level I). These agents do not cross the blood–brain barrier and will antagonize peripheral effects, both desired and not, without reversing desired central effects (e.g., analgesia) [19]. Low-dose oral naloxone may also be used for this indication, because it has poor oral bioavailability [20].

Opioid receptor antagonists may be administered in certain overdoses with non-opioids, including clonidine [21], and captopril [22]; however, the magnitude and consistency of effect are less pronounced than with its use in opioid toxicity (evidence level II-3). It is postulated that the mechanism may involve reversal of endogenous opioid peptides at opioid receptors. Naltrexone, especially the intramuscular depot form, may also be used for ethanol dependence, as it may disrupt endogenous opioid effects on the reward pathway (evidence level II-2) [23].

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Studies performed in North America [1–7] and in Great Britain [8–19] in the 1950s led to the introduction and assessment of several pralidoxime salts for military purposes (protection against nerve agent exposure). Pralidoxime was first used in humans to treat organophosphorus insecticide poisoning in 1956 [20].

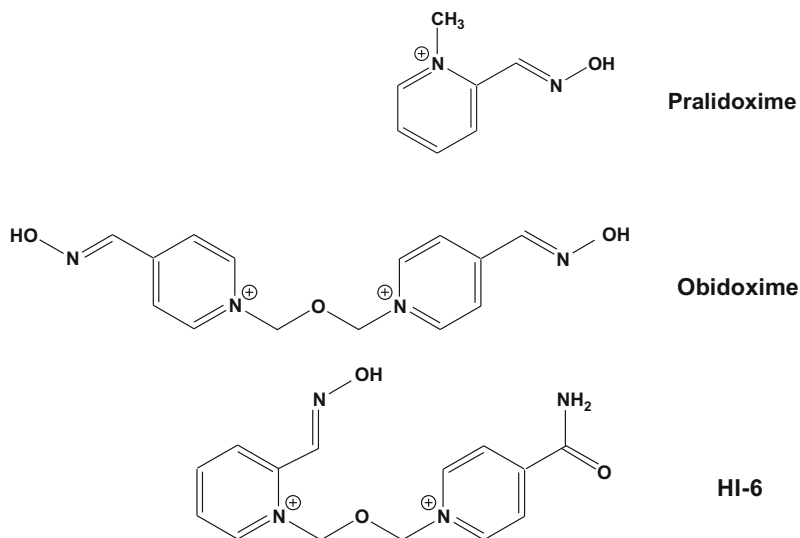
Pralidoxime was synthesized originally as the iodide salt, but this preparation was poorly soluble in water and produced iodism [21]. Alternatives were sought, though pralidoxime iodide remains in some pharmacopoeias and was used in Japan to treat some victims of the sarin releases [22, 23]. Pralidoxime chloride, pralidoxime mesilate (P2S), and pralidoxime metilsulfate (Contrathion™) are more soluble in water and produce fewer undesirable side effects. Pralidoxime mesilate was introduced for clinical use in the UK in 1961, and pralidoxime chloride was first licensed for use in the USA in 1964 [24]. Worldwide, pralidoxime chloride is now the most widely used pralidoxime salt.

Subsequently, obidoxime was developed by Lüttringhaus and Hagedorn [25] and von Erdmann and Engelhart [26] in an attempt to provide more effective treatment than pralidoxime for some types of nerve agent poisoning, such as tabun and soman poisoning. Obidoxime chloride (Toxogonin™) has also been employed in the treatment of organophosphorus insecticide poisoning [27].

More recently, a series of oximes were synthesized (and are known as Hagedorn or H-oximes)

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Fig. 1 Structure of three oximes



by Hagedorn's group at the University of Freiburg, Germany, with the intention of increasing the specificity and spectrum of activity of oximes in poisoning with nerve agents, including soman. The most important of these oximes are HI-6 and HLö7; the latter was first synthesized by Löffler [28] in Hagedorn's laboratory. HI-6 has been studied mostly in a military context [29, 30].

The structures of pralidoxime, obidoxime, and HI-6 are shown in Fig. 1.

In clinical practice, oximes are usually administered intravenously as this is the most convenient way of achieving and maintaining satisfactory plasma concentrations. Administration by the intraosseous route produces similar results as the intravenous, at least for pralidoxime chloride [31] and HI-6 [32], and produces much faster oxime absorption than by the intramuscular route [31]. Nonetheless, the intramuscular route is still employed for self-administration (using an autoinjector) in military subjects (see below).

Clinical Pharmacology

Pharmacokinetics

Pharmacokinetic data have not been collected in neonates, children, pregnant women, or the elderly. Experimental studies are insufficient with

respect to the effects of pralidoxime in pregnancy or on fetal development. However, for organophosphorus insecticide poisoning, the risk to the mother and baby is considerable if adequate oxime treatment is not instituted promptly. This consideration should override the minor possibility that fetal damage may ensue [33].

Pralidoxime

The majority of kinetic studies on pralidoxime have been performed in healthy, non-poisoned subjects. There is evidence from animal [34, 35] and human [36] studies that organophosphorus compounds can alter pralidoxime kinetics in a complex manner; this may be due to the cardiovascular changes and reduced blood flow seen in organophosphorus insecticide poisoning. It may be inappropriate, therefore, to extrapolate the results of volunteer studies to severely intoxicated individuals.

Being quaternary amines, pralidoxime salts and obidoxime are not well absorbed after oral administration, which is why parenteral administration is used, though pralidoxime tablets were available previously. The distribution of pralidoxime is largely determined by its small molecular size and quaternary amine structure. It is thus widely distributed in most body fluids and is not significantly bound to plasma proteins [37]. Pralidoxime penetrates the erythrocyte

Table 1 Pralidoxime kinetics after intravenous dosing in volunteers

Dose mg/kg (salt)	Half-life β min	Volume of distribution (L/kg)			Study
		V_1	V_2	$(V_D)_{ss}$	
5 (chloride)	78	0.27	0.54	0.82	Sidell et al. [37]
5 (chloride)	71	0.37	0.39	0.76	Swartz and Sidell [104]
5 (chloride)	67	0.18	0.42	0.60	Josselson and Sidell [50]
5 (P2S)	84	0.20	0.58	0.78	Sidell et al. [46]
10 (chloride)	79	0.30	0.46	0.76	Sidell and Groff [45]

V_1 central compartment, V_2 peripheral compartment, $V_{d_{ss}}$ volume of distribution at steady state

membrane by simple diffusion and does not bind either to red cell stroma or hemoglobin [38]. Pralidoxime does not pass readily into the central nervous system [39]. The values for the apparent volume of distribution in the central compartment (V_1) and peripheral compartment (V_2) and at steady state ($V_{d_{ss}}$), in volunteer studies, are given in Table 1, the values at steady state being 0.6–0.8 L/kg. However, in poisoned patients treated with the metilsulfate and the chloride salts, the mean (\pm SD) volumes of distribution were found to be 2.77 ± 1.45 L/kg [40] and 2.8 ± 2.2 L/kg [36], respectively.

Pralidoxime is metabolized only to a minor extent in man [41]. It is excreted rapidly in urine [37, 42–49] and there is no evidence of dose-dependent kinetics.

As urinary clearance of pralidoxime exceeds simultaneously measured creatinine clearance, it is probable that pralidoxime is secreted by the renal tubules, at least in part, by secreting mechanisms shared by several other bases [48]. Josselson and Sidell [50] investigated the effect of intravenous thiamine hydrochloride on the elimination of pralidoxime chloride 5 mg/kg body weight administered intravenously. The addition of thiamine lengthened the elimination half-life and the oxime concentration in plasma rose, while the intercompartment clearances and rate constant for elimination of oxime fell. The authors suggested either that thiamine and pralidoxime compete for a common secretory mechanism or that thiamine alters the membrane transport of pralidoxime. Pralidoxime is preferentially excreted in an acidic urine [51], and intravenous sodium bicarbonate markedly reduces pralidoxime excretion.

Most studies, whether performed in man or animals, appear to demonstrate first-order disappearance of pralidoxime from plasma [37, 43, 52], but more complex models have also been proposed [46].

In several volunteer studies, the pralidoxime elimination half-life varied from 67 to 84 min (Table 1) after intravenous dosing of pralidoxime at 5–10 mg/kg body weight. In poisoned patients treated with the metilsulfate and chloride salts, the mean (\pm SD) elimination half-lives were found to be 3.44 ± 0.9 h [40] and 2.9 ± 1.18 h [36], respectively.

Swartz and Sidell [48] observed that in six volunteers given pralidoxime chloride 5 mg/kg body weight (but not atropine), exercise alone and exercise plus heat stress significantly ($p < 0.05$) increased the pralidoxime elimination half-life and increased the volumes of distribution in both central and peripheral compartments. This suggests that exercise and heat not only reduced the renal elimination of pralidoxime but also changed oxime distribution.

Obidoxime Chloride

Obidoxime chloride is poorly absorbed after oral administration and is therefore given parenterally. Sidell and Groff [53] reported in volunteers that the mean plasma half-life was 1.38 h after obidoxime 2.5–10 mg/kg intramuscularly. Within 24 h, 84% of the administered dose was excreted in urine [53]. In another volunteer study, a mean (\pm SD) of $68 (\pm 8)$ % of the administered dose (0.5–1.0 mg/kg intravenously) was recovered in urine in 24 h [37]. The mean (\pm SD) elimination half-life was 1.2 ± 0.16 h, the mean (\pm SD) volume of distribution ($V_{d_{ss}}$) was $0.173 (\pm 0.022)$

L/kg, and the mean (\pm SD) plasma clearance was 133 (\pm 12) mL/min [37].

In keeping with the difference in molecular weight between obidoxime and pralidoxime, the plasma concentrations versus time curves were almost identical after intravenous administration of obidoxime 1 mg/kg and pralidoxime chloride 5 mg/kg [37].

Mechanisms of Action of Oximes

Organophosphorus compounds (OPs) phosphorylate/phosphonylate the serine hydroxyl group located at the active site of the enzyme, acetylcholinesterase (AChE). The inhibition of AChE by soman is shown in Fig. 2 (see also ► Chap. 135, “Nerve Agents”). Inhibition of AChE activity occurs in the blood, brain, and other tissues in a time-dependent manner. Inhibition of AChE results in accumulation of ACh at autonomic (both sympathetic and parasympathetic) preganglionic and some central synapses and at autonomic parasympathetic postganglionic and skeletal afferent nerve endings. Consequently, ACh binds to, and stimulates, muscarinic and nicotinic receptors. Phosphorylated/phosphonylated enzyme may become “aged” by partial dealkylation of the serine group at the active site of AChE (Fig. 2). “Aging” of the phosphorylated enzyme results in an inactive enzyme, after which reactivation is no longer possible.

The fundamental action of the pyridinium oximes is to reactivate AChE inhibited by OPs (Fig. 3), thus allowing ACh to be hydrolyzed in the usual way and resumption of normal cholinergic neurotransmission. It is generally held that the beneficial effects of pyridinium oximes in OP poisoning are confined to peripheral nicotinic sites and that peripheral muscarinic and central nervous effects are clinically insignificant. Thus, the beneficial effects of oximes are mainly on neuromuscular transmission, and there is little action on muscarinic parasympathetic effects such as bronchorrhea, bronchoconstriction, and rhinorrhea. As atropine acts largely at peripheral muscarinic sites, the therapeutic combination of

oxime and atropine is well established in the treatment of organophosphorus insecticide poisoning.

Oximes are much less effective than atropine at peripheral muscarinic sites, which is why the therapeutic combination of oxime and atropine is well established in the treatment of organophosphorus insecticide and nerve agent poisoning.

Although oximes such as pralidoxime and obidoxime act primarily as acetylcholinesterase reactivators, newer oximes such as HI-6 may exert pharmacological effects unrelated to reactivation of inhibited acetylcholinesterase [54].

The reactivation of inhibited AChE by oximes and the subsequent clinical improvement depends on:

- (i) The chemical form of inhibited AChE
- (ii) The plasma concentration of the OP insecticide [55, 56]
- (iii) Aging
- (iv) The plasma oxime concentration
- (v) The duration of oxime therapy

It is commonly, but erroneously, believed that within 1 day of OP insecticide exposure, virtually all (97–99%) of the inhibited AChE is in the “aged” form rendering oxime therapy useless. However, this interpretation derives from *in vitro* studies in which AChE is rapidly inhibited and is maintained fully inhibited thereafter by the presence of an excess of inhibitor and in the absence of oxime. Such experiments do not represent the case *in vivo* and should not be used as a reason not to institute the use of oxime therapy after 24 h or to abandon its use thereafter [57, 58]. If AChE were totally inhibited, it is probable that the patient would be dead! As the clinical signs of intoxication become more severe, concentrations of acetylcholine (ACh) are increased and tend to compete with the OP oxon for the active sites of remaining uninhibited molecules of AChE. This process will reduce the rate of further progressive inhibition to a marked but undefined degree [58]. Thus, the state of complete inhibition is more difficult to reach *in vivo* than in a study of

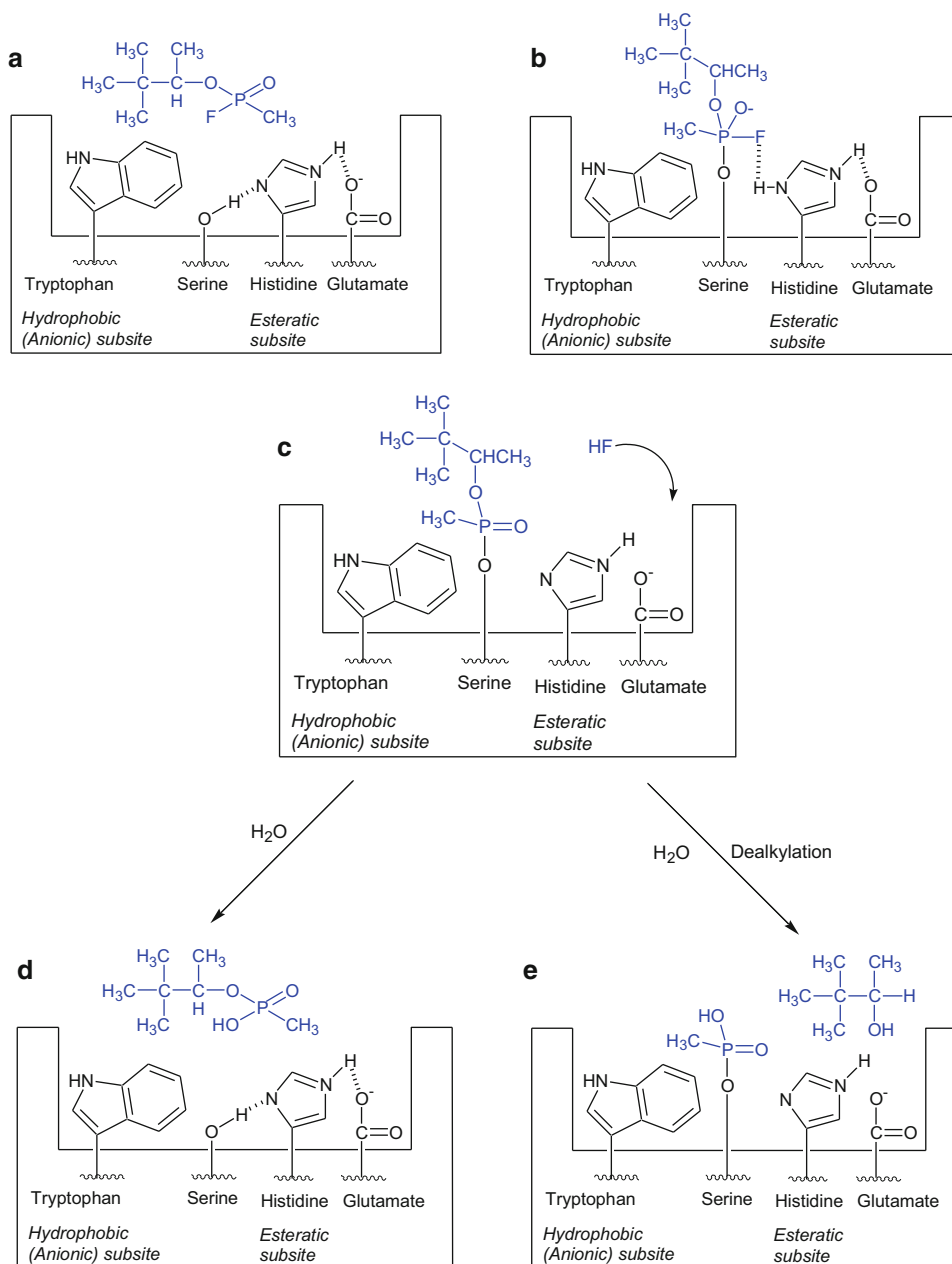


Fig. 2 Reaction of soman (GD) with acetylcholinesterase [86]. **(a)** Soman and the active site of AChE shown together but not having undergone any reaction. **(b)** Soman combined with AChE to form an inhibitor-enzyme intermediate. **(c)** The leaving group (F) has been lost, leaving a complex of soman with AChE. **(d)** The ester link in the phosphorylated AChE has been hydrolyzed,

the enzyme has reactivated, and an alkylphosphate has been formed. **(e)** The link between the large pinacolyl group and phosphorus has been cleaved with the formation of a stable monoalkyl-phosphonylated complex with AChE and pinacolyl alcohol. This process is known as aging

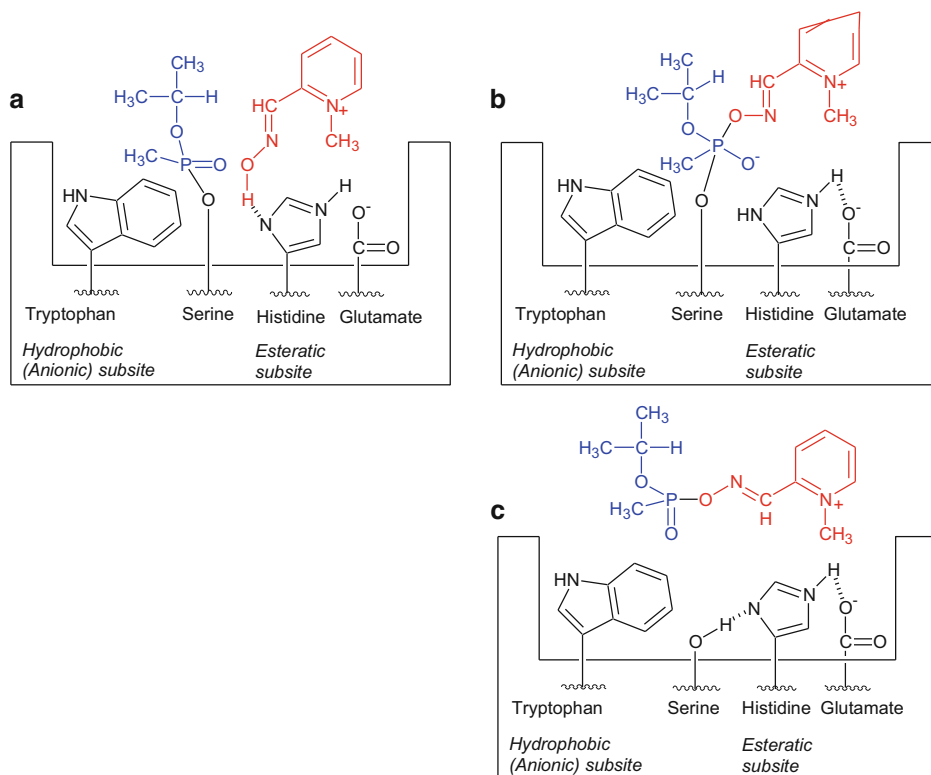


Fig. 3 Reactivation of sarin-inhibited AChE by pralidoxime [86]. **(a)** Sarin has inhibited AChE by forming an esteratic bond with the hydroxyl group of a serine residue, with loss of the leaving group (F⁻): meanwhile pralidoxime forms a hydrogen bond with a histidine

residue. **(b)** A short-lived complex is formed between the inhibited enzyme and the oxime. **(c)** Pralidoxime binds to the isopropyl methylphosphonyl moiety, and the enzyme is reactivated

AChE in vitro. Furthermore, timing should not be made from the point at which first signs of intoxication are seen; these may appear, while about 50% of AChE remains uninhibited [58]. Even when signs of intoxication are marked, some spontaneous reactivation (and even some synthesis of fresh enzyme) will be going on: re-inhibition by persistent inhibitor may be less rapid than in vitro [58].

As Johnson and Vale [57] have argued, there are good biochemical and clinical reasons for suggesting that as soon as an effective concentration of oxime is achieved in vivo, the balance of aging and reactivation reaction rate for inhibited AChE is altered in favor of the latter. Progress toward complete inhibition may be slowed markedly by the use of oximes. It is probable that benefit would ensue even if oxime therapy were

started or continued several days after poisoning [59]. Oximes are of particular value in cases of intoxication from diethyl phosphates because the rate of spontaneous reactivation is very slow.

While monodealkylation occurs to some extent with all dialkylphosphorylated AChE complexes, aging is generally only of clinical importance in relation to the treatment of soman poisoning. The human in vitro aging half-life for soman-inhibited AChE is 1.3 min [60], for sarin-inhibited AChE (human in vitro data) 3 h [61, 62], and tabun-inhibited AChE (human in vitro data) 13 h. In the case of soman, therefore, once aging has occurred, recovery of enzyme function depends on resynthesis of AChE. As a result, it is important that an oxime is administered as soon after soman exposure as possible so that some reactivation of AChE occurs before all of the

enzyme becomes aged. The phenomenon of soman-induced aging led to the development of carbamate prophylaxis for nerve agent poisoning (see review of Inns and Marrs [63]). Even though aging occurs more slowly and reactivation occurs relatively rapidly in the case of other nerve agents, such as tabun and sarin, early oxime administration is still clinically important.

The dose of oxime to produce the appropriate area under the curve (AUC) of [concentration] \times [time] required to achieve the desired reactivation of phosphorylate/phosphonylated enzyme is not known with certainty. It should be noted that the AUC to reactivate a certain percentage of human AChE may well be different for human dimethyl and diethylphosphorylated enzyme. Moreover, estimates of appropriate AUCs are often derived from animal or in vitro studies with nerve agents, which are chemically distinct from OP insecticides.

Oximes are quite rapidly cleared from the body, and although some reactivation may be achieved, another cycle of inhibition (and, possibly, of “aging” of inhibited AChE) may follow. This is particularly so in the case of massive overdose where residual insecticide may persist in the body for a number of days causing a continuous release of inhibitory oxon (active metabolite) into the circulation [56]. Clearly, the initial benefit of an effective dose of oxime may be overcome by such a process, and only persistent treatment can be expected to bring about lasting clinical improvement.

Efficacy of Oximes

Animal Studies

There are consistent animal data supporting the effectiveness of oximes, when given early [4, 13, 64–69]. While pralidoxime alone can reduce the mortality in OP intoxication [4, 70–72], in combination with atropine, the protection is far greater [4, 11, 64, 66, 68, 72, 73]. The addition of diazepam to pralidoxime and atropine adds further benefit [64].

The beneficial effect of continuous oxime therapy has been shown experimentally. Oxime was

delivered by continuous infusion from implanted minipumps to rats intoxicated orally with quinalphos, a diethyl phosphorothioate with a prolonged action. Treated rats received only one small dose of atropine and diazepam plus continuous oxime for 2–4 days and were able to survive more than $30 \times$ the usual LD₅₀ dose [64].

Human Studies

Grob and Johns [74] conducted a series of experiments in volunteers in whom neuromuscular block was produced by the intra-arterial administration of a number of anticholinesterase compounds, including sarin. Pralidoxime iodide was administered either intra-arterially or intravenously. The neuromuscular block induced by sarin was “promptly and strikingly reversed in the injected extremity immediately after the intra-arterial injection” of pralidoxime iodide. Moreover, the prophylactic intra-arterial administration of the oxime protected against the action of sarin on neuromuscular transmission. Intravenous therapy was less effective than intra-arterial therapy though generalized weakness was “ameliorated” to a moderate degree following the injection of pralidoxime iodide 500–2000 mg. Muscle fasciculations were also reduced to a lesser degree than after intra-arterial injection. Approximately 20 min after pralidoxime administration, there was usually some return of weakness and fasciculation, but not to the original level.

Pawar et al. [75] administered two pralidoxime-dosing schedules in 200 patients who had moderately severe OP insecticide poisoning. Patients ($n = 100$) who received the high-dose regimen (pralidoxime iodide 2 g loading dose over 30 min, then 1 g/h for 48 h, and finally 1 g every 4 h until weaned from the ventilator) had a lower mortality (1% vs. 8%; $p = 0.03491$), less need of intubation ($p = 0.0001$), and a shorter time on ventilator support ($p < 0.0001$) than the 100 patients receiving a lower-dose regimen (pralidoxime iodide 2 g loading dose and then 1 g every 4 h until weaned). They also developed less muscle weakness and required less atropine in the first 24 h (median 6 mg vs. 30 mg; 95% CI

24–26 $p < 0.0001$) and fewer developed pneumonia ($p < 0.0001$).

Yet, the value of oximes in patients poisoned with organophosphorus insecticides has been challenged in a Cochrane Review [76] which concluded that:

Current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute OP pesticide poisoning. The World Health Organization recommended pralidoxime regimen (30 mg/kg pralidoxime chloride bolus followed by 8 mg/kg/h infusion) is not supported by outcomes to date. Lower doses have also shown worse outcomes in one RCT. Thus the published RCTs provide limited guidance for clinicians. Despite this, there are consistent animal data supporting their effectiveness, when given early. Based on our understanding of the mechanism, in vitro and animal data, benefit–risk ratio is more likely to be favourable when they are given early, to patients with serious poisoning by diethyl OPs. However, the RCTs have not defined effective doses or sub-groups that are likely to benefit.

The Cochrane Review [76] identified seven RCTs (845 people) in those poisoned with OP insecticides. Three of the RCTs (366 people), reported in four publications [77–80], compared pralidoxime treatment with placebo and the outcomes of mortality and ventilation requirement. Reporting of methods in the RCTs was poor. The Review noted that many studies did not account for factors that would affect outcomes. In some studies, characteristics of participants in different groups were not balanced at baseline. Only one RCT [78], comparing pralidoxime treatment with placebo, used doses of pralidoxime recommended by the World Health Organization (at least 30 mg/kg loading dose and then 8 mg/kg/h intravenous infusion) [81, 82].

In the three RCTs, oximes were given either as a dose of 4–12 g infused daily over 3 days without a loading dose or as a 2 g loading dose over 20 min followed by a constant infusion of 0.5 g/h for a maximum of 7 days. The review found no significant difference between treatment with an oxime and placebo in mortality (three RCTs: 366 people; 47/186 [25%] with oxime treatment vs. 22/180 [12%] with placebo; OR 2.68, 95% CI 0.93–7.72) or need for ventilation (three RCTs: 70/186 [38%] with oxime treatment vs. 50/180

[28%] with placebo; OR 2.00, 95% CI 0.81–4.95). The review authors noted that the different oxime doses used in the studies and differences in the types of organophosphate poison meant that meta-analysis might not produce a true estimate of effect. One of the RCTs (110 people) identified by the review also reported the proportion of people developing intermediate syndrome [79, 80]. It was found that an infusion of pralidoxime 12 g over 3 days significantly increased the proportion of people developing intermediate syndrome compared with placebo (36/55 [65%] with pralidoxime vs. 19/55 [35%] with placebo; OR 3.59, 95% CI 1.64–7.88). However, baseline differences in this RCT suggested that people allocated to treatment with an oxime might have been more severely poisoned compared with those allocated to placebo [76].

Eddleston et al. [78] came to a similar conclusion after performing a double-blind, randomized, placebo-controlled trial comparing pralidoxime chloride (2 g loading dose, followed by a constant infusion of 0.5 g/h for up to 7 days) with saline. Despite clear reactivation of red cell AChE activity in diethyl OP pesticide-poisoned patients, there was no evidence of improved survival or reduced need for intubation [78].

Why is there this discrepancy between the experimental and clinical data? In an important study performed in mini-pigs using orally administered clinically relevant doses of dimethoate EC (agricultural emulsifiable concentrate), dimethoate active ingredient alone, or solvents, Eddleston et al. [83] found that administration of agricultural dimethoate EC, but not saline, caused respiratory arrest within 30 min, severe distributive shock, and NMJ dysfunction, which was similar to human poisoning. Moderate toxicity resulted from poisoning with dimethoate active ingredient alone or the major solvent, cyclohexanone. Combining dimethoate with cyclohexanone reproduced severe poisoning characteristic of agricultural dimethoate EC poisoning. A formulation without cyclohexanone showed less mammalian toxicity. These results indicate that solvents play a crucial role in OP (and specifically dimethoate) toxicity, which could explain why oximes seem to be less effective clinically than

in experimental studies where pure OP insecticide rather than marketed formulations is often employed.

In conclusion, there are consistent animal data supporting the effectiveness of oximes when given early to treat acute organophosphate insecticide poisoning (Level 1 evidence) [84]. Results from published RCTs in humans have not shown that oximes improve outcomes when compared with placebo, but most studies have been of poor quality, so a definite conclusion cannot be drawn. The results of one study indicate that solvents may play a crucial role in organophosphorus insecticide (and specifically dimethoate) toxicity. This could explain why oximes seem to be less effective clinically than in experimental studies where pure organophosphorus insecticide rather than marketed formulations, containing solvents, is often employed. It is not known how different regimens of oximes compare to each other as there is insufficient evidence.

Which Oxime?

This is largely an academic discussion since a choice is not usually available to critical care physicians. Furthermore, for nerve agent exposures, it is unlikely that it will be known with certainty which nerve agent has been released, in a clinically relevant timeframe. Hence, the oxime most readily available should be administered in the appropriate therapeutic dose. Various experimental studies in animals have claimed the superiority of one or another oxime in the treatment of poisoning by a particular organophosphorus compound (usually a short-lived nerve agent), but comparative studies in humans have not been reported.

Between-study comparisons should recognize that plasma concentrations measured by weight per unit volume need to be converted to molar units since the molecular weights of the available oxime salts are markedly different. Thus, the molecular weights of pralidoxime chloride, pralidoxime mesilate, and obidoxime chloride are 172, 232, and 359 g/mol, respectively. Furthermore, the potency of a particular oxime depends in part on the “goodness of fit” of its molecule to the region of the active site of the

inhibited acetylcholinesterase molecule. This “fit” will be influenced by the chemistry of the particular inhibitor and will vary between compounds. Therefore, conclusions drawn from studies with one organophosphorus insecticide cannot automatically be applied to all others (or to nerve agent poisoning) although class comparisons (e.g., for diethyl phosphates) may be valid.

In the case of the treatment of OP insecticides, no difference between the efficacy of pralidoxime and obidoxime has been demonstrated, though there is some evidence that if aging is substantial, HI-6 might have an advantage. Kusic et al. [85] suggested that the general improvement in the clinical condition of poisoned patients treated with HI-6, which was more rapid than the rise of AChE activity, indicated additional beneficial effects.

Experimental studies on the treatment of nerve agent poisoning have to be interpreted with particular caution [86]. Some studies have used prophylactic protocols, whereas the drugs concerned (oxime, atropine, diazepam) would only be given to an exposed population *after* exposure. The experimental use of pyridostigmine before nerve agent exposure, though rational, is not of relevance in the civilian context.

Experimental studies in guinea pigs and monkeys have shown that pralidoxime + atropine and obidoxime + atropine were less effective in soman poisoning than HI-6 + atropine, though pralidoxime + atropine was more effective than obidoxime + atropine [87]. Studies have shown invariably that higher oxime doses, together with atropine, have increased survival further, irrespective of the nerve agent [87]. There is no clear evidence from studies in vivo that any oxime can reactivate soman-inhibited enzyme, although there is some evidence from studies in vitro that HI-6 can [86]. The evidence for the superiority of obidoxime over pralidoxime in tabun poisoning depends on studies in vivo in the mouse and guinea pig (obidoxime was not superior in the rat) and on studies using human erythrocyte acetylcholinesterase in vitro [86]. If pretreatment with pyridostigmine has not been undertaken, a review of the available experimental evidence suggests that there are no clinically important

differences between pralidoxime, obidoxime, and HI-6 in the treatment of nerve agent poisoning, with the possible exception of the treatment of GF and soman poisoning, when HI-6 might be preferred [86].

Overall, however, pralidoxime and obidoxime are the oximes of choice for civilian use in many countries as they are the most widely available and are cheaper to synthesize than HI-6. In equimolar concentrations, pralidoxime may produce fewer adverse effects than obidoxime (see below).

What Dose?

Early experiments in anesthetized cats (possibly seven animals) given lethal doses of intravenous sarin and pralidoxime mesilate 10 mg/kg intramuscularly, but not atropine, established that plasma pralidoxime concentrations of above 4 mg/L were required to counteract neuromuscular block in vitro and bradycardia, hypotension, and respiratory failure in vivo [88]. Crook et al. [89] gave dogs oral pralidoxime (mesilate and lactate) 30–115 mg/kg body weight, 1–5 h before exposure to sarin vapor. Atropine 5 mg/kg body weight was administered 1 min after the dogs were exposed to sarin. The authors extrapolated from this study in dogs to man and concluded that a plasma pralidoxime concentration of at least 3 mg/L would be required “for reasonably protective attenuation of the toxic effects of organophosphorus anticholinesterases.”

The relationship between plasma oxime concentrations after dosing with pralidoxime and obidoxime and protection against sarin poisoning has been investigated by Shiloff and Clement [69] in rats (Table 2) and by Bokonjic et al. [64] in quinalphos-poisoned rats given pralidoxime (Table 3). Taken together, these studies support the recommendation that plasma oxime concentrations of more than 4 mg/L are required to produce a significant reduction in mortality in experimental organophosphorus poisoning.

Studies in poisoned patients have shown that reactivation of dimethoate-inhibited enzyme was not achieved with a plasma pralidoxime concentration of 6.37 mg/L [55]. In the same study, it was shown that reactivation of inhibited enzyme did not occur even in the presence of a plasma

Table 2 Relationship between plasma oxime concentrations and mortality in sarin-poisoned rats also given atropine^a (After Ref. [69])

Oxime	n=	Mean (± SD) oxime concentration (mg/L)	% mortality
Pralidoxime	5	0.7 ± 0.1	100
Pralidoxime	4	2.0 ± 0.4	80
Pralidoxime	5	3.3 ± 2.3	20
Obidoxime	10	3.6 ± 0.2	90
Obidoxime	8	9.2 ± 0.6	62.5
Obidoxime	5	19.7 ± 3.7	0

^aAtropine dose, 17.4 mg/kg

Table 3 Relationship between plasma pralidoxime concentrations and LD₅₀ in quinalphos-poisoned rats also given atropine and diazepam^a (Modified from [64])

Mean (± SEM) plasma pralidoxime concentration (mg/L)	Mean (± SEM) LD ₅₀ (mg/kg)	Protective index
0	10.5 ± 3.8	—
0.8	353.6 ± 33.6	33.7
1.5 ± 0.6	457.9 ± 121.6	43.6
2.9 ± 0.7	498.7 ± 137.9	47.5

LD₅₀, median lethal dose

^aAtropine dose, 10 mg/kg; diazepam, 2.5 mg/kg

pralidoxime concentration of 14.6 mg/L when plasma ethyl and methyl parathion concentrations were >30 µg/L [55]. Data from case reports suggests that pralidoxime concentrations of >40 mg/L may be required in very severe cases of organophosphorus insecticide poisoning to produce reactivation of inhibited AChE [59, 90]. Thus, the modest doses of pralidoxime that have often been recommended in the past (to achieve plasma oxime concentrations of approximately 4 mg/L) will be insufficient to produce not only reactivation of phosphorylated enzyme but also a lasting clinical improvement, unless the patient is only mildly poisoned.

Pralidoxime chloride 30 mg/kg by intravenous injection should be administered as soon as possible in any severe or progressive case of intoxication and repeated at 4–6 h intervals; alternatively, an intravenous infusion of 8–10 mg/kg/h in an adult may be employed. These regimens are based on reported clinical studies [40, 55, 90] and

have been recommended by WHO [81] and ourselves [91]; these are Level 3 recommendations.

Based on pharmacokinetic data of obidoxime in healthy human volunteers [37], Thiermann et al. [92] considered a bolus dose of obidoxime 250 mg IV, followed by a continuous infusion at 30 mg/h, an appropriate therapeutic regimen, which they employed in single patients [27, 93] (Level 3 recommendation). The efficacy and safety of this regimen was evaluated in an observational study [94, 95]. These authors further investigated this regimen in 34 severely poisoned patients [92]. The mean (\pm SD) total dose of obidoxime infused over 65 (\pm 55) h was 2,269 (\pm 1,726) mg, which resulted in a mean steady-state plasma concentration of 5.2 (\pm 2.6) mg/L. Reactivation of inhibited erythrocyte AChE was achieved in 23 of 34 patients, while in seven patients, aging was complete before the commencement of obidoxime. In four patients, high OP insecticide load prevented significant reactivation and complete aging ensued in spite of this obidoxime regimen.

Thiermann et al. [27] reported that in parathion poisoning, obidoxime 250 mg IV as a bolus followed by 750 mg/day by infusion was effective, but that in severe poisoning, AChE reactivation did not occur until the concentration of inhibitor in the plasma had declined. The same dosage regimen was ineffective with oxydemeton methyl when oxime therapy was delayed more than 1 day after poisoning. In another series, involving parathion poisoning, reactivation was possible 7 days after poisoning, whereas with oxydemeton-methyl, a response was only seen when obidoxime therapy was instituted soon after poisoning [96]. Similarly, Zilker et al. [97] found that obidoxime (750 mg/day by infusion) reduced the need for atropine in parathion poisoning, but demeton-S-methyl poisoning only responded if obidoxime therapy was instituted shortly after intoxication.

Administration of oxime should continue for as long as inhibitory oxons (active organophosphorus compounds) are circulating, as judged clinically by the need for atropine. That is, continue therapy until clear, irreversible clinical improvement is achieved, which may take many

days while residual insecticide is cleared from the body stores.

Prolonged, high-dose treatment with pralidoxime iodide and with obidoxime chloride should be avoided, if possible, because of potential adverse effects (see below).

Which Route?

In the hospital, the intravenous route will be preferred in most cases, though the intraosseous route produces similar results as the intravenous, at least for pralidoxime chloride [31] and HI-6 [32], and produces much faster absorption than by the intramuscular route [31].

Outside the hospital, the self-administration of oxime (and atropine and a benzodiazepine) can be done conveniently by the use of an autoinjector, the contents of which are injected intramuscularly. For example, the ComboPen (UK version) L4A1 contains pralidoxime mesilate 500 mg, atropine 2 mg, and avizafone 10 mg (a diazepam precursor). The US version of the autoinjector (Antidote Treatment Nerve Agent Autoinjector [ATNAA]) contains pralidoxime chloride 600 mg and atropine 2.1 mg. Severely poisoned casualties may require the self- or buddy administration of the contents of up to three autoinjectors at 5–10 min intervals.

Adverse Effects

Pralidoxime

Sidell et al. [98] gave military personnel pralidoxime chloride 3–9 g orally; only individuals receiving 8–9 g experienced diarrhea. Volunteers were administered pralidoxime chloride, iodide, and mesilate 1.5–10 g orally [52]. Those subjects receiving the iodide salt experienced the signs and symptoms of iodism, coryza, pharyngeal burning, and painful parotid glands; consequently, the iodide salt is now rarely used. No subjective complaints were made by the volunteers ingesting pralidoxime chloride and pralidoxime mesilate in this study.

Jager and Stagg [99] found that medical students given a single dose of pralidoxime iodide

15–20 mg/kg body weight intravenously experienced dizziness, blurred vision, diplopia, impaired accommodation, headache, and nausea. Single oral doses of pralidoxime chloride 1, 2, or 4 g did not lead to changes in blood pressure or pulse, whereas the intramuscular administration of pralidoxime chloride 30 mg/kg produced a pressor response and T-wave elevation in the EKG [42]. Clinically significant EKG changes due to pralidoxime have not been observed in practice. The same dose of pralidoxime chloride given intravenously had similar effects, but pralidoxime chloride 45 mg/kg body weight also produced prolongation of the PR interval. Headache, disturbance of accommodation, and epigastric discomfort were also noted.

Volunteers, who received pralidoxime chloride daily for 6 months, tolerated the oxime well, though elevation of transaminase (aminotransferase) activity, transient lymphocytosis, and clinically insignificant EKG changes were noted in some subjects [42]. The same workers found that oral mesilate was less well tolerated than pralidoxime chloride, as it produced more gastrointestinal disturbance.

Soldiers given repeated *oral* doses of pralidoxime for 48 h experienced diarrhea (often recurrent), anorexia, and malaise [98].

Obidoxime

It has been recognized since the introduction of obidoxime that treatment for several days, particularly in high dosage, may result in liver damage, which is usually transient. Finkelstein et al. [100] have shown an association between liver dysfunction and the cumulative dose of obidoxime. The liver damage usually manifests as an increase in hepatic enzyme activities and hyperbilirubinemia [27].

Contraindications to Use

There are no absolute contraindications to the use of oximes, though it is possible that in patients with renal impairment, dosage adjustment of pralidoxime and obidoxime may need to be considered if the GFR is <30 mL/min

(Level 3 recommendation); further data are required to support this recommendation. Caution is also required when pralidoxime is administered to patients with myasthenia gravis as it may precipitate a myasthenic crisis.

Shelf Life of Preparations

Calculated shelf lives allowing for 10% degradation of 50% (w/v) pralidoxime chloride solution are 37 years, 7 years, and 1.6 years at 10 °C, 20 °C, and 30 °C, respectively [101]. Pralidoxime mesilate can be stored for at least 5 years at 5 °C with less than 7% decomposition [102]. Schroeder et al. [103] have demonstrated that an autoinjector solution (pralidoxime chloride 300 mg/mL) stored at 5 °C for more than 10 years contained more than 90% pralidoxime chloride.

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D-penicillamine (DPA) is a heavy metal chelator and is the drug of choice for management of Wilson's disease, a copper-overload disease state. It may also be effective in arsenic, mercury, and lead chelation. Although the toxicity of DPA is relatively low, there are more effective and less toxic chelators, for most heavy metals, with the exception of copper. This chapter focuses on the general uses of D-penicillamine as a chelator. L-penicillamine is not used clinically due to its strong inhibition of pyridoxine-dependent enzymes, leading to neurotoxicity in animal experiments.

History

D-penicillamine is a naturally occurring base of penicillin and was discovered incidentally by Dr. John M. Walshe in the urine of a patient with liver damage who had taken penicillin [1]. Previously, Wilson's disease was experimentally being treated with various chelators including dimercaprol (British Anti-Lewsite [BAL]) and ethylenediaminetetraacetic acid (EDTA). However, adverse responses and patient intolerance led to a trial of D-penicillamine. After 1 g of D-penicillamine was tolerated without adverse effect in a dose self-administered by Dr. Walshe, the drug was given to a patient with Wilson's disease who had previously trialed BAL. The patient was given 1 g of D-penicillamine and achieved good urinary excretion of copper. From this experiment, limited

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studies on murine models were conducted for preliminary toxicity reports and subsequently trialed on patients with varying stages of Wilson's Disease [2]. No formal randomized controlled human clinical trials were identified prior to the US Food and Drug Administration's (FDA's) approval of D-penicillamine in 1970, but numerous case reports supported the benefits predicted by Walshe on copper metabolism. In 1957, two case reports of D-penicillamine's effectiveness in lead chelation were published, and small controlled trials were further published in the early 1960s [3–5]. Chelation of mercury with N-acetylpenicillamine was also demonstrated in the 1950s; however, this was never widely implemented in a clinical setting.

Properties

Chemical

D-penicillamine (Fig. 1) is supplied as 3-mercapto-D-valine, having a molecular formula of $C_5H_{11}NO_2S$ and a molecular weight of 149.2 g/mol. The thiol group of this substituted amino acid leads to its ability to function as a chelator [6]. N-acetyl-D-penicillamine has a molecular weight of 191.2 g/mol. Although some benefit was reported using N-acetyl-D-penicillamine as a chelator, the result remains controversial, and it is not commercially available for medical therapy.

Physical

D-penicillamine is a white or practically white, crystalline powder supplied as a capsule or tablet. It is freely water soluble, slightly soluble in alcohol, and insoluble in ether, acetone, benzene, and carbon tetrachloride. It has a slight acetic odor and

tastes slightly bitter. The melting point of D-penicillamine is 202–206 °C (395.6–402.8 °F).

Pharmacokinetics

Kinetic characteristics of D-penicillamine in acute heavy metal poisoning have not been well described; however, information relating to pharmacokinetics of D-penicillamine in the copper-overload state associated with Wilson's disease, as well as metabolic data associated with D-penicillamine's use in rheumatoid arthritis and cystinuria, have been described in a limited number of small studies summarized in Table 1. Some additional data describing pharmacokinetics of D-penicillamine in healthy volunteers also exist [7, 8].

D-penicillamine is approved for oral administration, although intravenous and intramuscular studies have also been conducted. Formulations currently available are tablets, capsules, and a powder for liquid oral reconstitution. Oral absorption, although moderate, produces chelation results similar to those observed with intravenous administration. Therefore, oral formulations are encountered more frequently in clinical use. Absorption is significantly reduced by food, milk, and medications such as antacids and ferrous sulfate [9].

D-penicillamine is an amino acid, distributes with extracellular water and remains predominantly in the extracellular compartments. A sizeable proportion of the disulfide metabolites complex with albumin and distribute in plasma [10–12]. Approximately 80% of D-penicillamine is circulated in plasma, typically bound to plasma proteins (particularly, albumin). Oral plasma distribution of D-penicillamine begins 15–21 min

Fig. 1 Chemical structure of D-penicillamine

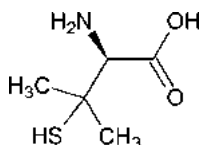


Table 1 Pharmacokinetics of D-penicillamine

Oral absorption: 50% (40–70% gastrointestinal tract)
Volume of distribution: 57–93 L (0.8–1.3 L/kg)
Excretion in breast milk: unknown
Clearance: primarily renal cleared as disulfide metabolites
Elimination half-life: 1–7.5 h
Cleared by extracorporeal techniques: unlikely

after ingestion with peak concentrations seen 1–4 h after ingestion. Distribution is best described by a two-compartment model. The oral volume of distribution is approximately 151 ± 31 l, with a clearance rate of $103 \pm 1 \cdot \text{h}^{-1}$. The AUC for D-penicillamine is $19.4 \pm 4.13 \mu\text{M}\cdot\text{h}$. Metabolism of D-penicillamine is not well understood, and two forms of penicillamine byproducts have been identified: penicillamine disulfide and cysteine-penicillamine disulfide. Metabolites of S-methyl-D-penicillamine have been found in the urine of patients taking therapeutic doses of penicillamine, and a small amount of metabolism, including methylation, occurs in the liver. Elimination is primarily renal and typically monophasic, although biphasic peaks have been reported in several studies. The lower molecular weight disulfide metabolites (20–30% of administered drug) are quickly excreted in the urine; however, excretion of other D-penicillamine metabolites has been reported up to 3 months after cessation of therapy in patients receiving prolonged treatment (>3 months). Approximately 30–60% of a D-penicillamine dose is excreted as unchanged drug within the first 48 h after administration. The small amount of D-penicillamine that is not excreted renally is described as free drug and is excreted in feces [6, 13–15].

The degree of chelation is dependent on the type and amount of the heavy metal present. Generally speaking, D-penicillamine is relatively safe and has a very low toxicity profile compared to other chelators, but it is unlikely to be removed by current extracorporeal methods.

Pharmacodynamics

Although D-penicillamine will bind several heavy metals, in the USA, it is only FDA approved for chelation of copper in Wilson's disease. D-penicillamine is considered first-line therapy for copper toxicity and second- or third-line treatment for lead, mercury, and arsenic toxicity [9, 16].

Optimal binding of D-penicillamine to copper ions occurs at a pH of 6.5 at a molar concentration ratio of 2:1 (D-penicillamine to Cu(II)) [17, 18].

D-penicillamine binds to cuprous (Cu(I)) ions with a slightly lesser affinity compared with cupric ions (Cu(II)), but penicillamine also has the ability to reduce copper ions and may thereby slightly increase its own binding [19].

Copper absorption ranges from 12% to 60%, depending on a variety of factors. (Copper also freely changes to and from the Cu(I) to Cu(II) states when unbound.) Copper is typically ingested in the cupric (Cu(II)) form from food and is predominantly reduced prior to transport at the basolateral surface of the intestinal cells where the Cu(I) ions are transported intracellular via copper transporter (CTR1). Humans have two ATPase copper transporters (ATP7A and ATP7B), which transport cuprous (Cu(I)) ions from the cytosol to various places, including enterocytes and hepatocytes. Once in the hepatocyte, ATP7B transports copper complexes into the trans-Golgi network where it is incorporated into ceruloplasmin and either secreted into the blood or bile. Approximately 90% of serum copper is found in the cupric (Cu(II)) valence bound to ceruloplasmin [20–22].

The therapeutic mechanism of action of D-penicillamine is not fully understood. Although there are some contradictory accounts, most reports suggest D-penicillamine competes for the cupric (Cu(II)) ions with serum albumin and ceruloplasmin (two important copper carriers), as well as acting as a reducing agent [23]. D-penicillamine is a poor competitor for freeing copper from albumin, though it mobilizes copper very well from the liver and kidney. This is in contrast to triethylenetetramine, another copper chelator, which does not enter the liver but does compete to release copper from albumin in the serum [17].

D-penicillamine also complexes with other metals including lead, mercury, and arsenic. It is suggested that lead (Pb(II)) forms a complex with D-penicillamine in a 1:1 M ratio; however, newer research suggests that several complexes can be formed at varying pHs and in molar ratios of up to 2:1 (penicillamine/Pb) [24]. Mercury (Hg(II)) is bound to penicillamine in a 1:1 M ratio at neutral pH; however, it is more effective in removing mercury from extracellular, than intracellular, compartments [25, 26]. Although clinical reports have suggested the effectiveness of arsenic

chelation with D-penicillamine [27, 28], experimental investigations have not demonstrated this effect [29, 30]. Further, D-penicillamine-As complexes have not been fully characterized.

Special Populations

Pregnancy and Breast-Feeding Patients

D-penicillamine is an FDA category D drug, demonstrating evidence of human fetal risk; however, the benefits may outweigh the risks in specific situations and therefore should not be routinely used in pregnant or breast-feeding patients. Human reports are comparable to rodent models in showing teratogenic effects including cutis laxa, arthrogryposis, and occasionally CNS defects such as corpus callosum agenesis, blindness, and hydrocephalus [31, 32]. D-penicillamine is known to cross the placenta during gestation. It is currently unknown if it also crosses into breast milk, though this is suspected. Breast-feeding is therefore not recommended when using D-penicillamine.

Contraindications

Prior to the development of pharmaceutical synthetically produced D-penicillamine, trace amounts of penicillin were found in this drug. Consequently, desensitization or avoidance was recommended in patients with penicillin hypersensitivity or allergy. Today, cross sensitivity to penicillin may still cause an allergic reaction, but the incidence of this is relatively low, and D-penicillamine should be considered if no equivalent therapeutic option is available.

Precautions

Dosing adjustments for D-penicillamine should be made in patients with severe renal impairment. Recommendations for dosing adjustment include avoidance in patients with a GFR less than 50 mL/min and thrice-daily dosing of 250 mg in patients on hemodialysis [33, 34].

D-penicillamine should not be used in combination with gold therapy, antimalarial, cytotoxic drugs, or the anti-inflammatory drugs oxyphenbutazone or phenylbutazone. Although the evidence is conflicting, some case reports describe patients who had previously developed rash with gold therapy who also developed a similar rash with penicillamine therapy [35–37]. Additional reports report gold therapy and D-penicillamine can be given in combination; however, due to the risk of myelosuppression, it is not recommended [38].

Adverse Effects

Major side effects are typically observed with chronic (>3 months) use of D-penicillamine in disease states such as Wilson’s disease, cystinuria, and rheumatoid arthritis. Little has been reported with adverse reactions related to acute, short-term exposure to D-penicillamine. The most common side effects include diarrhea (17%), dysgeusia (12%), mouth ulcers (7–13%), nausea, anorexia, proteinuria (6%), skin rash (5%), thrombocytopenia (4%), and leukopenia (2%) (Tables 2, 3, and 4).

Administration

Although previous reports describe D-penicillamine therapy with toxicities from several heavy metals, there are no widely accepted standards of therapy for heavy metals such as mercury, arsenic,

Table 2 Acute adverse reactions (exposure to D-penicillamine <3 months)

Skin	Urticaria, generalized drug rash (morbilliform, pruritic), herpetiform pemphigus
GI	Nausea, diarrhea, vomiting, colitis, dysgeusia
Heme	Agranulocytosis
Rheum	Polymyositis, DPA-induced lupus erythematosus-like syndrome
Neuro	Dystonia, extrapyramidal symptoms
GU	Proteinuria, nocturnal enuresis
Pulm	Bronchospasm, rhinitis
Other	Drug fever

Table 3 Adverse reactions in chronic exposure (exposure to D-penicillamine >3 months)

Skin	Elastosis perforans serpiginosa, nail damage, pemphigus, late generalized rash
Endo/metabolic	Zinc deficiency, copper deficiency, gynecomastia
Heme	Leukopenia, thrombocytopenia
Immune	Myasthenia gravis and ocular myasthenia gravis
Renal	Goodpasture's syndrome, kidney disease including acute renal failure and nephritic syndrome, nephrolithiasis
Pulm	Alveolar pneumonopathy, dyspnea, pleural effusions, pulmonary hemorrhage

Table 4 Dose relation to adverse reactions to D-penicillamine exposure

Dose related	Non-dose related
Cheilosis	Glomerular nephritis
Gingivostomatitis	Nephrotic syndrome
Glossitis	
Stomatitis	
Mouth ulcers	
Extrapyramidal symptoms	

or copper in acute toxicity. While D-penicillamine chelation therapy has been used with lead, clinical evidence demonstrates there are more effective lead chelators available, including succimer and EDTA. The American Academy of Pediatrics Committee on Drugs considers D-penicillamine to be a third-line agent for chelation therapy in lead toxicity [39].

Copper Toxicity

As noted, D-penicillamine is useful in managing copper-overload states such as Wilson's disease and is an effective copper chelator (Grade II-2 evidence). The typical initial adult dose is 1,500–2,000 mg daily in two to four divided doses and decreased to 750–1,500 mg/day (divided doses) for maintenance therapy. The objective is to increase urinary copper excretion to more than 2 mg/24-h urine, and treatment is usually continued for approximately 3 months.

The pediatric dose is 15–30 mg/kg/day in two to four divided doses [40].

Lead Toxicity

According to the US Centers for Disease Control and Prevention (CDC), chelation therapy should be initiated in adults with blood lead levels exceeding 100 µg/dL(4.8 umol/L) [41]. Reports of up to 2 g per day of oral D-penicillamine have been administered; however, no large randomized controlled trials have been reported. In a more recent publication, Cuprimine (D-penicillamine) that was given at doses of 25–35 mg/kg/day in divided doses showed an increase of lead excretion (short term) by 20–30 times the average daily excretion [42, 43].

While the CDC does not recommend chelation therapy for blood lead concentrations below 45 µg/dL (2.2 umol/L), case reports have shown some benefit of D-penicillamine for blood lead levels between 25 and 45 µg/dL (1.2–2.2 umol/L). A dose of 15 mg/kg/day demonstrated benefit in reducing by half the original blood lead level in children (Grade II-3 evidence). Up to 30 mg/kg/day has been administered with minimal adverse effect [44, 45].

Mercury Toxicity

D-penicillamine increases mercury excretion and decreases body burden in animal studies with inorganic mercury poisoning [46, 47]. A few case reports in children have also alluded to efficacy for mercury chelation [48–50]. If used, the dose for children and adults is similar to that used in lead chelation.

Arsenic Toxicity

While its efficacy has not been proven in animal studies, D-penicillamine can enhance the renal excretion of arsenic in humans. However, efficacy is higher with other chelating agents resulting in D-penicillamine from being used for the heavy

metal poisoning. If used, the dose for children and adults is similar to that used in lead chelation.

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Decorporation therapy is based on the principle that accelerating the excretion of internalized radioactive materials results in fewer acute adverse acute and long-term health consequences. Reducing the amount of radioactive material inside the body, and the duration of its residence in proximity to cells and organs, reduces the committed effective dose of ionizing radiation delivered to these tissues. The committed effective dose is estimated from intake of the radioactive material over 50 years for adults and to age 70 years for children [1].

For over five decades in both the United States and Europe, diethylenetriaminepentaacetic acid (pentetic acid; DTPA) has been used to treat individuals internally contaminated with actinide elements by enhancing the renal clearance of these radionuclides [2]. Pentetic acid is compounded into a salt with either calcium or zinc forming chemically stable and water-soluble actinide chelates which are easily excreted in the urine. The US Food and Drug Administration (FDA) has approved both Ca-DTPA and Zn-DTPA formulations for the removal of the actinide elements plutonium (Pu), americium (Am), and curium (Cm). (Fig. 1).

Although, this chapter will focus on the management of internal contamination of Pu, Am, and Cm (which are FDA-approved indications), there is evidence that DTPA can be used in the medical management of internal contamination with a number of other radioactive elements, according

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Fig. 1 1 g/5 ml vials

to the National Council on Radiation Protection and Measurements (NRC) [3] (see Table 1).

Properties

There are two formulations of DTPA (Fig. 2): a calcium and a zinc salt. The calcium salt has an empirical formula of $\text{Na}_3\text{CaC}_{14}\text{H}_{18}\text{N}_3\text{O}_{10}$ and a molecular weight of 497.4 g/mol. The zinc salt has an empirical formula of $\text{Na}_3\text{ZnC}_{14}\text{H}_{18}\text{N}_3\text{O}_{10}$ and a molecular weight of 522.7 g/mol [4]. Both salts are formulated in sterile water for injection as clear, colorless, and odorless liquids.

Pharmacokinetics

Both calcium and zinc DTPA salts form chemically stable, water-soluble chelates when combined with actinide metals that can then be excreted in the urine [5]. Calcium and zinc DTPA have a 100% bioavailability when administered intravenously. They are incompletely absorbed when administered orally or by inhalation (less than 10% and 20–30% respectively), although there is an increasing number of animal

studies evaluating the safety and efficacy of orally administered DTPA formulations [6–8].

A small portion of DTPA (10%) binds to plasma proteins resulting in somewhat delayed elimination. However, the elimination half-life is typically 20–60 min. Renal excretion by glomerular filtration is the primary mechanism of elimination, with a very small percentage (<3%) excreted in the feces [4].

Administration

The use of DTPA is indicated when internal contamination with Pu, Am, or Cm is sustained by inhalation, ingestion, or injection (e.g., through a wound). Contamination with radioactive material most commonly occurs in occupational settings (e.g., nuclear weapons facilities or nuclear power plants) but can also affect large populations in the setting of the detonation of a radioactive dispersal device in wartime or terrorist acts [4, 9].

Possible Source of additional information: <http://emergency.cdc.gov/radiation/contamination.asp>

The efficacy of DTPA has been studied in animals where it has been shown to decrease the uptake of Pu from liver, bone, and lungs and decrease the incidence of radiation-related bone tumors. Efficacy in humans is based on registries of patients suffering occupational exposures in the United States, Europe, and Russia [4].

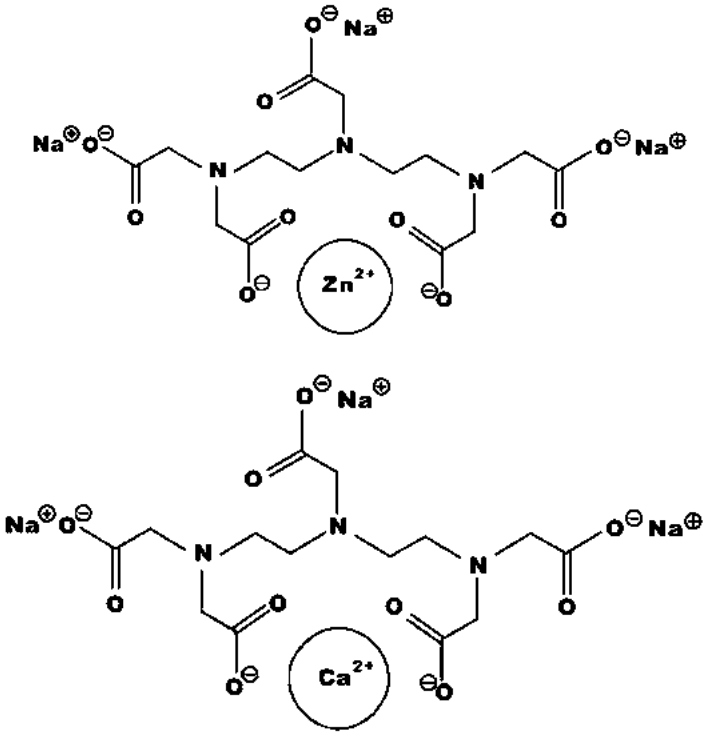
Calcium DTPA is considered to be approximately 10 times more efficacious than its zinc counterpart in the first 24 h after internal contamination. Unfortunately, the evidence to support this statement has not been published. Nonetheless, if additional chelation therapy is required or if treatment is initiated after the first 24 h, it is preferable to use zinc DTPA because it has fewer adverse effects [10].

The duration of therapy is dependent on the amount of radioactive material present inside the body and the response to therapy. Treatment can be monitored by measuring radionuclide excretion in the urine using 24-h collection. In several published cases, DTPA therapy was used for multiple doses without statistically or clinically significant adverse effects (Grade III evidence). Most

Table 1 Elements that can be chelated by DTPA according to the NCRP [3]

Berkelium (Bk)	Californium (Cf)	Cerium (Ce)	Chromium (Cr)	Cobalt (Co)	Einsteinium (Es)	Europium (Eu)
Indium (In)	Lanthanum (La)	Manganese (Mn)	Niobium (Nb)	Promethium (Pm)	Ruthenium (Ru)	Scandium (Sc)
Yttrium (Y)	Zinc (Zn)	Zirconium (Zr)	Actinium (Ac)	Iridium (Ir)	Neptunium (Np)	Thorium (Th)

Fig. 2 Molecular structure of DTPA



individuals require a few doses although some require much more extensive therapy in order to minimize as much as possible the dose delivered by the radionuclide to the organs. There is a documented case of an individual being treated over 4 years with a total of 245 doses [11].

Therapy should be initiated as soon as possible after exposure as DTPA chelation is most effective when the actinide elements are circulating in the blood. As tissue and solid organ deposition of the actinide progresses, the efficacy of chelation therapy decreases.

The standard dosing of DTPA is: 1 g every 24 h administered continuously over 30 min in 250 ml of D5W, Lactated ringer's or normal saline. Parenteral administration is the best studied; and this

route has been shown to be the most efficacious (Grade III evidence). However, there are numerous animal studies that suggest oral administration may also be useful in the setting of mass casualty or ingestion exposures [7, 8, 12, 13].

For internal contamination from inhalation, nebulized calcium or zinc DTPA therapy may be preferred in adults [14] (Grade III evidence). The dose is 1 g calcium or zinc DTPA diluted in a 1:1 ratio with sterile water, administered as a nebulized treatment over 15–20 min. If continued decontamination is indicated after the first dose of nebulized Ca-DTPA, the patient should receive Zn-DTPA parenterally for the remaining doses [12].

Wounds grossly contaminated with radioactive materials may be irrigated with a solution that

contains 1 g calcium or zinc DTPA and 10 ml 2% lidocaine in 100 ml of normal saline [4].

It is important to note that radioactive materials are excreted in the feces and urine, and these body substances should be treated as such. Care should be taken by healthcare workers to avoid radiation exposure when disposing of these radioactive bodily fluids.

Special Populations

Renal Failure

DTPA therapy is still a viable option for patients with renal failure as the chelate can be dialyzed. The dialysate will be radioactive and must be disposed of accordingly.

Pregnancy and Breastfeeding

Both salts of DTPA are listed as FDA Category C medications, meaning some evidence of teratogenicity was present in animal, but not in human, studies. Limited evidence in animal models supports the administration of zinc DTPA instead of calcium DTPA [15, 16]. It is important to note radionuclides can be excreted in breast milk. Lactating mothers should follow their physician's and public health official's recommendations about breastfeeding after a radiation emergency.

Children

Current prescribing information recommends dosing 14 mg/kg with a maximum of the adult dose of 1 g every 24 h. This dose was extrapolated from the adult dose [13]. Nebulized calcium or zinc DTPA has not been tested in children.

Adverse Effects

Calcium and zinc DTPA are generally well tolerated. DTPA chelates many metals, the most clinically relevant being zinc cadmium, manganese,

Table 2 Reported adverse effects

Allergic cutaneous reaction	Chills	Headache
Nausea, vomiting	Diarrhea	Reversible anosmia
Subjective weakness	Pruritis	Cough/wheezing from nebulized calcium DTPA

iron, copper, lead, and vanadium. As such, zinc, magnesium, and manganese deficiencies have been reported with calcium DTPA [10]. These complications are easily reversed with supplementation with therapy during treatment. Zinc DTPA does not result in zinc deficiency, but it can cause magnesium deficiency, and patients should be monitored for this complication [17]. As reported in the drug label, three deaths occurred in patients with severe hemochromatosis who were treated with daily intramuscular calcium DTPA to remove iron. These three patients received 4 g of calcium DTPA per day. The first patient had received 14 g before death and the other two had been treated for 2 weeks [12].

Other adverse effects reported in various publications are listed in Table 2 [1]. Based on the US registry that included 646 individuals who received either calcium or zinc DTPA, 20 adverse events were reported and these were primarily in patients receiving the calcium salt [12].

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Physostigmine salicylate (Antilirium®) is a short-acting, lipid-soluble, nonselective, carbamate cholinesterase (ChE) inhibitor used to increase acetylcholine (ACh) concentrations at cholinergic receptors and most commonly employed in the treatment of anticholinergic-induced delirium. Physostigmine was the first known anticholinesterase used by humans. The native Efik people of West Africa used dried, ripened Calabar beans (*Physostigma venenosum*) containing the alkaloid physostigmine in their “trial by ordeal” [1, 2]. First described in 1840, the Old Calabar “trial by ordeal” required an accused individual to consume 1–20 Calabar beans in various fashions. If the individual vomited (and thus cleared the gastric bean burden), he was deemed innocent; if emesis did not occur, a cholinergic crisis followed by death was considered a guilty verdict. Predictably, very few accused survived their ordeal [1].

In 1863, ophthalmologist Argyll Robertson described the first clinical use of Calabar bean extract to reverse the mydriatic effects of atropine. In 1864, the first clinical use of physostigmine as a systemic antidote was described in four prisoners who became severely anticholinergic after drinking bottles of atropine they mistook for alcohol. Kleinwachter, the prison physician, gave the most severely poisoned patient Calabar bean extract orally as an experiment. Although the physostigmine extract promptly made him vomit, it also resulted in

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Table 1 Anticholinergic toxicity-related hospitalizations and physostigmine use in the United States

Year	Anticholinergic plants	Anticholinergic drugs	Antihistamine drugs	Total ^a	Physostigmine use (%) ^b
1983	55	679	726	1460	6.6
1984	134	1855	2852	4841	7.6
1985	114	2356	4127	6597	3.7
1986	192	2226	5412	7830	4.8
1987	143	2137	6476	8756	3.5
1988	237	1836	9924	11,997	2.2
1989	259	2169	11,254	13,682	1.8
1990	329	2233	12,922	15,484	1.6
1995	586	2729	18,581	21,896	1
2000 ^c	511	2809	21,895	25,215	0.8
2005 [10]	566	3550	24,584	28,134	0.6
2010 [11]	476	2409	15,303	18,188	1.3
2013 [12]	192	1271	17,177	18,640	1.4
2014 [13]	191	1980	17,661	19,832	1.6

^aTotal = Anticholinergic drugs and plants and antihistamine drug exposures per year

^bUse = (Number of cases in which physostigmine used/total) × 100%

^cFrom Ref. [14]

rapid return to baseline cognition. The less severely poisoned prisoners did not receive the Calabar bean extract, and took longer to recover [2].

The clinical use of physostigmine as an antidote did not become popular until nearly a century later. In 1958, 4 mg of physostigmine by injection was reported to be “entirely effective” in reversing iatrogenic coma induced by 32–212 mg of intramuscular atropine, where “by 20 min there was complete restoration of the patient’s pretreatment psychophysiological status” [3]. In 1967, physostigmine (0.05 mg/kg, intramuscularly) given for iatrogenic scopolamine toxicity reportedly resulted in “dramatic, rapid improvement, which was noticeable at 10 min and maximal at 30 min, at which time [they] were alert, coherent and well-oriented” [4]. Also in 1967, 1–2 mg of parenteral physostigmine was reported to reverse central anticholinergic effects of antiparkinsonian drugs promptly in 26 consecutive patients [5, 6]. In 1970, successful use of physostigmine for tricyclic antidepressant (TCA) overdose was first reported, reversing amitriptyline-induced agitation in a toddler with a “normal” ECG [7]. For the next decade, physostigmine was commonly recommended for

TCA-induced agitation and cardiovascular toxicity. However, in 1980 a controversial case report was published by Pentel and Peterson in which two patients developed recurrent seizure and severe cardiotoxicity after intentional tricyclic antidepressant overdose. Both patients developed a widened QRS duration progressing to bradycardia and heart block. Physostigmine was administered to each without improvement in cardiotoxicity. Atropine was then administered, followed shortly by asystole. Sodium bicarbonate was never administered. The authors concluded that, due to the temporality of the events, physostigmine was causative of asystole [8]. Though their conclusions were challenged in the literature [9], there was, nonetheless, a dramatic decline in the use of physostigmine, especially in cases of TCA toxicity, despite an overall increase in the number of reported cases of anticholinergic toxicity (Table 1) [15–17].

Clinical Pharmacology

The neurotransmitter acetylcholine (ACh) is necessary for all preganglionic autonomic neurons and postganglionic parasympathetic neurons and

some postganglionic sympathetic neurons. During basal states, there is a low level of ACh release from these neurons. After release, ACh is catabolized by synaptic acetylcholinesterases (AChEs). There are two types of cholinesterases (ChEs): (1) tissue or acetyl and (2) plasma, pseudo, or butyryl (BuChE). Circulating ACh from ingested foods and various medications, such as various choline esters, succinylcholine, and cocaine, are BuChE substrates. Synaptic ACh is the primary substrate for AChE and rapidly deacetylates the neurotransmitter [18].

Acetylcholine and physostigmine bind to the same site on ChEs. Acetylcholine acetylates cholinesterase and physostigmine carbamoylates cholinesterase. After hydrolysis (deacetylation or decarbomoylation) of the enzyme, the cholinesterase is regenerated. Because hydrolysis occurs rapidly (150 ms) for acetylated cholinesterase, the effect of ACh is dissipated before the end of the refractory period of the postsynaptic potential. In contrast, decarbamoylation takes 15–30 min [19]. Physostigmine reversibly inhibits the degradation of ACh, resulting in synaptic accumulation and repetitive, asynchronous stimulation of neighboring cholinergic receptors. Excess postsynaptic cholinergic receptor stimulation may result in sustained depolarization and subsequent blockade, leading to weakness or paralysis. Excess presynaptic cholinergic receptor stimulation may induce antidromic firing of the motor neuron, leading to fasciculations [19]. Clinically, reversible inhibition of ACh metabolism by carbamoylation lasts 3–4 h [19]. In the setting of anticholinergic toxicity, the intended function of physostigmine is to reverse cholinergic receptor antagonism and normalize cholinergic tone.

The primary pharmacological, toxicologic, and antidotal effects of physostigmine result from increased ACh stimulation of muscarinic and nicotinic cholinergic receptors. Physostigmine is a nonselective cholinesterase inhibitor, thus exhibiting efficacy at cholinesterases throughout the body. The physiologic effects of physostigmine, which are the result of decreased ACh breakdown, are listed in Table 2. Physostigmine’s cardiac properties are complex, due to mixed effects from muscarinic and nicotinic

Table 2 Physiologic effects of physostigmine

Receptors	Organ system	Clinical effects
Muscarinic	Exocrine	Salivation, lacrimation, perspiration, bronchorrhea
	Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea, fecal incontinence
	Ocular	Miosis, ptosis, blurred vision
	Respiratory	Dyspnea, pulmonary edema, bronchospasm
	Cardiovascular	Bradycardia, hypotension
	Genitourinary	Micturition, urinary incontinence
	CNS (brain)	Sedation, confusion, extrapyramidal dystonia, coma, seizure
Nicotinic	Cardiovascular	Tachycardia, hypertension
	Ocular	Mydriasis
	Muscle (neuromuscular junction)	Muscle cramps, weakness, fasciculations, tremor, flaccid or rigid paralysis

CNS central nervous system

stimulation [20]. Muscarinic stimulation leads to increased conduction time at the sinoatrial and atrioventricular nodes, bradycardia, and diminished cardiac output, whereas nicotinic stimulation has the opposite effects. In one study of “anticholinergic” overdoses, physostigmine led to significantly increased mean arterial pressure (MAP) and cardiac output [21]. In a dog model of amitriptyline poisoning treated with physostigmine, cardiac output was increased, but systolic blood pressure and heart rate largely remained unchanged. These data, collected through controlled experimentation, conflict with the clinical case report of Pentel and Peterson published at roughly the same time [22].

The vasodilatory effects of physostigmine are mediated by ACh-stimulated presynaptic inhibitory receptors on vascular sympathetic fibers and

inhibitory vascular cholinergic receptors. Stimulation of the inhibitory vascular cholinergic receptors leads to release of endothelium-derived relaxing factor, resulting in smooth muscle relaxation and vasodilation [18]. In patients treated with the anticholinergic agent methscopolamine, who then received 0.022 mg/kg (≤ 2 mg) of intravenous (IV) physostigmine over 10 min, significant increases in blood pressure, heart rate, and serum epinephrine levels were observed [18, 23]. Physostigmine's catecholamine-releasing effects seem to be centrally mediated [23]. In contrast, neostigmine is an anticholinesterase that does not cross the blood–brain barrier and does not increase serum epinephrine levels. Scopolamine, a centrally acting anticholinergic, blocks the ability of physostigmine to increase serum epinephrine levels.

While physostigmine is often said to possess nonspecific CNS arousal properties, the origin of this concept stems primarily from various individual case reports or small case series in which physostigmine has been used to reverse sedation due to hepatic encephalopathy and many nonanticholinergic drugs, including barbiturates, benzodiazepines, ethanol, droperidol, volatile anesthetics, ketamine, opiates, and propofol. Various mechanisms of this nonspecific arousal have been proposed from these anecdotal reports without validation [24, 25]. Results from higher-quality randomized clinical trials have not conclusively supported these claims, and the data are conflicting, with some authors supporting [26–33] and others refuting [34–37] this concept. Therefore, the literature does not clearly endorse the use of physostigmine as a nonspecific arousal agent in the absence of true antimuscarinic-induced CNS alteration.

Chemical and Physical Properties

Physostigmine (Fig. 1) is a tertiary amine carbamate. At physiologic pH, this tertiary amine is in equilibrium between charged and uncharged forms, with the uncharged species readily crossing the blood–brain barrier [19, 20]. In contrast, neostigmine methylsulfite and pyridostigmine bromide, the other injectable anticholinesterases,

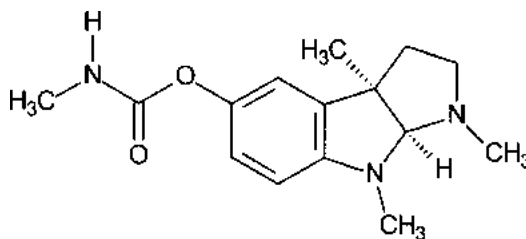


Fig. 1 Chemical structure of physostigmine

Pharmacokinetics of intravenous physostigmine^a

	Asthana [40] (SEM)	Hartvig [41] (SD)
<i>Volume of distribution</i>	186.1 L (53.7)	46.5 L (19.2)
<i>Elimination half-life</i>	16.4 min (3.2)	21.7 min (8.3)
<i>Clearance</i>	7.7 L/min (0.9)	1.54 L/min (0.63)

SD standard deviation, SEM standard error of the mean

^a1.5 mg of physostigmine given intravenously over 1 h to subjects with Alzheimer's disease and 1 mg of physostigmine given intravenously postoperatively

contain an ammonium ion (a cationic quaternary amine), inhibiting the ability of these compounds to cross the blood–brain barrier.

Physostigmine has a pK_a of 7.9; a 0.5% aqueous solution has a pH of 5.8 [38]. At physiologic pH, it exists primarily as a cation. Physostigmine is unstable at room temperature and should be stored in light-resistant packages at temperatures between 15 °C and 30 °C [36]. The solution develops a red tint when exposed to metals or with prolonged exposure to heat, light, or air and should not be injected if it is more than slightly colored [38].

Metabolism

Physostigmine is primarily metabolized through hydrolytic cleavage by acetylcholinesterase and other true cholinesterases [39]. Renal excretion is only a minor factor in physostigmine clearance. The pharmacokinetic profiles of physostigmine have received very little human study with

significant discrepancy between the two studies. Though not touched upon by the authors, the discrepancies are likely related to very different methodologies employed [40, 41].

Pharmacodynamics

Traditionally, physostigmine was thought to have very rapid onset of action after intravenous administration, with early literature suggesting an onset of action of 2 min and peak effect 5 min after intravenous administration, onset 23–30 min after intramuscular use [42]. These reported kinetics likely drove early use of recommendations of re-dosing intravenous physostigmine every 5 min. However, more recent rat, dog, and nonhuman primate studies using radio-labeled physostigmine suggest that peak cortical cholinesterase inhibition is delayed for up to 20–30 min following intravenous administration [43–45]. In the above-noted human pharmacokinetic studies by Asthana and Hartvig, the elimination half-life of physostigmine was noted to be approximately 15–20 min. However, central cholinesterase inhibition extends far beyond the simple plasma half-life of physostigmine, with numerous animal studies demonstrating continued inhibition of acetylcholinesterase (as a marker of physostigmine activity) lasting well beyond 100 min [40, 46–48]. This is fitting with clinical reports suggesting a duration of action of 30 min to several hours after intravenous physostigmine administration [4, 5, 42, 49]. Consequently, the dosing frequency recommended in early case series and case reports that may be more aggressive than the more recent data suggest is required and may result in inadvertent dose stacking. No well-controlled human trials exist with respect to variations in dosing frequency for physostigmine.

Contraindications

Cardiotoxicity

Recommendations regarding the use of physostigmine in the setting of anticholinergic-induced cardiotoxicity are conflicting. This discussion is

clouded by the cultural change in the use of physostigmine following the case report by Pental and Peterson, which limited availability of more modern clinical data. Although some authors recommend physostigmine only for anticholinergic toxicity without serious cardiovascular toxicity [50], others recommend it only for cases of anticholinergic toxicity with serious cardiovascular toxicity [51, 52]. Although the cautious approach is to consider seizures, hypotension, intraventricular or atrioventricular heart block, bradycardia, and ventricular dysrhythmias to be contraindications to physostigmine use, large case series and animal data argue against this position [49, 50, 53, 54]. Since the publication of Pental and Peterson's report, the conversation regarding the indications and contraindications of physostigmine use has divided into two separate discussions: TCA-induced cardiotoxicity and non-TCA-induced cardiotoxicity. It has become dictum in the emergency medicine culture to avoid physostigmine in the setting of TCA-associated QRS widening, despite meager and contradictory evidence [55]. However, a historical review of the evolution of physostigmine use in TCA toxicity reveals conclusions based on an incomplete understanding of the mechanisms of TCA toxicity and the therapeutic goals of physostigmine administration.

Routine practice of TCA-induced cardiotoxicity in the late 1970s and early 1980s did not involve usage of hypertonic sodium administration (e.g., sodium bicarbonate). During this era, TCA overdose conferred high mortality due to what was interpreted to be atropine and quinidine-like effects. The anticholinergic properties of TCAs prompted exploration of physostigmine as an antidote, which resulted in clear reversal of central anticholinergism [16, 56]. Case reports and small animal studies were subsequently published that suggested physostigmine may positively affect TCA-induced cardiotoxicity [57, 58]. It is important to note that the cardiotoxicity of TCAs is complex. Tachycardia may be related to a combination of antimuscarinic effects, inhibition of norepinephrine, and/or peripheral vasodilation. These effects may also be seen in concert with cardiac myocyte sodium channel blockade that

may result in widened QRS duration and other conduction abnormalities. Clearly, these are entirely different mechanisms of effect. Certainly, the antimuscarinic-driven tachycardia may be reversed by physostigmine. Indeed, it was tachycardia in TCA-poisoned patients that was the focus of the early cardioprotective claims of physostigmine, which was postulated to enhance vagal tone, which in turn, resulted in decreased tachycardia [56]. However, intraventricular conduction delay or profound bradycardia, which is an ominous sign of severe toxicity, was rarely present in these reported cases. These features of cardiotoxicity are not related to antimuscarinic effects, but instead related to the dose-dependent degree of sodium channel blockade – a mechanism entirely separate from the mechanisms inducing tachycardia [57]. To suggest that physostigmine reverses all aspects of TCA-induced cardiotoxicity may be erroneously generalized. From a pharmacologic perspective, it is unclear why enhancement of vagal tone should improve TCA-induced intraventricular conduction delays [59]. In fact, controlled experimental animal data has demonstrated no significant effect on either lengthening or shortening of QRS duration in TCA poisoning or non-poisoned controls, even with massive doses that induced signs of cholinergic excess [59, 60]. Larger human case series have provided support to these findings, with no evidence of cardiac conduction delay being induced or worsened by physostigmine in the treatment of TCA or non-TCA-induced altered mentation [50, 54].

Many emergency medicine and toxicology texts have recommended against usage of physostigmine in the setting of TCA overdose or prolonged QRS durations [55]. However, these recommendations stem from the same flawed understanding of the goals of physostigmine therapy noted above. Though various texts and articles suggest withholding physostigmine in the setting of widened QRS duration of >100 ms, the origin of this threshold does not appear to be experimentally derived and may instead be based on the clinical characteristics of the few case reports in the literature [55]. This threshold may also be an extension of the work of Boehnert and Lovejoy in which TCA-induced seizure occurred

with QRS durations ≥ 110 ms, though cardiac arrhythmias only occurred once the QRS duration was ≥ 160 ms [61]. Baseline QRS durations are physiologically variable. In a study of 1,254 healthy white males, the baseline QRS duration was defined as <120 ms (range from 80 to 116 ms) [62].

Based on the most recent assessment of the literature, the data suggest that physostigmine is not indicated for the specific treatment of intraventricular conduction delays, advanced heart block, or profound bradycardia in the setting of TCA or other anticholinergic overdoses. This is due in part to the lack of pharmacological effect of physostigmine on sodium channel conduction and in part due to more effective alternatives to management (grade II recommendation). Given that hypertonic sodium administration and serum alkalization are safe and effective for reduction of QRS widening due to sodium channel blockade attributed to cyclic antidepressants and certain other anticholinergic agents, the primary role of physostigmine in the management of this specific situation is further diminished [63–73].

Seizures

Seizures may be caused by both anticholinergic agents as well as cholinergic excess, making it difficult to separate seizure activity due to physostigmine from the natural course of the anticholinergic toxicity. In a case series of 41 patients who overdosed on maprotiline (a tetracyclic antidepressant with high seizure potential), 15 patients seized, only half of which were preceded by physostigmine use (dose not reported) [74]. Vance et al. reported seizure induction in all mice with TCA toxicity treated with physostigmine. However, the doses used were equivalent to nearly half the LD_{50} of physostigmine in these mice, arithmetically equating to an adult human dose of roughly 20 mg [55, 75]! More externally valid data from large human case series as well as double-blind rat studies demonstrate no increase in seizure rate with typical physostigmine doses in the treatment of anticholinergic toxicity [50, 76]. However, physostigmine should be used cautiously in those who have had a seizure, as this may indicate a propensity to seize in

response to the specific agent of overdose, which may be further potentiated by physostigmine administration (grade III recommendation).

Asthma

A history of asthma is noted as a contraindication to physostigmine in the package insert [38]. While bronchial hyperreactivity has occurred when physostigmine was given via nebulization to asthmatic subjects [77], the clinical relevance of this in the setting of anticholinergic toxicity is likely limited. In a series of 45 patients with anticholinergic poisonings given physostigmine, none of the 12 patients with a history of asthma developed bronchospasm [50]. Logic dictates that physostigmine should not be given to anyone with an active asthma exacerbation. However, as bronchodilation is a manifestation of anticholinergic toxicity, it is unlikely that the combination of anticholinergic toxicity and active asthma exacerbation will be clinically encountered.

Sodium Bisulfite Sensitivity

The product insert for physostigmine also cautions against administration of patients with known sensitivity to sulfur or sulfites, because the vehicle for parenteral physostigmine salicylate contains sodium bisulfite [38]. The true prevalence of sulfite allergy is unknown, and there is great variation in allergic response. As historical and allergy information is likely to be extremely limited in the setting of altered mentation due to anticholinergic toxicity, this can only be considered a relative contraindication to use. It is important to note that a sulfite allergy is not synonymous with the more common “sulfa” or antibacterial sulfonamide allergy in which susceptible patients react to the specific sulfur-containing sulfonamide moiety. There is no cross allergenicity between antibiotic sulfonamides and other nonantibiotic sulfur-containing agents, including sodium bisulfite [78].

Other Contraindications

Other traditional contraindications to cholinergic agents include coronary artery disease, gangrene, gastrointestinal or urogenital obstruction, diabetes, and use of other cholinergic medications

[38]. The clinical significance of physostigmine with these comorbidities in the setting of anticholinergic toxicity is unknown.

Treatment

Indications for physostigmine use can be broken up into three treatment categories with various levels of efficacy and potential risks: anticholinergic-induced agitation, cardiotoxicity, and CNS toxicity.

Anticholinergic-Induced Delirium

The US Food and Drug Administration-labeled indication for physostigmine is reversal of central anticholinergic toxicity [38]. Successful use of physostigmine to reverse central anticholinergic toxicity caused by over 700 different anticholinergic drugs and plants has been anecdotally reported [79]. In the largest published case series to date, Burns et al. retrospectively reviewed 52 laboratory-confirmed anticholinergic poisonings (including four TCAs) in a blinded fashion and noted that physostigmine controlled agitation in 96% of patients and completely reversed altered mentation in 87%. By comparison, benzodiazepines only controlled agitation in 26% of patients with no effective reversal of altered mentation. Additionally, those receiving physostigmine had a lower incidence of aspiration, lower rate of endotracheal intubation, and shorter mean time to recovery [50]. Watkins et al. demonstrated that in all-cause antimuscarinic-induced delirium, the use of physostigmine alone resulted in a significant reduction in the rate of intubation compared to other treatment groups (1.9% vs. 8.4%) [54]. Multiple smaller case series also confirm the superiority of physostigmine to benzodiazepines in pure antimuscarinic agitation without occurrence of significant adverse side effects [53, 80, 81]. Further indications for the use of physostigmine are anticholinergic toxicity with hyperthermia and hemodynamically significant sinus tachycardia. The goals of physostigmine therapy in these cases are to treat hyperthermia, to avoid

emergent intubation (needed to protect the airway) and artificial ventilation (in order to treat excess respiratory depression from sedatives), and to control behavioral abnormalities and rhabdomyolysis (caused by agitation and restraints).

Central anticholinergic toxicity is usually, but not always, accompanied by signs of peripheral anticholinergic toxicity and may be difficult to diagnose clinically (see ► Chap. 23, “Anticholinergic Syndrome”). In cases of marked delirium in which anticholinergic agents are suspected, published literature demonstrates safety of using physostigmine as a diagnostic test [42, 53, 80, 82] (grade III recommendation).

Anticholinergic-Induced Cardiotoxicity

Controversy abounds with respect to the utility of physostigmine to manage xenobiotic-induced cardiotoxicity. Effective discussion of anticholinergic-induced cardiotoxicity must differentiate between management of all-cause anticholinergic-induced tachycardia and TCA-induced cardiac conduction abnormalities.

The use of physostigmine for anticholinergic-induced tachycardia has received little direct study. Instead, research has focused on management of delirium from antimuscarinic agents. However, heart rate trends are often presented in the data which demonstrate a consistent decrease in mean heart rate and increased MAP without induction of symptomatic bradycardia. This holds true even in the setting of non-TCA-induced conduction abnormalities, such as can be seen in large diphenhydramine overdoses, for example [50, 53, 80].

With respect to TCA-induced cardiotoxicity, the discussion must be tailored around the etiology of the cardiotoxicity that is intended to be managed by physostigmine. While there exist various individual case reports where TCA-induced “cardiotoxicity” resolved after physostigmine use, these case reports often do not differentiate between types of cardiotoxicity treated (be it simple tachycardia, advanced heart block, or profound bradycardia), nor is physostigmine the sole agent employed for treatment

[21, 83–85]. Indeed, the quality of these reports is no better than the controversial report by Pentel and Peterson. Additionally, multiple animal models of TCA-induced cardiotoxicity demonstrate variable efficacy of physostigmine in correcting conduction abnormalities, often utilizing doses of many orders of magnitude beyond those typically used in human treatment and limiting external validity [73–77]. With respect to simple TCA-induced tachycardia (in the setting of altered mentation), the literature demonstrates physostigmine’s efficacy in heart rate reduction [16, 56].

However, with respect to TCA-induced sodium channel blockade, physostigmine serves no logical role. In a well-designed randomized, controlled study, Goldberger and Curtis induced QRS widening in rabbits using amitriptyline. In those given a massive dose of physostigmine, there was neither narrowing nor widening of QRS duration, despite a decrease in heart rate and induction of cholinergic signs [59]. Lum et al. also demonstrated that physostigmine had no influence in heart rate or QRS duration in cats, both in the setting of pretreatment with a large dose of physostigmine and in the setting of nortriptyline-induced sodium channel blockade [60].

Regardless, as noted previously, the safety and efficacy of hypertonic sodium administration and serum alkalization in TCA cardiotoxicity likely supplant any role of physostigmine for this toxicity [64–73].

Anticholinergic-Induced Seizures

Given that seizures are frequently seen in both anticholinergic toxicity and following excessive or unnecessary physostigmine administration, physostigmine is not indicated for seizure management. Human evidence for or against this recommendation in case reports and series is limited due to the characteristic abrupt onset of seizures with severe anticholinergic toxicity and the difficulty distinguishing the temporality of seizure induction or reversal with the variable-dosing regimens of physostigmine. However, in one double-blind rat model addressing this question, no therapeutic benefit of physostigmine was seen

in diphenhydramine-induced seizures compared to controls [76].

Gamma-Hydroxybutyrate-Induced Sedation

There exist several recommendations in the literature for the usage of physostigmine to reverse the profound sedation of gamma-hydroxybutyrate (GHB) intoxication. In the 1970s, two poorly designed studies reported that physostigmine could be used safely and effectively to reverse sedation from GHB used as an anesthetic agent [86, 87]. One author anecdotally reported the safe and effective use of physostigmine in reversing 50 cases of GHB overdose [88]. However, the timing of reversal in all of these studies was widely variable, as was the dosing and frequency of physostigmine administration. Given that GHB-induced sedation is almost entirely GABA driven and often rapidly self-terminates, reliable conclusions regarding the role of physostigmine cannot be made from these uncontrolled studies. A systematic review of the available literature found no convincing evidence of physostigmine's role in managing GHB-induced sedation and coma [89]. Furthermore, a recent double-blind, placebo-controlled rat study performed by Bania et al. demonstrated that not only did physostigmine not reverse GHB-induced sedation in any affected rats, 100% of those treated with typical human-equivalent doses of physostigmine developed muscarinic toxicity and seizures [90]. Therefore, it cannot be concluded that there is any role for physostigmine administration in the reversal of GHB-induced sedation.

Administration

Adult

Physostigmine salicylate is available in 2 mL ampules in a concentration of 1 mg/mL. The solution contains sodium bisulfite 0.1% and benzyl alcohol 2% [38]. In adults, the usual recommended dose is 1–2 mg, given intravenously

or intramuscularly (grade II-3 recommendation). When given intravenously, it should be given at a rate of 1 mg/min. The previous literature recommended repeat dosing in 5–10 min if no response and until the desired clinical response was achieved to a maximum of 2 mg per dose. However, as discussed above, that recent animal studies using radio-labeled physostigmine suggest peak cortical cholinesterase inhibition may not be achieved for 20–30 min after intravenous infusion [43–45]. As such, the 5–10 min re-dosing recommendations are not consistent with the now known time frame for maximal pharmacodynamic response. Waiting 5 min before re-dosing may be insufficient to determine the efficacy of the previous dose and could certainly result in dose stacking, potentially causing cholinergic excess (i.e., bronchorrhea, seizures, etc.) [91]. No prospective human data exist with respect to lengthened dosing intervals.

Pediatric

In children, the manufacturer-recommended physostigmine dose is 0.02 mg/kg intravenously or intramuscularly [38]. When given intravenously, it should be given at a rate of 0.5 mg/min (grade III recommendation). Historical recommendations suggest that the dose may be repeated in 5–10 min until the desired clinical response is achieved or adverse effects are seen. However, the same caveats with respect to dosing interval described for adults above also apply in children. Note that if physostigmine is administered intramuscularly, peak absorption may not occur for 23–30 min [40, 42].

Dosing Regimens

Because physostigmine is relatively short-acting, repeat dosing in 30–120 min may be required. When the desired clinical response is achieved, intermittent doses may be used to maintain clinical status. In 45 cases of anticholinergic poisoning treated with physostigmine, central anticholinergic symptoms recurred in 32 (78%) of cases, with

26 cases requiring multiple doses [50]. Oral, subcutaneous, transdermal, and nebulized dosing schemes have been reported for physostigmine administration, but these modalities have not been studied in the management of acute anticholinergic overdose.

The treatment protocol reported by Burns et al. begins with treatment of anticholinergic delirium with 1–2 mg of physostigmine, given by slow IV push over 5 min. Repeat dosing, though performed only 5 min after initial dose, was initiated at 0.5 mg, until resolution of delirium or signs of mild cholinergic excess were observed. With this protocol, 11% of patients developed mild cholinergic symptoms, though none developed seizures. The mean response time was 11 ± 5 min, with a mean duration of effect of 100 ± 42 min [50]. Dawson et al. summarized two different approaches to the amount of physostigmine administered in the initial dose and subsequent re-dosing and found equivalent outcomes despite one protocol utilizing 50% less physostigmine at the same dosing intervals [91]. This suggests that a similar time to response but at a much lower mean dose (2.2 vs. 1.3 mg physostigmine) titration may further support the notion that a 5 min re-dosing schedule may allow insufficient time to determine the efficacy of the previous dose.

In appropriate situations, very large cumulative doses of physostigmine appear to be safe and effective. Several cases have been reported in which large doses of physostigmine were administered over the course of many hours with excellent tolerance, though often in the absence of rational indication for its use. In one case, a 7-year-old girl who had ingested imipramine received 260 mg of physostigmine over 30 h to maintain arousal [92]. In another case, a 55-year-old woman who had ingested a large amount of amitriptyline received 196 mg of physostigmine over 36 h due to persistent sedation is reported [93]. Because this patient did not receive her first dose of physostigmine until 64 h post ingestion, it is questionable whether central anticholinergic toxicity was causing her sedation at that point. Finally, in 1975, a 27-year-old woman who had ingested 9850 mg of a TCA received 74 mg of

physostigmine (in 5–10 mg doses) over 6 h for recurrent ventricular tachycardia without adverse effects, despite there being no rational reason to administer physostigmine for this indication [84].

Successful and uncomplicated use of continuous physostigmine infusions has also been reported. In one case, marked olanzapine-induced anticholinergic delirium in a 6-year-old boy was successfully managed with a physostigmine infusion of 0.5 mg/h (0.167 mg/kg/h) over 16 h [94]. Similarly, a 13-year-old female with recurrent antimuscarinic delirium from a mixed drug ingestion was successfully managed with a physostigmine infusion of 2 mg/h over 8 h without adverse effects [95]. Finally, a 20-year-old female with antimuscarinic delirium from a mixed benztropine and amitriptyline overdose was safely managed with a physostigmine infusion over 8 h with additional boluses over the next 52 h (77 mg physostigmine total), again without apparent adverse effects [96]. There are no controlled experimental data with respect to continuous physostigmine infusion.

Summary

Physostigmine is the ideal antidotal agent for management of antimuscarinic delirium resulting from overdose of pure anticholinergic agents. When titrated appropriately, it can rapidly reverse agitation, reduce hemodynamically significant tachycardia and hyperthermia, and avoid the risks of excessive sedation, prolonged recovery, and emergent intubation when compared to other sedative agents. The complexities of TCA toxicity limit the utility of physostigmine in this setting, and its use is contraindicated in the setting of marked TCA-induced cardiotoxicity with signs of extreme sodium channel blockade. The use of physostigmine is probably best avoided in the management of overdoses associated with seizures. Careful titration is the key to management as cholinergic toxicity can result from rapid physostigmine administration (either in initial infusion or repeat dosing frequency). Appropriate use of physostigmine affords excellent patient benefit with low risk.

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Introduction

Prussian blue (PB) is an antidote used to treat patients with confirmed or suspected internal contamination with radioactive cesium (^{137}Cs), radioactive thallium (^{201}Tl), or nonradioactive thallium [1]. It has a molecular weight of 859.3 g/mol and an empirical formula of $\text{Fe}_4^{\text{III}} [\text{Fe}^{\text{II}}(\text{CN})_6]_3$. Two forms of PB exist: insoluble or ferric (III) hexacyanoferrate (II) and soluble or potassium ferric (III) hexacyanoferrate (II) [2]. In the USA, since October 2003, the Food and Drug Administration only approves the insoluble PB as a therapeutic agent (Fig. 1). For this reason, all subsequent references to “PB” in this chapter refer to the insoluble form. PB was introduced as an antidote in the USA for drug preparedness over concerns of the possibility of bioterrorism (e.g., radiologic dispersing device or “dirty bomb”) and other radiation event [3].

The latest report (no. 161, 2009) of the US National Council on Radiation Protection and Measurements states that PB is the preferred decorporation therapy for the radionuclides cesium, thallium, and rubidium (Grade III recommendation) [4]. However, PB is not FDA approved for rubidium.

In 2009, the *Expert Consensus Guidelines for Stocking of Antidotes in Hospitals That Provide Emergency Care* could not reach consensus regarding the stocking requirement for PB [5]. Thus, the majority of hospitals likely do not stock this antidote. Other authors suggest that

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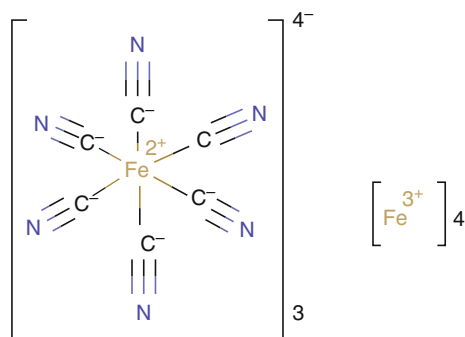


Fig. 1 Insoluble PB

hospitals should be prepared for chemical and radiological disasters and that most of them should stock at least 12 capsules of PB 500 mg (Grade III recommendation) [6]. However, in the USA, or its territories, in the event of a national emergency, PB is available through the Strategic National Stockpile [7].

Thallium

There are no human controlled studies on the use of PB as an antidote. The majority of available clinical data on the treatment of thallium poisoning or exposure with PB are derived from case reports [8–28]. These reports all describe cases of nonradioactive thallium ingestion.

Cesium

The majority of human data on the use of PB as an antidote for radioactive cesium are from observational prospective studies [29–32]. Radioactive cesium contamination incidents occurred in April 1986 in Chernobyl (Russia) [32] and in September 1987 in Goiânia (Brazil) [29–31]. Three of the 15 (20%) contaminated subjects in the Chernobyl incident received PB. In contrast, 46 out of the 90 (50%) contaminated subjects from the Goiânia incident were treated with PB, 13 of which were children. Goiânia victims were treated with a substantial delay of at least a week from the initial exposure.

Unfortunately, these articles do not report sufficient detail about the untreated patients to allow a meaningful appraisal of the clinical benefit of this therapy. Case reports of patients with nonradioactive cesium poisoning treated with PB demonstrated a reduction in apparent half-life by more than 50% [33, 34].

Treatment with PB is presumed to be more efficacious if administered as soon as possible after incorporation (Grade III recommendation). It may be difficult to obtain serum thallium or cesium concentrations in a clinically meaningful timeframe. Thus, most of the time the clinician has to resort to qualitative assessment of the likelihood of internal contamination to initiate treatment, especially in disaster situations where individuals closest to the source and those not wearing protective equipment have a highest risk of internal contamination.

Pharmacodynamics

PB is an ion exchanger [35]. It binds with high affinity to cesium and thallium isotopes that have been ingested or inhaled and are excreted in bile [35]. It acts by reducing both the primary uptake and then the gastrointestinal reabsorption of the toxic elements. In vitro studies show that binding of cesium or thallium by PB was maximal at pH 7.5 and decreased at lower pH [36–38]. Theoretically, PB is expected to reach its maximum efficiency when present in the small bowel.

PB acts by reducing the biological half-life of thallium and cesium respectively from about 8 days to 3 days and from about 110 days to 30 days. It also reduces the whole-body effective half-life of ^{137}Cs by 46% in adolescents and by 43% in children from 4 to 12 years of age [29].

The maximal absorptive capacity in vitro for various formulations of PB varies from 59 to 72 mg of thallium/g of PB [39, 40].

Pharmacokinetics

Absorption: PB is not significantly absorbed through intact gastrointestinal wall [35]. However, prolonged treatment in some patients who

received soluble PB resulted in benign and transient blue discoloration of their sweat and their tears, which is suggestive of a small amount of systemic absorption [41].

Distribution and metabolism: As most of the PB is not absorbed via the gastrointestinal system, distribution and metabolism are negligible, if not irrelevant.

Elimination: PB is eliminated unchanged in feces, thus its clearance is proportional to the gastrointestinal tract transit time [35].

Contraindications

According to the manufacturer, no identified contraindications to the use of PB exist [35]. It is generally well tolerated and is considered nontoxic, despite having a nitrile (cyano) moiety [42–44]. However, PB should be used with caution in patients with a history of gastrointestinal obstruction, peptic ulcer disease, preexisting cardiac arrhythmias, or electrolyte imbalances (Grade III recommendation) [4].

Adverse Effects

Constipation and asymptomatic hypokalemia are the most commonly cited adverse effects reported by humans taking therapeutic doses of PB [29, 45]. Toxicity from cyanide release seems to be minimal as reported in a simulated experimental study [46]. In another report of three volunteers each given 500 mg of PB, only 2 mg of radio-labelled cyanide was absorbed, which is negligible [42].

Special Populations

The FDA lists PB as pregnancy category C (teratogenic effects demonstrated in animals but not in humans) [35]. However, the risk of poisoning with thallium or cesium and the lack of systemic absorption of PB mandate an individual risk analysis evaluation [47].

Treatment

Given the delay in obtaining thallium and cesium concentrations, PB therapy must be initiated without laboratory confirmation when internal contamination with either cesium or thallium is suspected (Grade III recommendation).

The dose and schedule for PB has not been established with clinical trials. A volunteer study of two patients given PB for decorporation of radioactive thallium showed a dose-dependent relationship for thallium absorption and maximal absorption 1 h after administration. Thus, divided dosing is recommended [48].

For thallium poisoning, the dose used in clinical reports is 150–250 mg/kg/day divided in three or four doses (Grade III recommendation) [9]. For cesium poisoning, the dose recommended by the manufacturer is 9 g per day in three divided doses [35]. The FDA-approved dosing for PB for children from 2 to 12 years of age is 1 g taken orally three times daily (Grade III recommendation) [35]. The dosing for adolescents over 12 years old and adults is 3 g taken orally three times daily (Grade III recommendation) [35]. Doses may be reduced to 1 or 2 g three times daily when internal radiation levels have substantially decreased or for gastrointestinal intolerance (Grade III recommendation) [35].

The duration of treatment with PB should take into account the amount of contamination (whole-body counting) and the symptomatology and thus essentially rests on clinical assessment [35]. Expert advice can be sought. Radiation measurements, e.g., on a Geiger-Müller counter, should be done regularly to evaluate the degree of residual external contamination (Grade III recommendation) [4]. Radiobioassays should be done to evaluate internal contamination; however, the technology and expertise to measure fecal concentrations of thallium or cesium is unlikely to be available in medical facilities [4]. Arrangements with a designated laboratory should be considered [4]. Stool samples (total voidings) and 24-h urine collections to measure metal concentration prior to the beginning of the treatment and weekly afterwards are recommended to determine the rate of extraction of cesium or thallium,

but this might require sending specimens to a specialized laboratory [4]. Serum electrolytes, complete blood count, renal, and hepatic functions should be assessed prior to administration of PB and monitored weekly during treatment (Grade III recommendation) [35]. For nonradioactive thallium internal contamination, PB should be continued until a 24-h urine specimen results a thallium concentration below 5 mcg/L or until the patient is asymptomatic (Grade III recommendation) [35]. For radioactive thallium or cesium internal contamination, PB should be continued until radiation measurements are lower than the detectable threshold [35]. Therefore, it can be expected that treatment with PB may last more than 30 days.

Dosing of PB in infants and neonates has not been established and is not FDA approved. However, in 2011, the US Biomedical Advanced Research and Development Authority awarded a grant to a PB manufacturer to develop a safe and effective pediatric formulation [49]. At the Public Meeting of the US National Advisory Committee on Children and Disasters on August 8th, 2014, it was mentioned that there have been advances in the research of delivery formulations of PB and it appears some of them may have increased absorptive capacity to cesium over previous formulations [50].

Administration

PB is supplied as 0.5 g gelatin capsules for oral administration [35]. The capsules should be taken with food to stimulate the excretion of cesium or thallium (Grade III recommendation) [35]. In patients who cannot swallow a large quantity, capsules may be opened and mixed with bland or liquid food (Grade III recommendation) [35]. However, this can cause blue discoloration of the mouth and teeth [35]. In critically ill patients who cannot swallow the capsules (e.g., intubated patients), these may be opened and administered by orogastric or nasogastric tube (Grade III recommendation) [9, 15, 18, 19, 27].

Coadministration with a stool softener or mild laxative is suggested as constipation has been reported as the most frequent adverse effect following the use of PB (Grade III recommendation) [4, 29]. This adverse effect may be problematic, as constipation will decrease the fecal excretion of cesium or thallium. PB dissolved in 50 ml of 15–20% mannitol prior to administration is often reported in cases of nonradioactive thallium poisoning (Grade III recommendation) [8, 18, 19, 25, 28].

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Pyridoxine (Fig. 1) and the biologically similar compounds pyridoxal and pyridoxamine are as a group commonly known as vitamin B₆. They are found in several dietary sources including nuts, meat, fish, grain cereals, fruits, and vegetables [1]. Pyridoxine is used as an antidote primarily for the control of seizures following poisoning by isoniazid, monomethylhydrazine, *Gyromitra esculenta* mushrooms, and other hydrazines. It may also be useful to reverse the altered mental status associated with these compounds. Pyridoxine hydrochloride is available in both parenteral and oral formulations, is water soluble, and is mostly excreted in the urine. The parenteral formulation has a pH of 2.0–3.8 and can degrade when exposed to light [2].

Pharmacodynamics

The active form of pyridoxine is pyridoxal-5'-phosphate (PLP), which serves a critical role in multiple enzymatic reactions. Importantly, it is a necessary cofactor for the formation of γ -aminobutyric acid (GABA). Isoniazid and other hydrazines inhibit the conversion of pyridoxine to PLP via competitive inhibition of pyridoxine phosphokinase, resulting in decreased GABA, increased glutamic acid, and, subsequently, seizures (see Fig. 2).

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Pharmacokinetics

Pyridoxine is absorbed in the jejunum with oral bioavailability ranging from 61% to 81% with a mean of 71% [3]. Time to peak concentration after oral administration is 1.25 h [4]. The conversion of pyridoxine to PLP occurs in the liver, with release of active vitamin into circulating blood. Circulating PLP is bound to serum albumin, and small amounts can be stored in liver and muscle tissue. Of circulating vitamin B₆, 60% is PLP [1]. The half-life of pyridoxine is up to 20 days. The major inactive metabolite 4-pyridoxal acid is excreted in the urine [5]. Biliary excretion accounts for 2% of drug elimination.

Contraindications

The only known contraindication to the use of pyridoxine is known allergy to it or to a component of its preparation.

Adverse Effects

Although generally well tolerated, pyridoxine can be neurotoxic in large doses when used both parenterally and orally. Sensory neuropathy, sometimes delayed, is well reported after long-term, high-dose oral pyridoxine. Case reports of neuropathy have described doses of 2–10 g/day for months and years that have variable levels of improvement. A study of five volunteers treated with 1–3 g/day of pyridoxine showed subjective and electrophysiologic findings consistent with sensory neuropathy within 1.5–7 months of treatment in a dose-dependent fashion [6]. A retrospective series of 16 patients with neuropathy after pyridoxine use showed a possible relationship between dose and duration of use. Those who developed neuropathy after doses of 500 mg/day or less did so after a mean of almost 2 years, while those with doses of 5 g/day or more developed neuropathy after an average of 3 months. Eleven patients had at least some improvement in the months after stopping pyridoxine [7].

Perhaps more relevant to the use of pyridoxine as an antidote are reports of adverse events associated with parenteral administration. Two women who received 2 g/kg IV over 3 days developed severe, debilitating irreversible neuropathy resulting in inability to walk. Also, previously unreported central nervous system symptoms of transient autonomic dysfunction, mild weakness,

Fig. 1 Pyridoxine

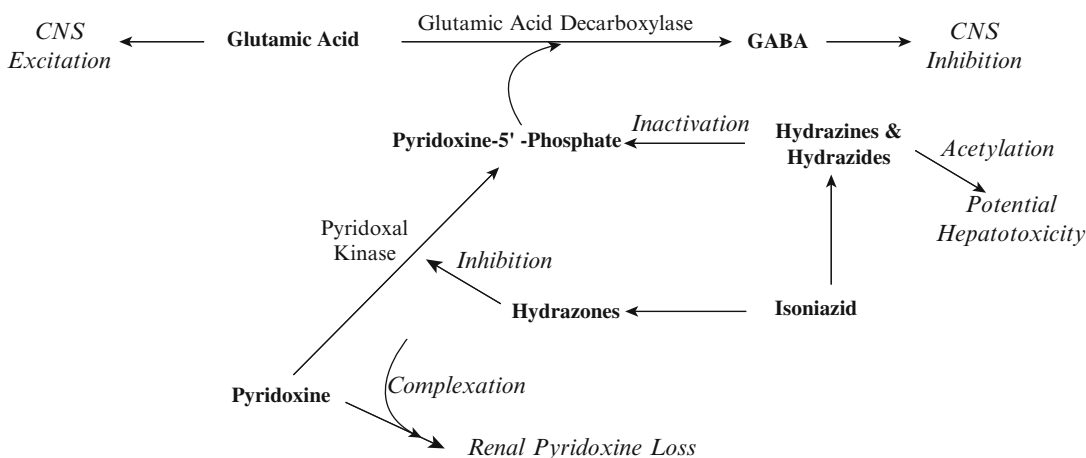
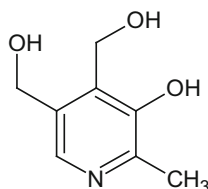


Fig. 2 Inhibitory effects of isoniazid on pyridoxine-related metabolic processes

nystagmus, lethargy, and respiratory depression were reported although there was some question as to whether that may have been as a result of the preservative used in the pyridoxine formulation [8]. The toxic dose is not clear; however there have been large doses of parenteral pyridoxine (4–25 g) used in the treatment of isoniazid toxicity without reported adverse event [9].

Pyridoxine may also reduce the effectiveness of levodopa in the treatment of Parkinson's disease via increasing the peripheral decarboxylation of levodopa [10].

Pyridoxine is Food and Drug Category A in pregnancy. There are no studies in the safety of high-dose pyridoxine for INH-induced seizures in pregnant women.

Treatment and Administration

Pyridoxine is indicated for the treatment of isoniazid or other hydrazine-induced seizures (Grade II-3 recommendation). Recommended dose is 1 g of pyridoxine for every gram of isoniazid up to a total of 5 g [9] (Grade II-3 recommendation). A suggested administration for an actively seizing patient is 0.5 g per minute IV until resolution of seizure activity with the remainder given over the next 4–6 h to maintain serum pyridoxine as isoniazid is metabolized [11] (Grade III recommendation). In children, standard recommended dosing is 70 mg/kg, although it has been proposed that a gram-for-gram dosing is indicated for isoniazid poisoning regardless of age [12] (Grade III recommendation). Co-administration of benzodiazepines has a synergistic effect in terminating seizures in animal models [13]. For seizures unresponsive to initial pyridoxine dosing, repeated dosing at 5–20 min intervals until seizure activity terminates has been effective [14] (Grade III recommendation). Pyridoxine may also be considered for persistent coma after isoniazid overdose. In a report of three cases, pyridoxine was used for continued depressed mental status in doses of 3–5 g given up to 42 h after isoniazid ingestion with apparent improvement in mental status [15] (Grade III recommendation). Improvement in depth of coma was also reported in

patients receiving pyridoxine for INH overdose compared to historical controls [9] (Grade II-3 recommendation). Given traditional stocking, a single overdose has the capability of depleting a large region's supply of pyridoxine, so in areas where isoniazid is largely prescribed, collaboration should be preestablished in order to transfer adequate supplies of isoniazid to locations in need [16, 17].

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Table 1 Commonly Used Sodium Bicarbonate Products Ref. [1]

Percentage	mEq	mEq/mL	mOsm	Size (mL) ^a
4.2	5	0.5	1	50
7.5	44.6	0.9	1.79	50
8.4	50	1	2	10

Definitions: *mEq* milliequivalents, *mEq/mL* milliequivalents per milliliters, *mOsm* milliosmols, *mL* milliliters

^aCommonly available sizes

Therapeutic administration of sodium bicarbonate (NaHCO_3) has the ability to alter xenobiotic pharmacokinetic properties, pharmacodynamic profile, or both. Sodium bicarbonate is available generically as 4.2%, 7.5%, and 8.4% intravenous solutions in water. NaHCO_3 is also available as a 500 milliliter (mL) 5% solution and as tablets; however, for purposes of this discussion, only the intravenous solution will be considered. The milliequivalent (mEq) and milliosmolar (mOsm) content of each percentage is included in Table 1 [1]. Due to its decreased osmolality, the 4.2% solution is often preferred for pediatric patients.

The therapeutic effect of sodium bicarbonate as related to different toxins is described below. Due to the inherent lack of controlled trials, all recommendations are based on level III clinical human or animal study evidence unless otherwise specified.

Pharmacodynamics

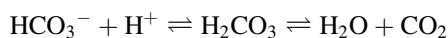
As a primarily extracellular cation, sodium (Na^+) is a major constituent to ionic balance in the serum. Sodium is also a driving force for the depolarization of cardiac Purkinje fibers responsible for cardiac contraction. Providing additional sodium ions is one mechanism for the therapeutic effects of sodium bicarbonate. Bicarbonate (HCO_3^-) is an extracellular anion and is a major constituent of the ionic and acid–base balance in the serum. Alteration in serum pH has the potential to alter xenobiotic protein and receptor binding, membrane permeation, and volume of distribution. Also, HCO_3^- is excreted by the

kidneys affecting urine pH and, as a result, may alter elimination kinetics of some xenobiotics.

The use of intravenous NaHCO_3 to correct metabolic acidosis is the subject of considerable debate due to concern over increasing arterial carbon dioxide concentrations resulting in intracellular acidosis [2, 3]. This chapter focuses on the use of NaHCO_3 for the treatment of specific xenobiotic exposures and will not address its use for undifferentiated acid–base disorders.

Pharmacokinetics

Once in the serum, sodium bicarbonate dissociates into Na^+ and HCO_3^- ions. The kidneys regulate acid–base balance of serum and urine by the action of the proximal tubules on bicarbonate excretion and reabsorption. HCO_3^- exists in an equilibrium in the serum:



HCO_3^- and carbonic acid (H_2CO_3) exist in roughly a 20:1 ratio at physiologic pH (7.4). Dissolved carbon dioxide (CO_2) is excreted through exhalation, highlighting the importance of adequate respiration following administration of NaHCO_3 .

Contraindications

Adverse effects of NaHCO_3 administration are generally related to hypernatremia and excessive alkalemia. No true absolute contraindications exist for the use of NaHCO_3 during the management of life-threatening drug toxicity. However, cautious use is advised in patients with volume overload, pre-existing alkalemia, or electrolyte and/or mineral imbalance. Bicarbonate causes the intracellular shift of both potassium and calcium, thereby lowering values of measured extracellular serum potassium and calcium without affecting whole-body stores.

Treatment

Sodium Bicarbonate for the Treatment of Sodium Channel Antagonist Toxicity

In the 1950s, reports of reversing cardiotoxicity (i.e., QRS prolongation, hypotension, and cardiac dysrhythmias) caused by quinidine and procainamide toxicity with the administration of sodium lactate were published [4–8]. The use of sodium lactate and sodium bicarbonate for the treatment of tricyclic antidepressant (TCA) cardiotoxicity was introduced shortly thereafter [9–12]. With successful treatment of quinidine and TCA toxicity, use of sodium bicarbonate spread to other agents with similar sodium channel-blocking effects.

Cardiotoxicity from myocardial sodium channel antagonists can be life-threatening, and NaHCO_3 is the treatment of choice for sodium-channel blockade-associated wide complex tachycardia. Rapid influx of sodium during phase 0 of depolarization is responsible for upstroke velocity and V_{max} of the myocytes. Blockade of fast sodium channels impairs depolarization, alters

myocardial function, and predisposes the heart to ventricular dysrhythmias. Altered depolarization is predictably heralded by characteristic electrocardiographic (ECG) changes including QRS widening, right axis deviation, including an R-wave in aVR, and, occasionally, a Brugada-like pattern in the chest leads [13–16]. An ECG demonstrating a wide-complex rhythm following TCA intoxication is shown in Fig. 1.

Electrocardiographic findings are similar among sodium channel antagonists (namely, QRS prolongation). Administration of NaHCO_3 boluses is considered the mainstay of therapy for poisoning by drugs causing sodium channel blockade with evidence of response across many pharmacologic classes (Level of Evidence (LoE) III). Adjunct therapies may be beneficial in some cases, but even though these therapies are being used in conjunction, they should be thought of separately with NaHCO_3 targeting the signs of cardiotoxicity. The benefits of NaHCO_3 administration in the treatment of sodium channel antagonist toxicity are likely multifactorial. The presence of an excess of sodium ions promotes sodium influx.



Fig. 1 Demonstration of TCA toxicity (Reprinted with permission: <http://lifeinthefastlane.com/ecg-library/basics/tca-overdose/>)

Alkalinization of the serum and receptor may decrease receptor binding, increase protein binding (making less drug available at the receptor), and promote change in ionized fraction of the drug, especially for acidic drugs. The comparative effects of sodium alone (3% sodium chloride (NaCl)), alkalemia alone, and combined sodium and alkalemia (NaHCO_3) have been evaluated in both in vitro and in vivo animal models [15, 17–20]. No true single benefit has been defined and the results vary depending on toxin. However, the use of NaHCO_3 has shown similar or improved benefit compared to hypertonic sodium chloride while alkalemia alone was the least beneficial amongst the treatments studied [15, 17–20]. Of note, the animals treated with sodium chloride received the equivalent of 15 mEq/kg sodium which is clinically unrealistic. In the case reports, retrospective reviews, and animal studies showing effective treatment, NaHCO_3 was administered as a bolus.

Important considerations when giving NaHCO_3 for sodium channel blockade include the following: (1) studies and case reports showing therapeutic effect from NaHCO_3 were done using bolus administration. Bolus dosing allows for administration of 50 mEq of NaHCO_3 in 5–10 min depending on catheter size, as opposed to an infusion such as the administration of 150 mEq with 850 mL of 5% dextrose in water (D5W) administered at 250 mL/h, in which case only 37.5 mEq NaHCO_3 will be delivered per hour. (2) Following the NaHCO_3 bolus, ECG monitoring is necessary to observe for response to therapy and the need to administer additional doses. (3) NaHCO_3 boluses may need to be repeated to an end point of dysrhythmia cessation or a significant decrease in QRS duration (generally <120 msec). Repeat bolus doses of NaHCO_3 may also be required if the QRS again widens. Serum sodium concentration and acid–base status should be monitored and, in general, NaHCO_3 therapy is discontinued if serum pH exceeds 7.55 or serum sodium concentration exceeds 155 mEq/L. Medications known or believed to cause sodium channel blockade through mechanism of action or similarity to other agents are reported in Table 2.

Table 2 Cardiac Sodium Channel Antagonists^{a,b}

Antidepressants	Analgesics
<i>Tricyclic antidepressants</i>	Propoxyphene
Amitriptyline	
Amoxapine	Anti-infectives and rheumatologic agents
Clomipramine	Chloroquine
Desipramine	Hydroxychloroquine
Doxepin	Quinine
Imipramine	Amantadine
Nortriptyline	
Protriptyline	Cocaine
Trimipramine	
<i>Selective serotonin reuptake inhibitors</i>	Antidysrhythmics
Citalopram	<i>Vaughan Williams Class Ia Agents</i>
Escitalopram	Disopyramide
<i>Serotonin norepinephrine reuptake inhibitors</i>	Procainamide
Venlafaxine	Quinidine
Desvenlafaxine	<i>Vaughan Williams Class Ic Agents</i>
<i>Other antidepressants</i>	Encainide
Bupropion	Flecainide
	Moricizine
Neuroleptics	Propafenone
<i>Dibenzoxazepines</i>	<i>Vaughan Williams Class II Agents</i>
Loxapine	Acebutolol
<i>Phenothiazines</i>	Labetolol
Mesoridazine	Propranolol
Thioridazine	
	Local anesthetics
Antiepileptics	Bupivacaine
Lamotrigine	Mepivacaine
Carbamazepine	Prilocaine
	Ropivacane
Antihistamines	Procaine
<i>Nonselective</i>	Tetracaine
Brompheniramine	
Chlorpheniramine	Muscle relaxants
Diphenhydramine	Cyclobenzaprine
Doxylamine	
Hydroxyzine	Plants
Promethazine	Taxines
	Grayanotoxins

^aTable may not include all agents from the class

^bIncluded xenobiotics have demonstrated sodium channel antagonism in animal studies or human case reports or are included because they structurally or mechanistically resemble these agents

Antidepressants

Sodium bicarbonate use for antidepressant toxicity, especially TCAs, has provided critical evidence for its effectiveness. As quinidine and procainamide provided an introduction to the use of NaHCO_3 during toxicity, research into TCA toxicity has provided guidelines for its effective use and dosing recommendations for managing toxicity of other cardiac sodium channel antagonists. In TCA overdose, hypotension, QRS prolongation, and tachydysrhythmias often occur. Significant TCA overdoses are frequently associated with an awake and mildly sedated patient, followed by a precipitous, and sometimes catastrophic, decline in both neurologic and cardiovascular status. The first few hours after overdose are critical for observation of symptom onset. Successful use of NaHCO_3 for the reversal of TCA-induced QRS prolongation and dysrhythmias has been reported in both adult and pediatric patients [11, 20–29].

During investigation for a dose–response effect in amitriptyline toxicity, a landmark paper reported the observation of a greater correlation between QRS duration for the development of seizures and ventricular dysrhythmias, than was seen with serum amitriptyline levels [13]. In this study population, 34% of patients with a QRS duration ≥ 100 msec experienced seizure activity and 50% of patients with a QRS duration ≥ 160 msec developed ventricular dysrhythmias. The presence of right-axis deviation in aVR has also been used as a prognostic indicator in TCA toxicity. In patients with an R-wave of at least 3 mm aVR, 43% developed seizures or dysrhythmia while 80% of those with an R-wave of at least 5 mm had seizures or dysrhythmias. The R/S ratio >0.7 was also associated with 46% of patients developing seizures or dysrhythmias [30]. However, not all sodium channel antagonists lead to such observable changes in aVR. Based on these observations, NaHCO_3 bolus therapy is recommended for a QRS ≥ 160 msec (LoE III). The indication for NaHCO_3 in patients with widened QRS between 100 and 160 msec is based on the combination of QRS duration and clinical manifestations such as hypotension, potential degeneration to ventricular tachycardia or ventricular fibrillation, acidemia, or seizures (LoE III).

The use of NaHCO_3 may also be reasonably considered if progressive QRS widening >100 – 140 msec is evident (LoE III).

Selective serotonin reuptake inhibitors (SSRIs) are generally much less cardiotoxic in overdose than TCAs. However, citalopram and its S-enantiomer, escitalopram, have been associated with reports of delayed onset seizures and cardiac dysrhythmias [31–34]. Case reports demonstrate adult and pediatric patients presenting with prolonged QRS intervals following citalopram or escitalopram overdose which were responsive to NaHCO_3 boluses [31–34]. Although QT_c prolongation with a normal QRS interval is the more commonly reported ECG abnormality associated with citalopram or escitalopram overdose, the use of NaHCO_3 should be considered for patients presenting with a widened QRS or ventricular dysrhythmias. Overdose of venlafaxine, a serotonin and norepinephrine reuptake inhibitor, may also result in sodium channel blockade with reported response to treatment with NaHCO_3 [35, 36].

Bupropion, an aminoketone antidepressant, has been associated with QRS prolongation and ventricular dysrhythmias in overdose [37–39]. Case reports describe both success and failure of NaHCO_3 for the treatment of QRS widening and dysrhythmias [38, 40]. One case describes failure of response to the NaHCO_3 while the other reports initial response and placement on a continuous infusion with later decompensation, highlighting the potential need for the higher doses of NaHCO_3 achieved with bolus administration compared to a continuous infusion [37, 39]. Animal data suggest bupropion toxicity may involve a mechanism other than sodium channel blockade, possibly also explaining the apparent lack of response to NaHCO_3 [40]. However, given bupropion's similar presentation to classic sodium channel antagonist toxicity, and the relatively low risk associated with sodium bicarbonate therapy, NaHCO_3 is considered an appropriate initial treatment for bupropion-induced cardiotoxicity (LoE III).

Neuroleptics

Thioridazine and its metabolite, mesoridazine, are phenothiazine neuroleptic agents. The

predominant therapeutic activity of thioridazine is due to dopamine inhibition, but sodium channel-related cardiotoxicity may occur during therapy or following overdose [41, 42]. In a prospective, observational study conducted between January 1987 and January 1994, cardiotoxicity from thioridazine was more commonly observed than with any other neuroleptic agent in use during the study period and was often delayed [41]. Given the similarity to other QRS prolonging agents, treatment with NaHCO_3 boluses is appropriate for thioridazine- and mesoridazine-induced cardiotoxicity (LoE III).

Antiepileptics

Lamotrigine is an antiepileptic medication that inhibits propagation of seizure activity from epileptic foci. In overdose, QRS prolongation leading to dysrhythmias and heart block suggestive of myocardial sodium channel antagonism have been reported [43–46]. Success and failure of NaHCO_3 therapy for lamotrigine-induced cardiotoxicity have both been reported [42–45]. However, it is noteworthy that the amount of NaHCO_3 administered is unclear and under-treatment may have contributed to reported failure [43]. Therefore, treatment with NaHCO_3 may be attempted for lamotrigine-related cardiotoxicity, but adjunct measures may be required in a severely poisoned, unstable patients or those unresponsive to ample (2–3 mEq/kg) bolus doses of NaHCO_3 (LoE III).

Antihistamines

Overdose with first-generation antihistamines such as diphenhydramine, doxylamine, and chlorpheniramine may result in myocardial sodium channel toxicity [47–52]. Diphenhydramine cardiotoxicity has been reported to respond to varying doses of NaHCO_3 from 44 to 200 mEq (4.3 mEq/kg) [47, 50]. Given the ECG findings and reported response, NaHCO_3 is recommended in patients exhibiting cardiotoxicity from first-generation antihistamines (LoE III).

Propoxyphene

Propoxyphene is a μ -opioid receptor agonist paired with other analgesics (e.g., acetaminophen)

for management of acute pain. Treatment of propoxyphene-induced QRS prolongation with NaHCO_3 has been reported [53]. Due to its toxicity and lack of robust analgesic data, the US Food and Drug Administration (FDA) recommended voluntary withdrawal of propoxyphene from the US market in 2010 [54]. Analogous agencies in several other countries have taken similar actions. In 2013 and 2014, 28 and 19 cases of exposure to propoxyphene were reported to US poison centers, respectively, demonstrating continued persistence of this drug even without continued prescribing in the US [55, 56]. Propoxyphene may still be available in some countries.

Anti-infectives and Rheumatologic Agents

Cardiotoxicity from the antimalarial and anti-inflammatory drugs, chloroquine and hydroxychloroquine, includes QRS prolongation and ventricular dysrhythmias. The use of NaHCO_3 has been effective in decreasing QRS duration and may be used in conjunction with electrolyte replacement, epinephrine, and high-dose diazepam [57–61]. These agents have also been associated with significant hypokalemia. Serum potassium concentrations must be monitored closely during alkalinization treatment as the intracellular shift of potassium from the alkalinization may compound the hypokalemia from the ingestion.

Quinine has several medical and nonmedical uses, including an antimalarial agent, abortifacient, treatment of leg cramps, and recreational drug adulterant. Quinine is a quinidine stereoisomer and quinine-induced QRS prolongation predictably responds to NaHCO_3 boluses [62]. These agents are discussed in greater detail in ► Chap. 64, “Chloroquine and Quinine.”

Cocaine

Cocaine is a stimulant derived from coca leaves and acts by increasing the concentration of norepinephrine, epinephrine, and dopamine in the synaptic cleft. Additionally, cocaine acts as a local anesthetic and has sodium channel antagonist properties. Cardiotoxicity from cocaine may include tachycardia or bradycardia, chest pain,

palpitations, QRS prolongation, and ventricular tachycardia as well as signs of vasospasm. Reversal of QRS prolongation and resolution of dysrhythmias has been reported in humans and animals [63–71]. NaHCO_3 is recommended in the treatment of cocaine-related cardiotoxicity (LoE III). One case in a series describing patients presenting with cocaine intoxication was treated with NaHCO_3 with resulting improvement in the QRS duration and right-axis deviation in aVR [64]. The responsiveness of cocaine-associated QRS widening to NaHCO_3 administration has been further supported through case reports and animal studies and it is considered first-line treatment (LoE III) [64–70]. Other therapies for cocaine toxicity are discussed in greater detail in ► Chap. 75, “Cocaine.”

Antidysrhythmics

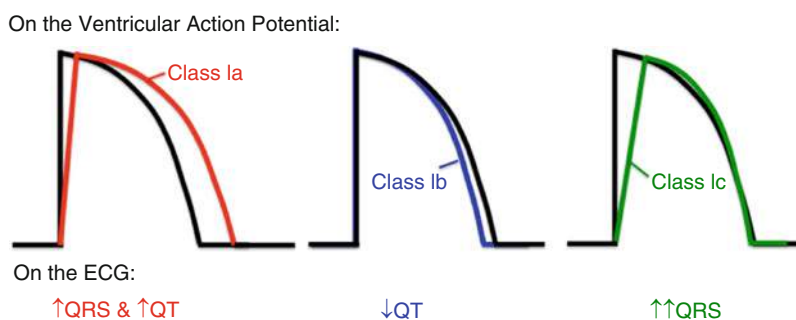
Vaughan Williams Class I antidysrhythmic agents are classified based on their antagonist effect and duration of activity at the cardiac sodium channels. These agents also have varied effects on the potassium rectifier channels. Excess effect predictably causes classic sodium channel antagonist cardiotoxicity. That being said, the three subclasses of Vaughan Williams Class I antidysrhythmics vary in their effect on sodium channel, especially the duration of channel blockade, as demonstrated in Fig. 2.

Class Ia agents include disopyramide, procainamide, and quinidine. Much of the current understanding of sodium channel toxicity and bicarbonate therapy is derived from experience with quinidine and procainamide. These agents block both sodium channels and potassium rectifier channels resulting in prolonged QRS and QT_c

intervals. Class Ia agents have a varying effect on cardiac sodium channels with time to recovery of 9, 18, and 3 seconds (s) for disopyramide, procainamide, and quinidine, respectively [72]. The majority of published human and animal experience in treating quinidine and procainamide cardiotoxicity is with sodium lactate [4–8]. However, due to lack of easily accessible sodium lactate and apparent similar effect, NaHCO_3 is considered the agent of choice in the treatment of QRS prolongation and dysrhythmias from these agents (LoE III).

Class Ib agents have the least impact on the upstroke velocity of the Class I agents and generally have very little, if any, effect on potassium rectifier channels. As such, these agents exert the greatest effect on conduction, and not repolarization, of the heart. Of the antidysrhythmic agents affecting sodium channels, lidocaine has the shortest blockade at 0.1 s [72]. With this “fast on, fast off” property, lidocaine has been employed in the treatment of sodium channel blockade refractory to NaHCO_3 and other treatments due to its ability to competitively inhibit the receptor while allowing for a rapid return of the receptor to its natural state. Other class Ib agents include mexiletine, phenytoin, and tocainide. These agents are also associated with rapid sodium channel recovery of 0.3, 0.2, and 0.4 s for mexiletine, phenytoin, and tocainide, respectively [72]. Cardiovascular collapse associated with intravenous phenytoin administration is proposed to be due to the propylene glycol diluent and is presumed unrelated to phenytoin itself. Outside of lidocaine, Class Ib agents have not been effectively employed in the treatment of patients with cardiac sodium channel blockade.

Fig. 2 Class I antiarrhythmic drug effects (Reprinted with permission from: <http://tmedweb.tulane.edu/pharmwiki/lib/exe/fetch.php/classI.png>)



Vaughan Williams Class Ic agents have the greatest impact on the upstroke velocity and are often difficult to treat in overdose. Reported recovery times for blocked sodium channels are 11, 10, and 1 s for flecainide, moricizine, and propafenone, respectively [72]. Cardiac effects in toxicity include bradycardia, tachycardia, QRS prolongation, and ventricular tachycardia with arrest [73]. Given their influence on several cardiac receptors (which may include influences on intracellular calcium), duration of action at the receptor, and varying pharmacokinetic profiles, toxicity from these agents can be difficult to treat [18, 73–76]. The ability of NaHCO_3 to reverse cardiotoxicity from flecainide, encainide, and propafenone has been demonstrated in neonates, pediatrics, adults, and in animal models. NaHCO_3 is recommended for all patients with QRS prolongation or dysrhythmias from Class Ic drugs (LoE III) [73, 77–88].

For patients with toxicity from Class I antidysrhythmic agents that present with a prolonged QRS, sodium channel antagonism is likely. If the patient is experiencing a significantly prolonged QRS interval, administration of IV bolus NaHCO_3 with a repeat ECG and repeated dosing when necessary is appropriate (LoE III). As these intoxications can be difficult to treat, additional therapies may be required.

Beta Adrenergic Receptor Antagonists

In a prospective, poison center-based study, ECGs in patients with reported overdoses including beta antagonists were collected and evaluated. In the 17 patients with ECG changes, acebutolol, labetalol, and propranolol appeared to have the greatest effect on QRS duration, suggesting cardiac sodium channel blockade occurred [89]. Prolongation of the QRS interval has been observed in a case of propranolol overdose [90]. Animal studies of propranolol toxicity using isolated heart preparations suggest that increased sodium may increase contractility and augment other therapies [91]. In patients with QRS prolongation after ingestion of beta-antagonists, including NaHCO_3 with other treatment modalities discussed in the beta-antagonist chapter is appropriate (LoE III).

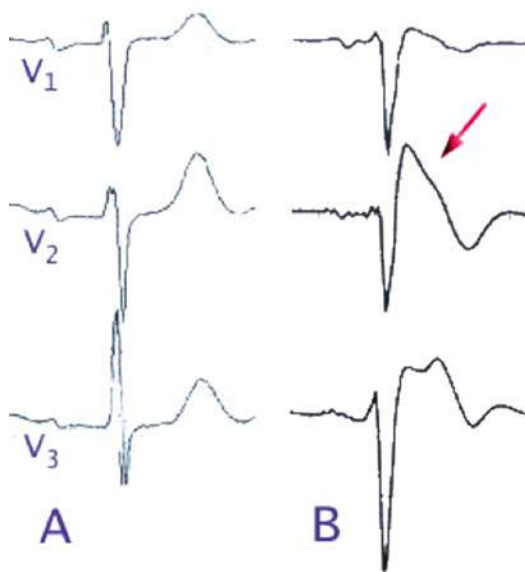


Fig. 3 Figure A is from a normal patient and Figure B is from a patient with Brugada syndrome (Figure courtesy of Dr. J Heuser under a Creative Commons license)

Brugada syndrome is described as a triad of clinical and ECG findings characterized by Martini and Brugada in the 1980s and 1990s [92, 93]. These characteristics include (Fig. 3):

1. ST-segment elevation (permanent or transient) in V_1 – V_3
2. Presence of a right bundle branch block (RBBB) in the precordial leads (may be absent in 1/3 of patients)
3. Sudden cardiac death

These patients often have no signs or symptoms of cardiac disease [93, 94]. Brugada syndrome may be related to mutations in the cardiac sodium channel and is treated with the implantation of a cardioverter-defibrillator. Electrocardiograph changes including permanent or transient ST-segment elevation in V_1 – V_3 (with or without RBBB in the precordial leads (“Brugada sign”)) have also been associated with right ventricular pathology, electrolyte abnormalities, and exposure to xenobiotics. Sodium channel antagonists have also been reported to uncover latent Brugada

syndrome, leading to reports of a drug-induced Brugada sign [94, 101]. Brugada sign has been reported in multiple sodium channel blocking agents including TCAs, cocaine, Class Ia and Ic antidysrhythmic agents, propranolol, venlafaxine, and propoxyphene [25–28, 67, 92–101]. NaHCO_3 has occasionally been successful in reversing drug-induced Brugada sign [25–29, 31–39, 67]. Due to the occasionally evolving or transient nature of the syndrome, determining the role of the agent in causing versus unmasking Brugada sign is difficult. ECG findings due to genetic sodium channel defects and drug-induced sodium channel blockade are indistinguishable. Therefore, in the face of potential drug toxicity, patients with Brugada sign ECGs are candidates for NaHCO_3 bolus therapy (LoE III).

This topic is discussed in greater detail in ► Chap. 39, “Sodium Channel-Blocking Antidysrhythmics.”

Based on the above, the author recommends the following in patients with a known or suspected toxicity from a sodium channel antagonist:

1. Patients with a new QRS duration ≥ 100 msec, a terminal R-wave in aVR ≥ 3 mm, or an R/S ratio in aVR ≥ 0.7 be closely monitored for progression of clinical effects (LoE III).
2. Sodium bicarbonate bolus beginning at 2–3 mEq/kg is the first-line treatment for a wide-complex dysrhythmia (e.g., ventricular tachycardia) with repeat dosing as needed (LoE III).
3. Patients with a QRS ≥ 160 msec represent the highest risk of developing ventricular dysrhythmias and NaHCO_3 administration (2–3 mEq/kg) is appropriate (LoE III).
4. Sodium bicarbonate administration in patients with a QRS ≥ 100 msec when other major manifestations consistent with sodium channel toxicity are present is reasonable (LoE III).
5. Endpoint of NaHCO_3 therapy is the cessation of ventricular dysrhythmia, significant narrowing of the QRS duration, serum pH > 7.5 , or sodium > 155 mEq/L. Except in cases of significant alkalemia or hypernatremia, sodium bicarbonate boluses can be repeated (LoE III).

Sodium Bicarbonate to Enhance Urinary Elimination of Xenobiotics

In addition to treating xenobiotic-related sodium channel antagonism, sodium bicarbonate is also employed therapeutically to enhance urinary elimination of acidic compounds. Xenobiotics exist in the human body in a balance of ionized and nonionized forms. The acid dissociation constant (pKa) is defined as the environmental pH at which the compound will exist in a 50% ionized state. Since pKa is a logarithmic function, a small change in blood pH can lead to substantial changes in the ionized fraction of a compound. For a weak acid such as salicylic acid, as serum pH decreases, the fraction of nonionized drug, which readily crosses membranes, increases. As a result, penetration into the central nervous system (CNS) increases. In contrast, increasing the pH causes the ionization equilibrium to shift in favor of the ionized fraction of acidic xenobiotics. When ionized (i.e., charged), less of the compound is able to freely cross membranes, including in the blood–brain barrier and renal cells. When the urine is alkaline, the higher pH causes the ionized xenobiotic to become “trapped” in the urine and subsequently leads to a reduction in reabsorption and greater excretion, and greater excretion. Although urine pH and “ion trapping” of xenobiotics in the urine are the focus of this discussion, the rise of the serum pH and prevention of penetration into other compartments (e.g., the CNS) follow a similar principle.

Historically, urinary alkalization for enhanced elimination was coupled with forced diuresis. However, forced diuresis does not generally result in enhanced xenobiotic elimination and is no longer recommended [102]. For toxins responsive to therapeutic urinary alkalization, increased excretion is achieved without the requirement of specialized equipment or invasive measures and may be used independent of hemodialysis in patients with adequate renal function. Alkaline therapy can also serve as a bridge when hemodialysis is not emergently available. To be effective, adequate renal perfusion and kidney function are imperative. In addition to the renal function and pKa of the toxin, effective treatment

with urinary alkalization is also dependent on the extent of urinary excretion of the active compound and the urine pH. For example, if 5% of the dose is excreted in its unchanged form, doubling and even tripling that rate will not appreciably change overall elimination rate to a clinically meaningful degree. Urinary alkalization as a treatment modality has been proposed in salicylate, barbiturate, methotrexate, chlorophenoxy herbicide, fluoride, and chlorpropamide toxicity [102]. Fluoride and chlorpropamide will not be discussed, as this intervention is not likely appropriate for toxicity caused by these agents. Patients should be evaluated for appropriateness of alkalization therapy based on serum drug concentration (e.g., plasma salicylate) when available and clinical manifestations of toxicity. Underlying disease states that may limit tolerability of large fluid load or impaired excretion of the drug (e.g., the presence of cerebral or pulmonary edema or liver, heart, or renal failure) must be considered.

No fully evidence-based protocol for achieving urine alkalization with NaHCO_3 is available. However, the components of urine alkalization include initial bolus administration of NaHCO_3 followed by continuous infusion, monitoring for target urine pH, maintenance of adequate potassium, and monitoring for adverse effects. One expert consensus position paper recommends a NaHCO_3 dose over the first hour of treatment in adults of 225 mmol (mEq) and 25–50 mmol (mEq) for children to promote adequate urinary alkalization [102]. Delivery of the proper dose for an adult can be accomplished through administration of a bolus with 150–200 mEq of 8.4% NaHCO_3 followed by a continuous infusion (LoE III). The infusion is prepared by the addition of 150 mEq of NaHCO_3 (150 mL of 8.4% NaHCO_3 to 850 mL of 5% dextrose in water (D5W), with 20–40 mEq potassium chloride or acetate. The recommended infusion rate is 200–250 mL/h (i.e., double the typical maintenance fluid rate of 100–125 mL/h) (LoE III). D5W is the preferred base solution to limit risk of hypertonic fluid administration and potential hypernatremia (0.9% sodium chloride (NaCl), i.e., “normal saline”, contains 154 mEq/L of sodium). No controlled studies have addressed

the effect of a bolus on achieving goal urine pH; however, in patients receiving only the infusion achievement of goal pH may be prolonged. The NaHCO_3 infusion is then used to maintain a urine pH of 7.5–8. Urine pH should ideally be checked every 15–30 minutes (but no longer than every 60 minutes) until the target pH is achieved and hourly, thereafter. This necessitates foley catheter placement to aid in frequent urine testing. Other laboratory parameters requiring close observation during alkalization therapy include acid–base status (arterial pH <7.50), serum potassium (>4.0 mEq/L), and plasma xenobiotic concentrations, when clinically feasible (LoE III). Once alkalization therapy is initiated, the serum pH must be monitored for development of excessive alkalemia (pH >7.5) that might interfere with oxygen delivery. With this shift, oxygen less readily dissociates from hemoglobin. As such, the serum pH must be evaluated prior to initiating alkalization therapy and monitored closely throughout.

The addition of 40 mEq of potassium to the infusion is recommended (LoE III). Close observation of serum potassium concentration is essential as administration of NaHCO_3 causes potassium to shift from the extracellular to the intracellular space. Additionally, hypokalemia causes the kidneys to retain potassium and excrete a proton (H^+), subsequently preventing effective urine alkalization. Serum potassium concentrations can be expected to fall once adequate NaHCO_3 treatment is initiated. Patients may require significant potassium replacement to maintain the goal serum potassium >4.0 mEq/L and achieving any degree of urinary alkalization is unlikely unless there is concomitant potassium replenishment.

Serum calcium must also be monitored as symptomatic hypocalcemia has also been described in patients receiving NaHCO_3 infusions (LoE III) [102, 103]. Therapeutic alkalization requires significant bedside attention to ensure laboratory assessments are performed and appropriate adjustments are made. Not all patients will clinically require a critical care setting; however, placement on a hospital unit with a lower nurse-to-patient ratio may be necessary to optimize patient care.

Salicylates

In the early twentieth century, patients were observed to tolerate higher salicylate doses without symptoms of toxicity when receiving concurrent alkalinization [103]. In the 1940s, this observation prompted attempts at therapeutic alkalinization for the management of salicylate toxicity and the clinical utility of urinary alkalinization was pursued [104, 105]. A urine pH above 7 was shown to decrease salicylate elimination half-life, increase clearance, and increase the excretion of the parent compound, with variable effects on metabolites in adults and children (LoE III); this has also been reproduced in animal models [105–110]. This increased elimination rate has been reported as much as threefold in one report and was reported to increase from 5.2 to 7.1 mg/kg/h in children [106, 108]. The rate of excretion is affected by three factors: plasma salicylate concentration, rate of urine flow, and pH (specifically, alkalinity) of the urine [107]. Salicylate protein binding is saturable with >95% binding at serum salicylate concentrations up to 20 mg/dL, versus 30–40% total binding with levels greater than 70 mg/dL [107]. This increase in unbound drug allows for greater urinary excretion of the parent compound. With therapeutic alkalinization, patients can manifest a degree of alkalemia (pH > 7.45), though typically with an unappreciable increase in plasma sodium concentration, and a slight decrease in plasma potassium concentration, averaging 1.1 mEq/L [107]. A rat model of salicylate toxicity also demonstrated the addition of NaHCO₃ to correlate with a decrease in salicylate concentrations in muscle, brain, and liver tissue [110].

The pKa of salicylic acid is 3.3. Alterations in the acid–base balance can significantly alter salicylate tissue penetration with an increase in CNS penetration associated with worsening acidemia [110]. Therapeutic alkalinization can serve as a temporizing measure in severe salicylism during preparation or transfer of the patient for emergent hemodialysis. Additionally, therapeutic alkalinization may serve as the primary mode of enhanced elimination in patients with significant, but not immediately life-threatening, salicylate toxicity in whom hemodialysis may not be indicated.

In addition to acid–base status and serum potassium, hydration status impacts alkalinization. Dehydration and subsequent decreased glomerular flow limits the effectiveness of alkaline therapy. Vomiting, diaphoresis, hyperpnea, and tachypnea associated with salicylate toxicity may create significant insensible fluid loss. Therefore, to enhance therapeutic alkalinization, salicylate poisoned patients frequently need fluid resuscitation. Fluid bolus of at least 20–40 mL/kg of 0.9% NaCl for adults with normal renal and cardiac function (20 mL/kg for pediatric patients) is recommended (LoE III). The ideal serum salicylate concentrations to initiate or discontinue therapeutic alkalinization remain unknown. However, given changes in unbound drug and propensity to cause significant symptoms, serum salicylate concentrations greater than 40 mg/dL is a reasonable threshold (LoE III). Therapy may also be initiated in severely symptomatic patients with lower salicylate concentrations but may be less effective as a smaller fraction of free drug is present and the risk may outweigh the potential benefit. Discontinuation of alkalinization therapy should be considered when symptoms resolve and serum salicylate concentrations fall below 30–35 mg/dL in adults or 25 mg/dL in pediatric patients [102]. Salicylate toxicity and its treatment are discussed in greater detail in ► Chap. 63, “Salicylates.”

Phenobarbital

Phenobarbital, a barbiturate sedative-hypnotic GABA_A receptor agonist, has been used for treatment of status epilepticus and alcohol withdrawal in the hospital and seizure prophylaxis in the community. Phenobarbital is also a commonly used veterinary antiepileptic. The half-life of this drug can be extraordinarily long (1.5–4.9 days with therapeutic use) and, with large doses, phenobarbital can exhibit zero-order (saturable) kinetics. Evidence supporting therapeutic alkalinization in the setting of phenobarbital toxicity is mixed. Alkalinization of the urine decreased the half-life of phenobarbital but multidose activated charcoal (MDAC) was superior [102, 111–113]. A recent systematic review concluded that urinary alkalinization was not an effective mode of enhanced elimination of phenobarbital but supports use of MDAC

and hemodialysis or hemofusion [112]. However, the studies comparing MDAC with therapeutic alkalization had several limitations including a lack of urine pH reporting making it unclear if adequate pH was achieved. Given the relatively high pKa of phenobarbital (~7.4), urine pH likely requires a significant increase to clinically change elimination half-life and a lack of alkaline pH may have contributed to the varied results. Given the potential to decrease half-life and little risk of harm, therapeutic alkalization can be employed as an adjunct therapy in phenobarbital toxicity with careful evaluation for goal urine pH (>7.5) (LoE III). All therapies are discussed in greater detail in ► Chap. 46, “Barbiturates.”

Methotrexate

Methotrexate is a folate reductase inhibitor used in the treatment of certain cancers, extrauterine pregnancies, and rheumatologic or other autoimmune disorders such as rheumatoid arthritis and psoriasis. Treatment modalities for toxicity include hydration, folinic acid (leucovorin), and glucarpidase. Dosing recommendations for methotrexate are highly variable ranging from a high-dose administered intravenously over 4 h followed by “leucovorin rescue” to a once weekly oral dose, depending on indication and therapeutic goal. High doses of methotrexate can approach the solubility limit of the drug in the kidneys leading to crystalluria with renal impairment or damage. A NaHCO_3 infusion has been used along with intravenous hydration for renal protection from methotrexate [102, 114–117]. By raising urine pH, the solubility of methotrexate is increased and the fluid assists in dilution. Urinary alkalization can also increase methotrexate excretion rate and decrease elimination half-life [114, 115]. Administration of NaHCO_3 in pediatric patients receiving high-dose methotrexate for acute lymphocytic leukemia was found to be associated with lower 21- and 44-h blood methotrexate concentrations, as well as fewer reports of methotrexate toxicity [116]. Though likely not as effective as hemodialysis, therapeutic alkalization can be considered in patients at risk for methotrexate toxicity (LoE III) [102]. Given potential effects of methotrexate on the kidneys, therapeutic alkalization should be

employed early with close monitoring of urine output. This topic is discussed in greater detail in ► Chap. 60, “Methotrexate.”

Chlorophenoxy Herbicides

Chlorophenoxy compounds, such as 2,4-dichlorophenoxyacetic acid (2,4-D), are widely used herbicides. Though effects from occupational dermal exposure are often limited to local skin irritation, ingestion can lead to significant local and systemic toxicity. In conjunction with volume loading, urinary alkalization has been proposed to increase excretion of chlorophenoxy compounds. Therapeutic benefit is likely due to a combination of alkalization and fluid loading, as the greatest benefit was observed when urine output exceeded 600 mL/h [117]. In the event of ingestion of the chlorophenoxy herbicides, therapeutic alkalization may be considered (LoE III). However, focus should remain on maintaining high urine output (>600 mL/h) (LoE III) [102]. Due to the inability to retrieve levels, discontinuation of therapy should be considered with symptom improvement (LoE III).

Sodium Bicarbonate for the Treatment of Chlorine Gas Inhalation

At room temperature, chlorine exists as a dense, yellow-green gas. Chlorine gas is classified as a pulmonary irritant and exhibits intermediate water solubility. Water solubility is a significant determinant for the time-course between exposure to irritant gases and development of symptoms.

Though once employed as an agent of chemical warfare, present-day chlorine gas exposures are generally from more routine nonwarfare practices such as mixing cleaning chemicals, working with swimming pool chemicals, and in various industrial settings. While most reported cases involve individuals, accidental mass exposure to chlorine has also been reported [118–129]. Adding an acid to sodium hypochlorite (bleach) causes chlorine gas to be released and when ammonia is combined with bleach, chloramine is produced. This circumstance is the cause of many residential chlorine exposures [129]. Swimming pools are chlorinated

for the purpose of disinfection and pH is adjusted using different chlorine-containing products.

Though exposure to pulmonary irritants like chlorine gas is the most common source of toxic inhalants. Specific recommendations for medical management of symptomatic patients has not been well-defined remaining symptomatic and supportive measures (e.g., bronchodilators, humidified oxygen, steroids, and antibiotics when clinically indicated) [125]. The recommendation for use of nebulized, inhaled sodium bicarbonate solutions reportedly originated with Done in a 1976 review of chlorine gas exposure [127, 128]. The postulated benefit of inhaled NaHCO_3 solutions is due to its buffering capacity of the hydrochloric acid (HCl) created by chlorine gas contact with moist mucous membranes [127]. Although chemically this approach is reasonable, most of the HCl has already been neutralized by the membranes when a patient arrives for medical care. If NaHCO_3 aids through buffering the environment, then the benefit to its use should be greatest near the time of exposure. Published cases report symptom improvement following NaHCO_3 even when given several hours after chlorine exposure [119, 123–128].

The available literature on this topic includes one study, retrospective reviews, and case reports [119, 123–128]. In the prospective, double-blind, placebo-controlled study, patients presenting with reactive airways dysfunction syndrome (RADS) following chlorine exposure from April 2004 to April 2005 were included for treatment with intravenous prednisolone (1 mg/kg/day) and salbutamol inhaler (5 mg), plus either nebulized placebo (undefined) or nebulized NaHCO_3 (4 cm³ of 4.20% NaHCO_3 solution). Pulmonary function tests showed an increase in FEV₁ at 120 and 240 min following treatment in the NaHCO_3 group versus placebo. Quality of life scores showed improvement from baseline in both groups with no difference between the treatment groups [124]. In a retrospective poison center review, one patient reportedly experienced immediate relief of symptoms following administration of nebulized NaHCO_3 . However, temporal response was not reported in other patients, and this study did not include control patients

[124]. Another retrospective review described soldiers exposed to chlorine gas in their barracks following improper mixing of cleaning agents. Those patients not responding to initial treatment of bronchodilators and humidified oxygen received NaHCO_3 and an inhaled corticosteroid. In patients presenting with cough and dyspnea, those receiving additional treatment ($n = 15$) did not differ in discharge rate (67% discharged and 33% admitted in both groups) from those receiving no additional treatment ($n = 3$) [118]. Patients with a sore throat and chest pain were included in the review. Two pediatric case reports and one adult case series report rapid improvement in symptoms following the administration of nebulized NaHCO_3 [126–128].

Risk and prognostic indicators for patients for developing delayed pulmonary edema following chlorine gas exposure are not fully defined. As such, it is unclear what, if any, treatment may aid in prevention of this condition. Also, patients with significant chlorine gas exposure may develop chronic pulmonary pathology and the effectiveness of initial treatment strategies at prevention of chronic sequelae is unknown.

In patients with symptomatic upper and lower airway symptoms following chlorine gas exposure, nebulized NaHCO_3 solutions may be considered in addition to other symptomatic treatment measures (LoE I). The solution can be created with the mixture of 3 mL NaHCO_3 with 2 mL of 0.9% NaCl. Other suggested concentrations include: 2 mL 8.4% NaHCO_3 with 2 mL 0.9% NaCl for 4.2% total concentration or 2 mL 7.5% NaHCO_3 with 2 mL 0.9% NaCl.

The treatment of chlorine gas inhalation is discussed in greater detail in ► Chap. 100, “Irritant and Toxic Pulmonary Injuries.”

Sodium Bicarbonate in the Treatment of Methanol Toxicity

Methanol is a toxic alcohol often used in automotive and camping equipment. The parent compound, methanol, may cause mild inebriation but is not associated with significant systemic toxicity. In humans, methanol is metabolized first by

alcohol dehydrogenase (ADH) to formaldehyde which is in turn converted by aldehyde dehydrogenase (ALDH) to formic acid, the entity presumed to be primarily responsible for the toxic effects of methanol exposure. Formic acid accumulates and causes significant anion gap metabolic acidosis. Additionally, formic acid may increase lactate production through inhibition of the mitochondrial cytochrome c oxidase activity. The resulting lactate accumulation may further contribute to the acidosis and acidemia, but formate remains the primary driver of acid–base disturbance and formation of the anion gap [130–132]. Formic acid has a pKa of 3.7 and, at physiologic pH, exists primarily in the de-protonated anionic form known as formate. However, using the Henderson-Hasselbach equation, with a decrease in blood pH of only 0.3, the predicted concentration of uncharged formic acid doubles [131]. This unionized molecule can readily penetrate tissues and more readily partition into the CNS [133, 134]. Also, with worsening acidosis, further inhibition of cellular respiration, increasing hypoxia and lactic acid production will also worsen acidosis and again favor increased formic acid concentrations in a cycle termed “*circulus hypoxicus*” [130]. NaHCO_3 may be beneficial adjunct therapy for methanol poisoning due to its ability to affect formate ionization equilibrium and increase urine elimination [132]. Although the use of sodium bicarbonate as a sole treatment is insufficient to manage methanol intoxication, administration may be considered as an adjunct or temporizing measure in patients with metabolic acidosis following methanol ingestion or dermal exposure [130]. Large doses of sodium bicarbonate (e.g., 400–600 mmol (mEq) in the first few hours) may be necessary to significantly impact the metabolic acidosis [130]. Although the blockade of methanol metabolism through competitive inhibition of ADH and hemodialysis remain the mainstay of treatment, administration of NaHCO_3 in patients with serum pH <7.3 may be considered to attempt to correct the acidosis (LoE III) [135]. Administration of NaHCO_3 in patients with methanol toxicity will not prevent end organ damage and likely will

be insufficient to fully correct the metabolic acidosis. This topic is discussed in greater detail in ► Chap. 88, “Methanol and Formaldehyde.”

Sodium Bicarbonate for the Treatment of Uranium Nephrotoxicity

Uranium is an element commonly used as a fuel in nuclear power plants. With accidental or intentional exposure to uranium, nephrotoxicity and deposition into the long bones can be seen. Uranium rapidly reaches the systemic circulation and the majority is renally eliminated with subsequent accumulation in the renal proximal tubules. Tubular damage and necrosis can be seen in significant exposures due to the uranyl ion form. Urine alkalization favors binding of the uranyl ion to bicarbonate thereby decreasing the release of the toxic ion in the proximal tubule. The US National Council on Radiation Protection and Measurements recommends early decontamination strategies for persons exposed to uranium, including the administration of sodium bicarbonate either intravascularly or orally with a target urine pH of 8–9 [136]. One recent animal study evaluated the impact of one-time administration of oral NaHCO_3 on renal pH, excretion and deposition of uranium in renal tissues, renal function markers, and renal histopathology [136]. In the highest-dose treatment group (1 g/kg) the following effects were observed (versus placebo): (1) an increase in urine pH occurred at 2 h and was maintained for 9 h; (2) uranium excretion was significantly higher in the first 5 h following exposure but continued for 24 h; (3) the blood urea nitrogen and serum creatinine levels were significantly lower on days 3 and 7; (4) renal histopathology demonstrated no change on day 1, mild degeneration and necrosis on day 3, and mild and focally regenerated tubules on day 7 [136]. The role for NaHCO_3 administration for chronic exposure (e.g., uranium-laden well water) is unclear. In the event of an acute exposure to uranium, NaHCO_3 administration is recommended as soon as possible by oral or intravenous routes (or both) (LoE III).

Special Populations

Pregnant Patients

No specific trials have been conducted to evaluate the use of NaHCO_3 for the treatment of toxicity during pregnancy. Certain xenobiotics have demonstrated penetration of the placenta and subsequent toxicity in the fetus (i.e., salicylate and methanol) [137–139]. Toxic effects in the fetus may vary depending on gestational age and specific properties of the xenobiotic including molecular weight, lipophilicity, polarity, and protein binding (see specific xenobiotic for in-depth discussion). In general, stabilization of maternal hemodynamic and acid–base status will decrease the risk of spontaneous abortion or severe fetal compromise.

In a review conducted in the Toxicology Investigator's Consortium[®] (Toxic[®]) registry over a 3-year period, 103 (0.6%) of patients evaluated at the bedside by a toxicologist were pregnant. NaHCO_3 was used in 9 patients (13.2% of pregnant patients that received specific treatments). The indications for treatment with NaHCO_3 included TCA and salicylate toxicity. No specific maternal or fetal effects were reported; however, patients were not followed up to or beyond delivery [140]. In a recent review of the use of antidotes in pregnancy, NaHCO_3 was not included [141].

Treatment with NaHCO_3 is appropriate in pregnant patients experiencing toxicity from a xenobiotic with demonstrated resolution from this therapy (LoE III).

Pediatric Patients

Pediatric patients are at risk for accidental or intentional overdose from variable concentrations of high-risk medications, improper remixing of suspensions between doses, improper measuring tools (i.e., the use of a kitchen teaspoon), metabolic and physiologic differences, and exploratory ingestions to name a few. No trials have been conducted to evaluate the use of sodium bicarbonate in neonatal or pediatric patients. However, successful use of

NaHCO_3 in this population has been reported. The use of 4.2% NaHCO_3 (vs. 8.4%) in pediatric patients has been suggested given its lower osmolality but there is no evidence of superiority. Careful attention should be given toward ensuring the use of 2–3 mEq/kg of NaHCO_3 despite a change in concentration. Given the potential benefit and relatively low risk NaHCO_3 use is acceptable in pediatric patients demonstrating toxicity from the aforementioned xenobiotics (LoE III).

Administration Summary

Treatment with NaHCO_3 can include intravenous, inhalation, or, in rare select circumstances (e.g., uranium exposure), oral administration. The specific toxicity and treatment goal should be considered when choosing the optimum method of NaHCO_3 administration. When administering as an intravenous bolus, 2–3 mEq/kg is considered the starting dose, though higher starting doses and additional boluses may be necessary. In adult patients, the dose is rounded up to the nearest ampule (50 mEq) size; however, pediatric patients are dosed within the 2–3 mEq/kg range with repeated doses in all patients as necessary. In all patients requiring intravenous bolus dosing of NaHCO_3 , the drug is given IV push over 1–5 minutes.

When used as a continuous infusion, 150 mEq (3 ampules of 8.4% solution) is added to 850 mL of D5W with 20–40 mEq of potassium for a total quantity of 1000 mL. Adjustment of the total fluid volume in the bag to allow for the added 150 mL of volume from the NaHCO_3 solution is necessary to limit excessive free water. Additionally, the total concentration of NaHCO_3 in the solution will change from 150 to 130 mEq/L. D5W is the preferred base solution in order to avoid the hypertonicity associated with the addition of 150 mEq to the 154 mEq of sodium already present in 0.9% sodium chloride solution. In general, potassium should be administered along with bicarbonate to combat NaHCO_3 -induced hypokalemia due to a flux of potassium to the intracellular

compartment. Nebulized sodium bicarbonate can be prepared using mixture of 3 mL NaHCO_3 with 2 mL of 0.9% NaCl and administered using a standard nebulizer. Other concentrations have also been used, though no consensus exists on preferred concentration. Anecdotally, a more concentrated solution can precipitate in the nebulizer and patients report a foul salty taste.

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Succimer is the generic name for meso-2,3-dimercaptosuccinic acid (DMSA).

History

In 1954, Froitzheim and Olligs [1] described the utility of the dimercaprol analogue DMSA in the chelation treatment of experimental mercuric chloride poisoning in mice. In 1957, Liang and associates [2] reported experimental evidence of the antidotal effects of the sodium salt of DMSA (sodium dimercaptosuccinate) against the toxicity of antimony-containing antiparasitic drugs, and in 1958, these Chinese investigators began the first clinical trials in humans [3]. Additional investigations showed the value of sodium dimercaptosuccinate in the treatment of other metal poisonings. In 1965, Wang and colleagues [4] reported its clinical use as an intravenous therapy for occupational lead and mercury intoxication. Okonishnikova [5] reported the utility of DMSA in experimental arsenic poisoning in the Soviet literature. A stable formulation of DMSA for the oral chelation of heavy metal poisoning was introduced in China in 1977 [6]. The clinical use of oral DMSA for lead poisoning was the subject of a report in the Western literature in 1978 [7]. Phase I clinical trials of DMSA were begun in the United States in 1980, and Graziano and coworkers [8] reported a dose-ranging study of DMSA in occupational plumbism in 1985. Phase II trials were conducted in lead-poisoned children [9].

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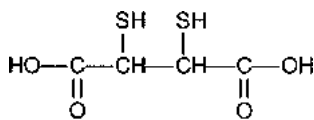


Fig. 1 Chemical structure of succimer (*meso*-2,3-dimercaptosuccinic acid)

The generic name of DMSA is *succimer*. It has been approved for use in many countries. Under the trade name Chemet, oral DMSA was approved by the US Food and Drug Administration in 1991 as an orphan drug for the treatment of childhood lead poisoning.

Chemical Properties

Succimer ($C_4H_6O_4S_2$; molecular weight 182.2 g/mol) (Fig. 1) is a white crystalline powder that is soluble in aqueous alkaline solutions, such as 5% sodium bicarbonate. The vicinal thiol groups of the crystalline solid are relatively stable at room temperature. The drug has a mercaptan-like odor. Although succimer forms stable complexes with several metals in vitro, it may be several disulfide biotransformation products that are responsible for metal complexing action in vivo. A preformed complex of 1.2 mg of succimer and ^{99m}Tc has been licensed in the United States as a diagnostic agent for scintigraphic imaging of the renal parenchyma. The form of succimer marketed as a chelating agent (US brand name Chemet) is supplied as capsules containing 100 mg of succimer adsorbed onto inactive beads.

Pharmacodynamics

In addition to increasing excretion of toxic metals, such as lead, mercury, and arsenic, in human and animal studies, succimer has been associated with increases in the urinary excretion of zinc and copper in human trials [10–12]. Pharmacodynamic effects on cardiovascular, hepatic, or renal function have not been noted after oral administration.

Pharmacokinetics

Approximately 20% of orally administered succimer is recovered in the urine as the parent compound or metabolites in human studies [10, 13]. Although not definitive, the data on urine and fecal recovery are consistent with an oral bioavailability of approximately 20%. After absorption, greater than 90% of succimer in the blood is found in the plasma fraction, where it is highly bound (92%–95%) to plasma proteins (mainly albumin) by disulfide linkages [14]. Peak blood concentrations are reached in approximately 3 h. Most succimer seems to be distributed extracellularly. Minor amounts may penetrate erythrocytes [15], and some succimer transformation products are excreted in the bile and undergo enterohepatic circulation [13]. Succimer is excreted predominantly in the urine, where 80%–90% appears as mixed disulfides [10, 16]. In humans, approximately 70% of the mixed disulfide occurs as a 2:1 cysteine-DMSA adduct, 20% occurs as a 1:1 cysteine-DMSA adduct, and 10% occurs as cyclic disulfides of DMSA [16]. The increased urinary excretion of metals such as lead that follows administration of succimer parallels the urinary excretion of the mixed disulfides [10, 13]. The collective data suggest that it is a biotransformation product (or products) of succimer, and not the unaltered parent drug, that is responsible for its metal-mobilizing activity. The elimination half-life of transformed succimer is approximately 2–4 h. Some evidence suggests that renal clearance of the drug and its metabolites may be diminished in lead intoxication [12, 15] and that the higher the pre-chelation blood lead concentration, the smaller the percent decline in blood lead associated with a course of succimer treatment [17].

Contraindications and Precautions

Because succimer and its metabolites are excreted predominantly in the urine, the safety and utility of the drug in patients with severe renal insufficiency are uncertain. The intrarenal metabolism of succimer to the mixed disulfides that appear responsible for formation of metal chelates (see

above) may possibly be reduced in patients with renal insufficiency. It would be prudent to individually evaluate the utility of succimer in any patient with renal insufficiency by early and prompt laboratory assessment of metal mobilization. Limited experience yields no evidence that succimer can increase the hemodialysis clearance of toxic metals in anuric patients.

Succimer should not be administered to patients with a history of allergy to the drug. One case report [18] linked succimer with hemolysis in an adult with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In an open-label clinical trial [19], five children with glucose-6-phosphate dehydrogenase deficiency tolerated succimer without incident. Therefore, if needed it is reasonable to administer succimer to G6PD-deficient patients as long as they are closely monitored for hemolysis (Grade III recommendation).

Succimer has fetotoxic effects when administered to pregnant rats at oral doses of 100 mg/kg/day [20] and teratogenic effects in pregnant mice at oral doses of 400 mg/kg/day [21]. However, chelation with succimer also has mitigated the adverse reproductive effects of several heavy metals in animal models [22, 23]. A report [24] described succimer chelation in a pregnant woman with a blood lead concentration of 44 µg/dL (2.1 µmol/L) at 29 weeks' gestation and subsequent succimer chelation of the neonate. The child exhibited no evidence of teratogenicity or overt drug toxicity. While it is reasonable to presume that use of succimer to treat overt or incipient metal-induced maternal toxicity may also benefit the fetus, potential benefit to the fetus in the absence of maternal toxicity is unclear. Oral chelation with succimer was used successfully to lower blood lead concentration in an asymptomatic 6-month-old infant with a blood lead concentration of 84 µg/dL (4.1 µmol/L) [25].

Adverse Effects

Succimer chelation generally is well tolerated. Patients should be advised that the drug may impart a mercaptan-like odor to the urine. During clinical trials, gastrointestinal symptoms (e.g.,

nausea, vomiting, or diarrhea) or mild, reversible serum transaminase elevation was observed in approximately 10% of patients. There were isolated reports of mild-to-moderate neutropenia. These adverse effects were not associated with succimer, however, in an open-label trial of 59 children [19] or a randomized, placebo-controlled, double-blind clinical trial of 780 children [26]. In a report of 3,180 courses of succimer chelation in 1,156 children treated for epidemic lead intoxication, no serious adverse effects attributed to the drug were observed [27]. A moderate increase in serum alanine aminotransferase that did not require discontinuation of therapy occurred in less than 1.5% of the children [27]. The manufacturer recommends monitoring serum transaminases at the inception of therapy and at weekly intervals. The drug should be stopped if there is an increase in ALT or AST ≥ 10 times above the upper limit of the reference range [28]. Rashes, some necessitating discontinuation of therapy, have been observed in approximately 4% of patients. Rare instances of drug-related mucocutaneous vesicular rash have been reported [17, 29]. A 3-year-old child tolerated a succimer overdose of 185 mg/kg without adverse effects [30]. During clinical testing in adults, succimer doses of 80 mg/kg were associated with an occasional report of mild-to-moderate drowsiness and mild abdominal disturbance [31]. An adult experienced no significant adverse effects after an intentional succimer overdose of 43–87 mg/kg [32].

Juvenile rats treated with a single 3-week course of oral succimer alone in the absence of prior or concurrent lead exposure demonstrated persistent deficits in learning, attention, and arousal that were similar in magnitude to those produced by high lead exposure [33]. In a different rat model, in utero exposure to succimer alone was associated with alterations in immune function in juvenile offspring [23]. The mechanism responsible for these persistent effects of early life exposure to succimer is uncertain but may involve detrimental succimer-induced changes in zinc and/or copper status. These observations reinforce the importance of considering potential risks and benefits before instituting treatment with succimer and other chelators [34].

Administration

In accordance with the Food and Drug Administration – approved regimen for lead poisoning – succimer has most often been administered at an oral dose of 10 mg/kg (pediatric dose, 350 mg/m³) every 8 h for 5 days, decreasing to 10 mg/kg (pediatric dose, 350 mg/m³) every 12 h for another 14 days. Repeat courses and extended dosing have been performed in some cases, depending on the patient's clinical status. Although sodium dimercaptosuccinate is not available in parenteral form elsewhere, in China, it has been administered intravenously (10% solution in normal saline) at daily adult doses of 1–2 g [4].

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Thiamine (vitamin B1, thiamine, aneurin) (Fig. 1) is a water-soluble vitamin essential for the generation and utilization of cellular energy. Therapeutically, thiamine supplementation is used primarily for treatment of those who are thiamine deficient or at risk of deficiency. Thiamine is neither generated nor stored in large quantities; whole body stores in well-nourished individuals range from 30 to 50 mg, with hepatic stores of 2–4 mg [1]. Thiamine is found in leafy green vegetables, eggs, grain, and meats. Inadequate dietary intake is the most common cause of thiamine deficiency. The adult dietary requirement is 1–1.5 mg/day, and the thiamine content of many foods may be diminished by processing or heating [2]. Measures to avoid thiamine deficiency in the general population include enrichment of flour, cereals, and infant formulas [1–3].

Besides malnutrition, thiamine deficiency may result from malabsorption syndromes (including bariatric surgery), eating disorders, HIV/AIDS, chronic liver disease, folate deficiency, renal dialysis, and parenteral nutrition [4–11]. In developed countries, the most common reason for thiamine deficiency is poor oral intake and diminished thiamine absorption associated with chronic alcohol abuse [12]. Ethanol may decrease thiamine absorption by as much as 50% [1]. Thiamine deficiency may progress to the often missed or misdiagnosed syndrome of Wernicke's encephalopathy (WE).

The diagnosis of WE is clinical. Postmortem examination reveals a prevalence of WE (Fig. 2)

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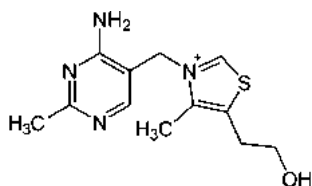


Fig. 1 Chemical structure of thiamine chloride



Fig. 2 Pathologic sample from a patient with Wernicke's encephalopathy showing necrosis of mammillary bodies (Courtesy of Pathology Learning Centre, Department of Pathology, University of Cape Town (www.digitalpathology.uct.za), with permission)

in up to 12.5% in chronic alcoholics, though as few as 20% of cases were diagnosed prior to death [13, 14]. Although earlier studies showed MR imaging to have a low sensitivity in detecting WE, later studies determined that FLAIR sequences or diffusion-weighted imaging may be helpful, especially in those patients with atypical presentation [15–17] (Fig. 3). The clinical syndrome of WE, first described in 1881, presents with the triad of mental confusion, ataxia, and ophthalmoplegia. The encephalopathic presentation of WE may range from apathy to profound confusion, which may be difficult to discern in patients suffering from ethanol withdrawal. The permanent neurologic manifestation of amnesia and confabulation was first described by Korsakoff in patients initially presenting with symptoms consistent with WE. The combination of these disorders is called Wernicke–Korsakoff syndrome

(WKS) in recognition of the fact that they are manifestations of the same disease. The ataxic component of WE may range from mild gait instability to a complete inability to stand [20]. Ophthalmologic manifestations reflect cranial nerve involvement; complete ophthalmoplegia is rare. Ocular abnormalities may include dysconjugate gaze and sixth nerve palsies, papilledema, and ptosis, though the most common presentation is nystagmus [9, 18, 19].

Thiamine deficiency, historically termed “beriberi,” has several different presentations. The neurological manifestations of WKS are often referred to as “dry” beriberi. “Wet” beriberi presents as cardiovascular disease, typically with high-output cardiac failure, predominantly right sided, although variations may occur, such as low output or biventricular [12]. A thiamine-deficient gastrointestinal syndrome of vomiting, abdominal pain, and lactic acidosis has been termed “gastrointestinal beriberi,” and peripheral neuropathy affecting lower extremity sensorimotor nerves more than upper, often painful, has been termed “neuropathic” beriberi [18–20]. Combinations of these various clinical syndromes may be present; whether they are distinct entities of thiamine deficiency or are simply part of the clinical continuum of the disease is unclear [19].

Thiamine is also used as an adjunct antidote in ethylene glycol poisoning. It serves as a cofactor in the conversion of glyoxylic acid (an ethylene glycol metabolite), by α -ketoglutarate glyoxylate carboligase to the nontoxic α -hydroxy- β -keto adipate. This is a minor pathway of glyoxylic acid metabolism, and, while shunting metabolism toward α -hydroxy- β -keto adipate is of theoretical benefit, there is no direct evidence that thiamine administration enhances glyoxylic acid metabolism or decreases ethylene glycol toxicity [21].

History

The relationship between beriberi and a nutritional deficiency was first described in 1885 though the syndrome of a deficiency causing paralysis of the hands and feet was described as

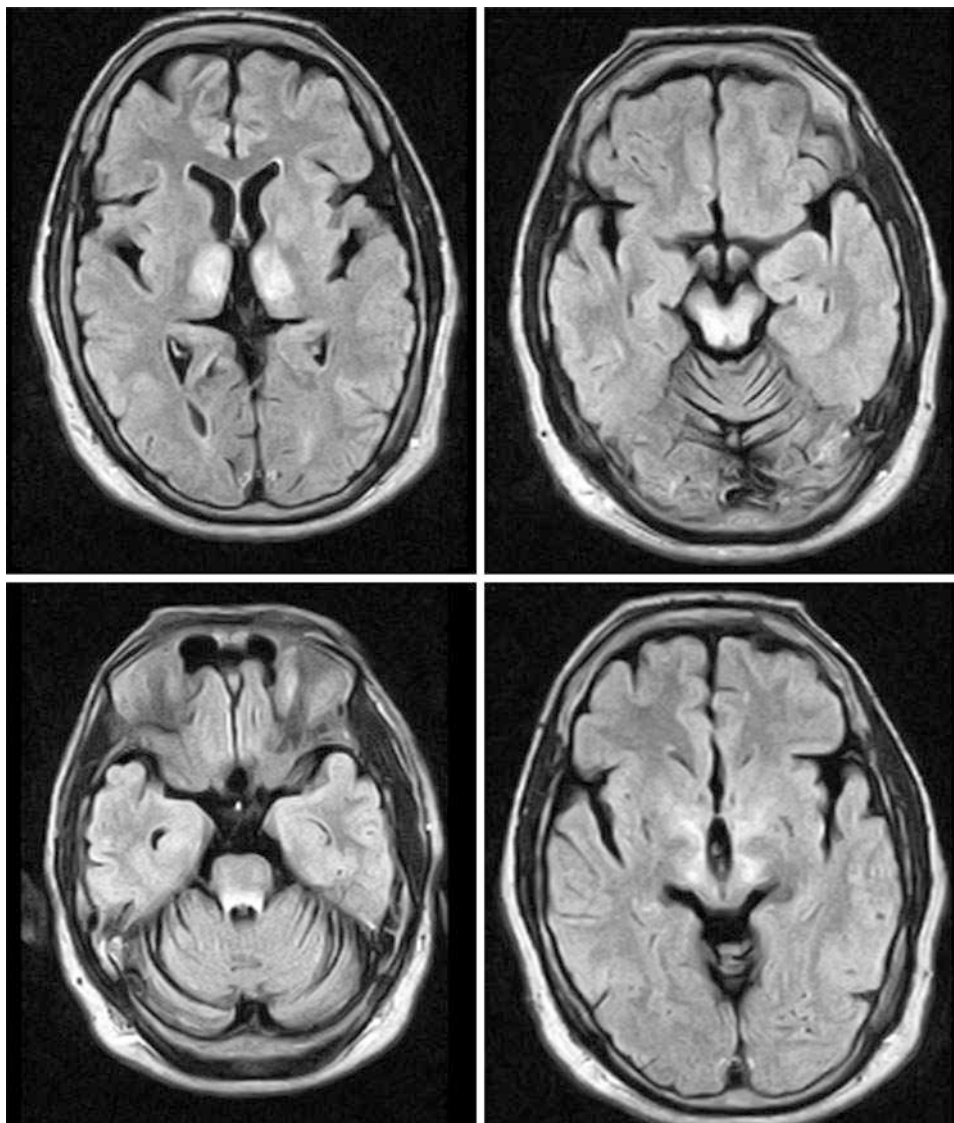


Fig. 3 This is neglected, alcoholic with complaints of ataxia with MRI features consistent with Wernicke's and cerebellar atrophy. Wernicke's encephalopathy is characterized by a quite distinct pattern of MR alterations, which include symmetrical alterations in the thalami, mammillary bodies, tectal plate, and periaqueductal area. In WE, the

blood–brain barrier is defective in the periventricular regions, in which there is a high rate of thiamine-related glucose and oxidative metabolism (MRI contributed by Dr Swati Shah and Dr Sumer Sethi, from Sumer's Radiology Blog (<http://sumerdoc.blogspot.com/2012/06/wernickes-encephalopathy-mri.html>) with permission)

early as 1611 in writings by Pieter Both, then Governor of the Dutch East Indies [2]. It was not until 1926 that the specific vitamin involved was isolated from rice polishings. The structure of thiamine was then elucidated in 1931, with the synthesis of thiamine being described in 1936, which enabled large-scale production [2].

Pharmacodynamics

Thiamine is an important cofactor in a number of metabolic processes. Conversion of thiamine to thiamine diphosphate and thiamine triphosphate occurs in the liver. Thiamine diphosphate, the active form of thiamine, is necessary for the

conversion of pyruvate to acetyl coenzyme A (ACoA) in the pyruvate dehydrogenase complex. This is the link between anaerobic glycolysis and the Krebs cycle. During glycolysis, two moles of pyruvate and two moles of adenosine triphosphate (ATP) are generated from every mole of glucose. Pyruvate and coenzyme A, with the cofactor thiamine diphosphate, form ACoA, which then enters the Krebs cycle, generating another 36 mol of ATP. In thiamine-deficient states, the accumulated pyruvate is converted to lactate, resulting in lactic acidosis [11, 12, 19]. Within the Krebs cycle, thiamine is also a necessary cofactor for the catalysis of α -ketoglutarate to succinyl coenzyme A. The lack of adequate thiamine stores causes a buildup of α -ketoglutarate, shunting conversion to favor formation of glutamic acid. The increased concentration of glutamate also contributes to the primary metabolic acidosis seen in thiamine-deficient states [12, 19].

In the pentose phosphate pathway, thiamine diphosphate is a cofactor for the enzyme transketolase, generating reduced nicotinamide adenine dinucleotide phosphate for further reductive biosynthesis, including formation of fatty acids [11].

Pharmacokinetics

Thiamine is readily absorbed in the proximal small intestine. Initially it was believed this active transport system was saturable and limited oral dosing. However, subsequent study demonstrated absorption also occurs via a passive process enabling large oral doses to be utilized [23]. In a study comparing equal oral and intravenous doses of thiamine, a multi-compartment model for absorption and distribution was demonstrated [24]. This conclusion was reached in measuring blood, plasma, and tissue concentrations of thiamine, thiamine monophosphate, thiamine diphosphate, and thiamine triphosphate. After IV administration, thiamine reached a peak plasma concentration in 2 min, with peak concentrations of thiamine diphosphate (the most active form) in 2–6 h; high

levels were maintained for up to 12 h. Following oral thiamine administration, almost complete absorption was seen in 40 min, with peak thiamine levels being achieved between 20 and 120 min and a return to baseline within 12 h. Thiamine half-life in plasma was determined to be 96 min or less [24, 25]. A study comparing equal oral and intramuscular thiamine doses concluded that oral dosing could produce almost equivalent concentrations as parenteral administration [26].

A more recent randomized, double-blinded, crossover study demonstrated that the thiamine passive absorption process is not saturable in oral doses up to 1,500 mg. Further, blood thiamine concentrations approaching those seen with IV administration were achieved within 1 week of initiating oral thiamine supplementation, despite the oral bioavailability of 3.7–5.3% reported in earlier studies [23, 27].

Adverse Effects

The overall safety profile of oral and intravenous thiamine is very good. One retrospective survey of 300,000 patient administrations identified no serious adverse reactions [28]. While rare, anaphylactic reactions to thiamine do occur [28–30], one study of 989 patients estimated the incidence of serious reactions to be only about 0.1% [31]. Thiamine is routinely given intravenously to patients believed to be predisposed to WE as a delay in administration may be life-threatening. With the low relative incidence of adverse reactions, it is considered good practice to administer thiamine without delay [32].

Special Populations

Pregnancy and Lactation

The US National Academy of Sciences recommended dietary allowances (RDAs) of thiamine during pregnancy and lactation are 1.4 and 1.5 mg, respectively [34]. Thiamine is classified by the US Food and Drug Administration as

pregnancy category A (safe) with dosing at RDA and category C (evidence of teratogenicity in animals but not in humans) if doses exceed the RDA. It is considered safe for use while breastfeeding [33].

Pediatric Patients

Recommended dietary allowance for birth to 5 years of age is 0.2–0.5 mg. Since there is no acute toxicity with larger doses, 1 mg doses may be used. Since thiamine deficiency has been seen in infant fed formula, caregivers should confirm that it is present in the formulation being used [10]. Thiamine deficiency may occur with malabsorption syndromes and food allergies and in breast-fed infants of a thiamine-deficient mother.

Geriatric Patients

This population may be at particular risk for thiamine deficiency. Poor intake and absorption, hepatic insufficiency, and ethanol abuse may all contribute to diminished thiamine stores. In noncritically ill thiamine-deficient geriatric patients, the recommended dose is 5–30 mg daily, in single or divided doses [34].

Dosing and Administration

The RDA in adults is estimated to be 1–1.2 mg, based on caloric intake [1, 34]. In a study evaluating dosing at nine large academic hospitals, the average daily dose was 100 mg, and the population most at risk for WE were most likely to receive oral dosing [35]. The following guidelines are based on the limited information available, the relative safety of large doses, and the adverse consequences of inadequate treatment; there are no good randomized clinical trials to guide clinicians on dose, frequency, or duration of therapy [36]. Those patients with low suspicion or for prophylaxis should receive a minimum of 100 mg, preferably intravenously (level III recommendation). Those who show any symptoms consistent with WE should receive doses of

>500 mg per day [19] (level III recommendation). Consensus guidelines recommend the administration of high (200–500 mg three times daily) oral or parenteral doses of thiamine for the treatment of WE, with a preference for parenteral dosing [3, 32, 37] (level III recommendation). Patients at risk for thiamine deficiency (malabsorption syndromes, dialysis patients, poor nutritional status, etc.) should receive 100 mg of parenteral thiamine in the ED, whether admitted or not, and continue with oral supplementation at the same dose when discharged [19] (level III recommendation).

The historical practice of thiamine administration prior to a carbohydrate load makes little pharmacologic sense. Thiamine uptake and enzyme system activation are much slower than glucose uptake. The negative impact of misdiagnosing a thiamine-deficient individual makes this practice worth continuing; thiamine administration at the recommend dose prior to a carbohydrate load should continue [38].

There is little evidence supporting thiamine administration in ethylene glycol poisoning [21]. There are animal models showing an increase in oxalate excretion in thiamine-deficient states in conditions of primary oxaluria which suggests that the minor pathway mentioned previously may be affected [3]. Thiamine's low adverse-effect profile with the potential of some benefits makes administration at standard doses worthwhile.

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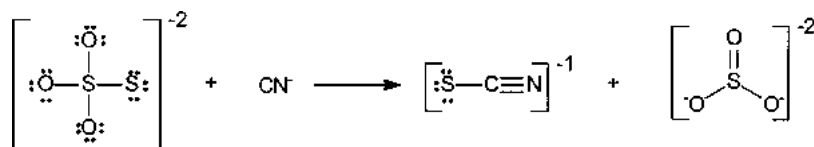
Thiosulfate is an inorganic compound used for a variety of medical and nonmedical applications. The antidotal use of thiosulfate stems largely from its powerful reducing capabilities, along with its ability to enhance endogenous enzymatic activity. Thiosulfate also exists naturally in humans, but at much lower concentrations than those found when used therapeutically. When used medicinally, it is virtually always in the form of its sodium salt.

History

Thiosulfate has a long history of use in industrial and medical settings. In industry, thiosulfate is used as an inorganic reducing agent for the production of finished materials [1]. Medical treatments using thiosulfate are quite diverse. Best known for the enhancement of rhodanese enzymatic activity in the mitigation of cyanide toxicity, thiosulfate has also been used in attempts at the treatment of toxic effects stemming from a variety of chemicals, including acrylonitrile, bromate, cisplatin, hypochlorous acid, paraquat, and platinum [2–9]. It is used topically in the treatment of selenium dioxide burns and is used as a treatment for cytotoxic drug extravasation involving cisplatin [10, 11]. A small amount of animal evidence supports the use of thiosulfate in hydrogen sulfide toxicity, although the exact mechanism is not clear [12]. Finally, thiosulfate has been studied and used in the treatment of several medical disorders, including tumor calcifications,

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Fig. 1 Reaction of thiosulfate in the detoxification of cyanide



thromboangiitis, calcium nephrolithiasis, calciphylaxis, and tinea versicolor [7, 13–16].

that is joined to one or more sulfur atoms to enhance the activity of rhodanese) (Fig. 1) [21].

Properties

Sodium thiosulfate is a white, transparent crystal or powder. In nature it can occur in the anhydrous form, but it is found most often in the pentahydrate form and is unstable as a powder unless maintained under dry conditions [17]. When solubilized as a 1.5% or 9.76% solution, sodium thiosulfate is stable in normal saline, dextrose 5% water, and dextrose 5%/0.45% sodium chloride for at least 24 h.

Biochemically, this naturally occurring sulfur compound is strongly nucleophilic and also has appreciable redox activity. In humans, it is produced as a systemic metabolic intermediate derived from the amino acid cysteine, where it serves to protect against the depletion of reduced glutathione [18, 19].

Pharmacodynamics

Exogenous administration of thiosulfate results in a rapid elevation in its serum concentrations. The pharmacologic activity of sodium thiosulfate is hypothesized to develop more slowly, however, and to last far longer than the biologic half-life of the parent compound ($t_{1/2} \sim 20$ min). The increased duration of effect was demonstrated in a canine model in which a single dose of thiosulfate resulted in at least 1–2 h of protection from nitroprusside-induced cyanide poisoning [20]. The extended duration in pharmacologic effect is thought to be due to the occurrence of thiosulfate activity in the mitochondria and the slow intramitochondrial diffusion of $\text{S}_2\text{O}_3^{2-}$ ions. The mitochondria are the location of enzymatic rhodanese activity. Mitochondrial thiosulfate donates a sulfane sulfur (a divalent form of sulfur

Pharmacokinetics

Thiosulfate exists naturally in healthy humans at plasma concentrations of 1.1 ± 0.1 mg/dL. After exogenous intravenous administration of sodium thiosulfate to healthy humans, it has a calculated volume of distribution of 0.151 L/kg, with a clearance half-life of 0.25–3 h [22].

Sodium thiosulfate is metabolized partially in the liver to sulfate and also excreted partially unchanged by the kidneys [23]. The renal excretion data are contradictory. Some authors report that it is filtered solely through the glomerulus [24, 25]. Others report additional tubular secretion and reabsorption [26, 27].

Thiosulfate is reported to be eliminated using both a one-compartment and a two-compartment model [28, 29]. Its reported elimination half-life ranges from 16 to 182 min [28, 30]. Using a one-compartment model, $28.5\% \pm 9.4\%$ of the drug was recovered in the urine, with 95% recoverable in the urine within 4 h. The mean total body clearance was 190 ± 76 mL/min/ m^2 , and renal clearance was 50.4 ± 11 mL/min/ m^2 [29]. Using a two-compartment model, clearance was 1.39 mL/min, with urinary excretion of $42.6\% \pm 3.5\%$ of the dose at 180 min postdose and $47.4\% \pm 2.4\%$ at 18 h postdose [28]. The renal clearance of thiosulfate is sometimes used as a marker for inulin or glomerular filtration rate.

Special Populations

Pediatric Patients

Thiosulfate is used successfully to treat cyanide toxicity in newborns and children with sodium nitroprusside-associated cyanide toxicity

[31]. There is no reason that this population would respond differently than adults after administration of thiosulfate.

Pregnant Patients

The use of thiosulfate was studied in animal models in terms of thiosulfate's ability to cross the placenta and its ability to improve outcome clinically after poisoning. Although sodium thiosulfate did decrease toxicity from cyanide in the mother and fetus of gravid ewes, thiosulfate did not cross the placenta in this model [32, 33]. The implications of this finding are not clear, but may include the contribution of improvement of maternal outcome to the well-being of the fetus. Based on these data, thiosulfate should not be withheld on the basis of pregnancy.

Adverse Effects

Thiosulfate is generally well tolerated, even when administered to healthy patients in large doses. In dogs, hypotension is seen after overdoses of 500 mg/kg, but this has never been reported in humans [34]. Intravenous infusion of sodium thiosulfate can cause nausea, vomiting, localized burning, muscle cramping, and twitching at the injection site [35]. A single case of metabolic acidosis has been reported [36]. With certain analyzers, thiosulfate administration may falsely elevate plasma chloride concentrations potentially resulting in erroneous anion gap calculations [37].

Administration

There are no unusual contraindications or precautions when administering sodium thiosulfate. Thiosulfate must be administered intravenously because absorption from the gastrointestinal tract is poor. For cyanide toxicity in adults, the usual dose is 12.5 g administered intravenously over 10 min, repeated at half of the initial dose if required [38]. Although all current dosing information relies on bolus dosing, animal data suggest

that an infusion may be more effective [39]. While animal studies have suggested that there is no benefit in administering thiosulfate in addition to hydroxocobalamin for cyanide poisoning [40], there are reported human cases of both antidotes being administered concomitantly with favorable outcomes [41]. For protection of cisplatin nephrotoxicity, 12 g of thiosulfate is administered intravenously over 6 h, or 9 g/m² is administered as an intravenous bolus, followed by 1.2 g/m²/h intravenously for 6 h [42].

In children, the recommended dose for cyanide poisoning is 1 mL/kg of body weight using a 25% solution (250 mg/kg or approximately 30–40 mL/m² of BSA) not to exceed 50 mL (12.5 g) total dose [43].

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Unithiol and *DMPS* are the commonly used generic terms for the compound 2,3-dimercaptopropane-1-sulfonic acid, sodium salt monohydrate.

History

The synthesis and metal-binding properties of 2,3-dimercaptopropane-1-sulfonic acid were reported by Petrunkin [1] in Kiev in 1956. By 1958, the agent had become available in the former Soviet Union as a pharmaceutical known as *unithiol* for the treatment of poisoning by certain heavy metals, particularly arsenic and mercury, as well as for other medical applications. In 1976, Heyl (Berlin, Germany) began marketing oral capsules of unithiol under the trade name Dimaval. Heyl has produced DMPS as a solution for injection (DMPS-Heyl) since 1991. Although it has not been approved as a pharmaceutical by the US Food and Drug Administration, DMPS has been included on the Food and Drug Administration's "list of bulk drug substances that may be used in pharmacy compounding" [2]. It is legally available for medicinal purposes in the United States.

Chemical Properties

Unithiol ($C_3H_7NaO_3S_3$; molecular weight 210 g/mol) (Fig. 1) is a crystalline solid that is freely soluble in water. It normally crystallizes as

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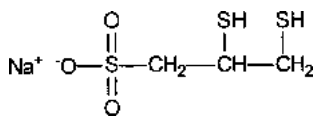


Fig. 1 Chemical structure of unithiol (DMPS; 2,3-dimercaptopropane-1-sulfonic acid, sodium salt)

a monohydrate. The thiol groups are relatively stable but become increasingly subject to oxidation under alkaline conditions ($\text{pH} > 7$). In addition to their role in the formation of complexes with numerous metals, the vicinal thiol groups contribute antioxidant activity under certain conditions. The polar sulfonate group is responsible for the agent's water solubility, in contrast to the low water solubility of 2,3-dimercaptopropanol (dimercaprol), which has a terminal hydroxyl group. Although unithiol forms stable binary complexes with many heavy metals *in vitro*, the precise structure of its complexes with metals *in vivo* is a topic of ongoing investigation. When DMPS is administered to humans with elevated exposure to inorganic arsenic, a complex of DMPS with monomethylarsonous acid but not with inorganic arsenic appears in the urine [3, 4]. *In vitro* analysis has suggested that the primary complex of DMPS with inorganic mercury would result in two molecules of DMPS binding one molecule of mercury: $\text{Hg}(\text{DMPS})_2$ [5].

Pharmacodynamics

Rapid intravenous injection may have a vasodilatory effect causing transient hypotension; for this reason, intravenous injections should be administered slowly over 15–20 min. A moderate diuretic effect has been observed in animal studies. Unithiol has not been shown otherwise to affect renal or hepatic function at therapeutic doses. Unithiol increases the urinary excretion of copper and zinc, as shown in several animal and human studies [6]. Prolonged high-dose administration to dogs (150 mg/kg/day for 6 months) decreased the copper content of many visceral organs and was associated with anemia, presumably as a consequence of the copper deficiency [7].

Pharmacokinetics

The oral bioavailability of DMPS is approximately 50 % [8]. Peak blood concentrations occur at approximately 3.7 h [9]. Almost all of absorbed unithiol undergoes transformation in the plasma, mostly to DMPS-albumin complexes and to a lesser extent nonprotein-associated DMPS disulfides [10]. A small amount of DMPS may enter erythrocytes. Greater than 80 % of an intravenous dose is excreted in the urine, with an elimination half-life of 20 h. The form recovered in the urine exists as 10 % unaltered DMPS and 90 % transformed products, the latter consisting mostly (97 %) of cyclic polymeric DMPS sulfides, with minor amounts (2.5 %) as a DMPS-cysteine (1:2) mixed disulfide and acyclic DMPS disulfides (0.5 %) [10]. Experimental animal studies suggest that renal elimination of DMPS may occur via tubular secretion and that metals such as mercury are extracted from the renal tubular epithelium during this process [11]. Oxidized or reduced DMPS in the blood enters proximal tubular cells via renal organic anion exchangers (OAT1/OAT3), binds with intracellular Hg^{2+} , and is secreted as DMPS-Hg complexes into the tubular lumen via the multidrug resistance-associated protein 2 and possibly another transporter [12]. In normal human volunteers treated with DMPS, urinary mercury excretion correlated well with urinary excretion of DMPS and its disulfide metabolites [8].

Contraindications and Precautions

Because DMPS and its metal complexes seem to be excreted predominantly via the kidney, caution should be exercised when administering unithiol to patients with severe renal insufficiency. This may include initiating treatment at low dose (i.e., 3 mg/kg every 4–6 h) and closely monitoring patients for adverse effects and evidence of metal excretion (Grade III evidence). Unithiol has been used as an adjunct to hemodialysis [13, 14] and continuous veno-venous hemodiafiltration (CVVHDF) [15] in patients with anuric renal failure from mercury salts.

Unithiol has not been associated with teratogenicity. In a murine model, doses of 300 mg/kg/day during gestational days 6–15 showed no evidence of developmental toxicity. Unithiol has averted or diminished adverse reproductive effects of certain toxic metals in experimental studies [16]. Clinical experience in the use of unithiol during human pregnancy is unavailable. While it is reasonable to presume that the use of unithiol to treat overt or incipient metal-induced maternal toxicity may also benefit the fetus, potential benefit to the fetus in the absence of maternal toxicity is unclear.

Adverse Effects

Unithiol is generally well tolerated, with a low incidence (<4 %) of adverse side effects [17]. The most common adverse effects are allergic cutaneous reactions, such as exanthems or urticaria, which have resolved on discontinuation of the drug or lowering of the dose. Isolated cases of major allergic reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported [18, 19].

Administration

Unithiol can be administered by oral, intramuscular, or intravenous routes. In general, the intravenous route is reserved for treatment of severe acute intoxications by heavy metals (e.g., arsenic, mercury, or lead) in which compromised cardiovascular or gastrointestinal status may interfere with rapid or efficient absorption by the oral route. The daily intravenous dose for acute heavy metal poisoning is 20–30 mg/kg/day. One sixth of the daily dose should be administered every 4 h by slow intravenous infusion over 20 min. For oral chelation, a daily dose of 20 to 30 mg/kg/day can be administered in four divided doses (i.e., every 6 h). In some cases, protracted long-term treatment has been administered at a dose of 100 mg orally three times daily in adults or 50 mg orally three times daily in small children [17]. The pharmacokinetic and clinical database that forms the basis for various dosing regimens is

limited, and the foregoing dosages represent the author's recommendation based on the best available data (Grade III evidence).

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Appendix: Sympathomimetic Pressors

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Dopamine

Action and Structure

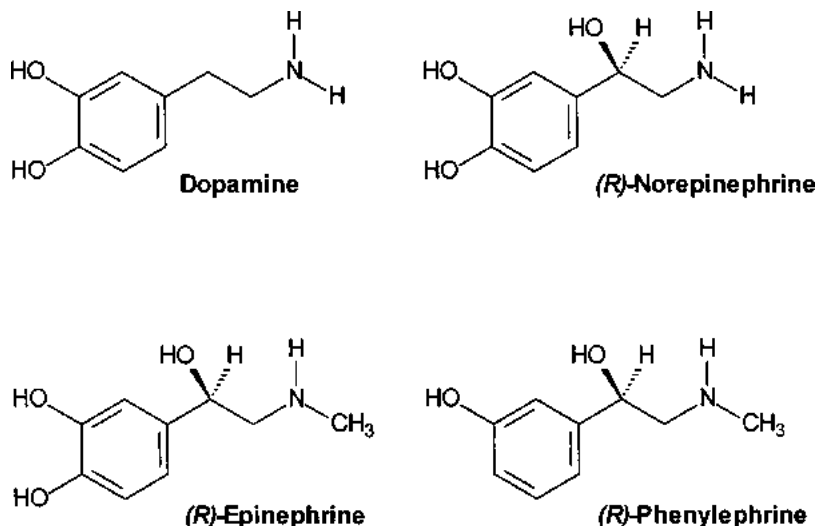
Dopamine (Fig. 1) exerts its action predominantly through the following three mechanisms:

1. *Dopamine receptor agonism*: Dopamine is an agonist for the dopamine receptor. Dopamine administration causes dopamine₁ (D₁) receptor-mediated vasodilation.
2. *β1-receptor agonism*: At doses higher than those required for D₁ receptor agonism (see subsequently), dopamine may cause stimulation of β₁-receptors.
3. *Generation of norepinephrine*: As shown in Fig. 2, dopamine is a precursor in the biosynthetic pathway of epinephrine and norepinephrine. Approximately 75% of an administered dose of dopamine is inactivated by either monoamine oxidase (MAO) or catechol *O*-methyl transferase (COMT), and only about 25% is stoichiometrically converted to norepinephrine. Because of this, norepinephrine-mediated α-receptor agonism is seen only when high doses (see subsequently) of dopamine are administered.

Based on animal data, it seems that dopamine does not cross the placenta, and it does not cross the blood–brain barrier except in preterm infants. Its volume of distribution has been reported to

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Fig. 1 Chemical structures of dopamine, norepinephrine, epinephrine, and phenylephrine. Where indicated, the (*R*)-isomer, which possesses the most adrenergic activity, is shown



range from 1.81 to 2.45 L/kg, and dopamine's primary metabolite by MAO and COMT is homovanillic acid. Its half-life is approximately 2 min in adults, although it can be significantly longer in small children. Plasma dopamine concentrations are normally less than 100 pg/mL.

Dosage and Administration

Dopamine should be administered intravenously. Solutions may be prepared by mixing 200–800 mg of dopamine in 250–1000 mL of any standard intravenous solution.

Because of the various mechanisms by which dopamine acts, its effects depend on the dose administered. There are several possible ranges of doses, as follows:

1. *Low dose*: Doses ranging from 1 to 3 $\mu\text{g/kg/min}$ act primarily to dilate renal, intracerebral, mesenteric, and coronary vascular beds through activation of the D_1 receptor. At these doses, there tends to be little observed effect on most monitored hemodynamic parameters, although in some cases the vasodilation of these beds may cause a decrease in mean and diastolic blood pressure.
2. *Intermediate dose*: At doses ranging from 3 to 10 $\mu\text{g/kg/min}$, predominantly β_1 -receptor effects are seen. There is still an increase in D_1 -mediated blood flow in the above-described vascular territories and in the β_1 -receptor effects on the heart, resulting in an increase in heart rate, cardiac contractility, cardiac index, and conduction. At these doses, there may be modest increases in blood pressure but generally few effects on systemic vascular resistance (SVR), although small decreases in SVR, may be seen.
3. *High dose*: At doses greater than 10 $\mu\text{g/kg/min}$, the α -adrenergic effects from norepinephrine synthesis tend to predominate and may overwhelm the D_1 receptor-mediated vasodilation of the above-described vascular beds. Doses greater than 50 $\mu\text{g/kg/min}$ predictably cause severe vasoconstriction and generally should not be used.

Precautions and Contraindications

Because MAO is a major enzyme in the catabolism of dopamine, patients taking an inhibitor of this enzyme (see ► [Chap. 50, "Monoamine Oxidase Inhibitors"](#)) are expected to have a

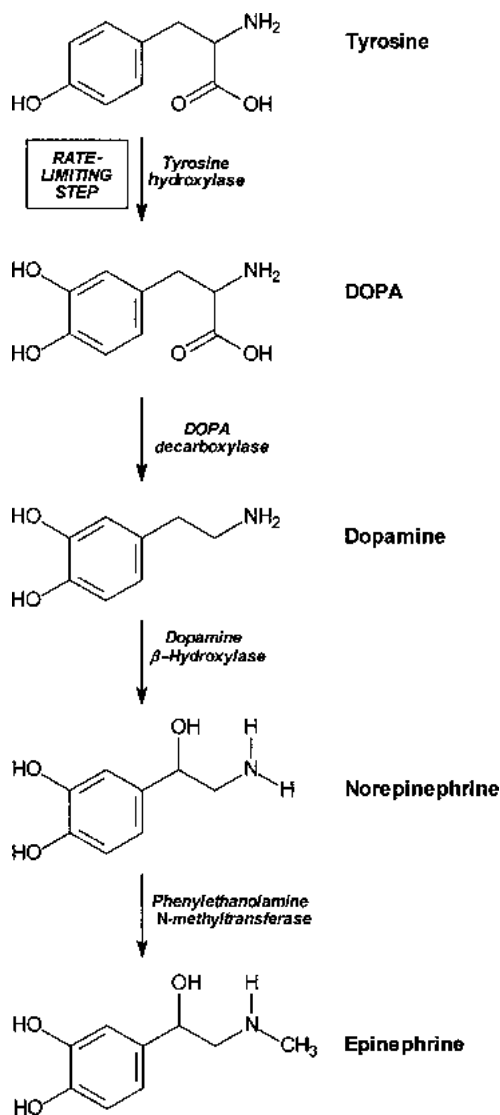


Fig. 2 Biosynthesis of catecholamines

substantially exaggerated effect. It is generally recommended that doses of dopamine approximating one tenth of standard doses be administered in patients taking these agents. If these doses are ineffective, the dose can be titrated to the desired clinical effect. Because many dopamine preparations contain sodium metabisulfite, patients with sulfite allergies may develop allergic reactions to dopamine administration.

Epinephrine

Action and Structure

Epinephrine (see Fig. 1), a term applicable only to the L-isomer of 1-(3,4-dihydroxy phenyl)-2-methylamino ethanol, exerts its action predominantly through the following two mechanisms:

1. *β-Receptor agonism*: Epinephrine is an agonist at β-receptors causing an increase in cardiac index, contractility, conduction, and heart rate. At low doses (see subsequently), the vasodilating effects of β-receptor agonism predominate, resulting in a decrease in SVR and widening of the pulse pressure. Epinephrine is not an ideal first-line vasopressor except in cases of anaphylactic shock.
2. *α-Receptor agonism*: At higher doses (see subsequently), epinephrine has significant α-receptor agonism resulting in an increase in SVR and mean arterial blood pressure. These effects may result in a reflex decrease in heart rate.

Plasma epinephrine concentrations normally are 15–55 pg/mL. It is metabolized by MAO and COMT (Fig. 3). Its half-life is 2–3 min.

Dosage and Administration

Epinephrine is compatible with most standard intravenous fluid solutions. Autooxidation may occur in bicarbonate-containing solutions, however. It is generally constituted as a 1:1000 (1 mg/mL) or 1:10,000 (100 µg/mL) solution; 10 mL of 1:100,000 is equivalent to 1 mg. When given as a constant infusion, typically 1–2 mg is diluted into 250 mL (i.e., 4–8 µg/mL) of 5% dextrose in water or normal saline.

Epinephrine is best administered intravenously. If access is not immediately available, other routes are possible. It can be given subcutaneously, typically as a 1:1000 solution, but the effects are delayed and variable, particularly because of the local vasoconstriction it causes.

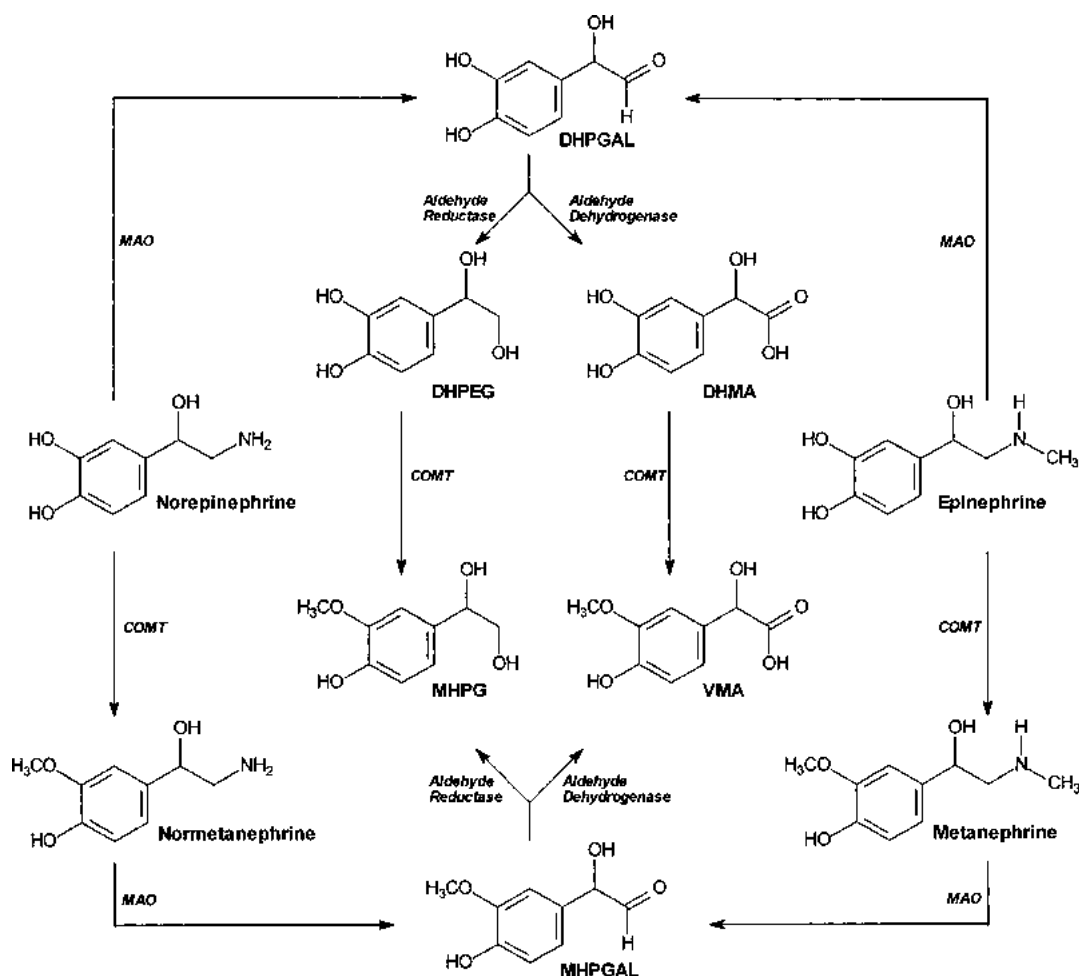


Fig. 3 Metabolism of norepinephrine and epinephrine by monoamine oxidase (MAO) and catechol *O*-methyltransferase (COMT). *DHPGAL* 3,4-dihydroxyphenylglycolaldehyde, *DHPEG* 3,4-dihydroxyphenyl ethylene

glycol, *DHMA* 3,4-dihydroxymandelic acid, *MHPG* 3-methoxy-4-hydroxyphenylethylene glycol, *VMA* 3-methoxy-4-hydroxymandelic acid, *MHPGAL* 3-methoxy-4-hydroxyphenylglycol aldehyde

Epinephrine also can be administered via an endotracheal tube in an emergent situation, whereby its pharmacologic effect is approximately half of that which would be achieved by intravenous administration.

In almost all circumstances in a critically ill patient, epinephrine should be infused intravenously, typically at doses ranging from 1 to 10 $\mu\text{g}/\text{min}$ (0.02–0.2 $\mu\text{g}/\text{kg}/\text{min}$) and subsequently titrated to the desired effect. At the lower end of this dose spectrum, β -adrenergic effects predominate. As the dose is increased,

α -adrenergic effects become evident and eventually predominate. The exact doses at which these effects occur in the individual patient are variable and should be determined based on the assessment of the clinical response.

Precautions and Contraindications

Patients on β -receptor antagonist therapy may have an exaggerated hypertensive effect after the administration of epinephrine due to unopposed

α -receptor agonism. In patients taking these agents, epinephrine should be used at the lowest possible doses, which can be titrated as necessary. This effect potentially is seen even with patients using β -receptor antagonist eye drops. Because patients taking tricyclic antidepressants or venlafaxine have reduced reuptake of sympathomimetic amines, their response to epinephrine may be exaggerated. Here too doses should start low and be titrated gradually to the desired clinical effect.

Because of a possible “catecholamine-sensitizing” effect of halogenated hydrocarbons on the heart, epinephrine and other β -receptor agonists should be used cautiously in patients poisoned by these agents. If it is necessary to use sympathomimetics such as epinephrine in these patients, therapy should be initiated at the lowest possible dose and titrated as necessary.

For patients with circulatory shock, the β_2 -adrenergically mediated decrease in SVR of epinephrine may be detrimental. Agents with predominantly α -adrenergic activity and few β_2 -adrenergic effects, such as norepinephrine or phenylephrine, are preferable.

Norepinephrine

Action and Structure

Norepinephrine (levarterenol) (see Fig. 1), a term applicable only to the L-isomer of 1-(3,4 dihydroxy phenyl)-2-amino ethanol, exerts its action predominantly through the following two mechanisms:

1. *α -Receptor agonism:* Norepinephrine is a direct-acting agonist at α -receptors and is predominantly used for this effect. Although it is a less potent α -receptor agonist than epinephrine, the lack of β_2 -agonism makes norepinephrine a preferable α -adrenergic vasoconstrictor (see later).
2. *β_1 -Receptor agonism:* Norepinephrine is a direct-acting agonist at the β_1 -receptor. Its agonistic properties at this receptor are roughly equal in potency to that of epinephrine.

Norepinephrine generally is used primarily for its α -receptor-mediated vasoconstrictive properties. As described earlier, it is preferable to epinephrine in this regard despite norepinephrine's lower potency at the α -receptor because of epinephrine's vasodilating effect secondary to its agonist properties at the β_2 -receptor. The net result of the administration of norepinephrine is an increase in SVR and mean arterial blood pressure.

Norepinephrine is metabolized by COMT and MAO. The product of COMT metabolism is normetanephrine, which is inactive. MAO action forms norepinephrine aldehyde, which is subsequently methylated by COMT to the inactive vanillylmandelic acid.

Norepinephrine generally is supplied as the bitartrate (Levophed); 2 mg of the bitartrate is equivalent to 1 mg of norepinephrine base. When specifying doses, it is important to be unambiguous about the bitartrate versus the base. It is preferable to express dosage in terms of norepinephrine base, and that convention is followed here.

Dosage and Administration

It is best to dilute norepinephrine bitartrate in dextrose-containing solutions because the latter inhibits its oxidation. It is generally prepared by adding 1 ampule (4 mg of norepinephrine base) to 250–1000 mL. Infusions should start at 0.5–1 $\mu\text{g}/\text{min}$ and should be titrated to the desired clinical effect. Pediatric infusion should begin at 0.05–0.1 $\mu\text{g}/\text{kg}/\text{mL}$ (or approximately 2 $\mu\text{g}/\text{m}^2$). Because of the powerful vasoconstricting effect of norepinephrine, it should not be given subcutaneously or intramuscularly, and precautions should be taken to prevent extravasation by its administration into large peripheral or central veins.

Precautions and Contraindications

As described earlier, it is important to avoid extravasation of norepinephrine. In the event of an extravasation, the local vasoconstriction should be treated by α -receptor blockade, which

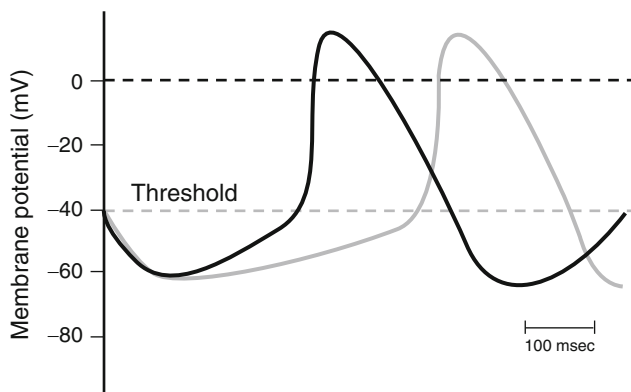


Fig. 4 Transmembrane potentials of pacemaker cells of mammalian heart illustrating slowing of the rate of diastolic depolarization produced by vagus nerve stimulation (*darker curve*). Threshold is the potential for generation of

an action potential (From Smith CM, Reynard AM [eds]: Textbook of pharmacology. Philadelphia, WB Saunders, 1995, with permission)

can be accomplished by the administration of phentolamine. A typical dose is 5–10 mg of phentolamine diluted in 10–15 mL of normal saline administered through a fine needle; this should be infiltrated diffusely in the area of extravasation.

Patients taking guanethidine may have an exaggerated hypertensive effect from norepinephrine or other direct-acting α -adrenergic agonists because guanethidine decreases the uptake of these agents and may induce receptor supersensitivity. Patients taking amine uptake-inhibiting antidepressants, such as tricyclic antidepressants, also can be expected to have an exaggerated effect of direct-acting sympathomimetic amines such as norepinephrine secondary to decreased uptake. Patients taking any of the aforementioned agents should be treated with minimal doses of norepinephrine initially, which can be titrated to the desired clinical effect.

Phenylephrine

Action

Phenylephrine (Neo-Synephrine) (see Fig. 1) is primarily a direct-acting α_1 -adrenergic agonist and is devoid of activity at β -adrenergic receptors. It also seems to have a component of indirect action causing the release of dopamine and

norepinephrine. The latter activity is probably not responsible for its pressor effects, although it can have some significance for potential drug interactions, which are explained subsequently (Fig. 4).

When administered as a vasopressor, phenylephrine can be given intravenously, subcutaneously, or intramuscularly. The intravenous route is always preferred and except in extraordinary circumstances should be used exclusively when seeking a vasopressor effect. Phenylephrine's duration of action after intravenous use is approximately 15 min, in contrast to hours after subcutaneous or intramuscular injection. The long duration of action for these routes is probably the result of the delayed release from these sites because of phenylephrine's α -adrenergic vasoconstricting properties.

Approximately 16% of an intravenous dose is excreted unchanged. It is not appreciably protein bound. Its volume of distribution is reported to be 4.9 L/kg. Peak serum concentrations are generally in the vicinity of 200 ng/mL.

Dosage and Administration

Phenylephrine infusions generally are administered at a rate of 40–360 $\mu\text{g}/\text{min}$, although it is unusual to require dose rates greater than 180 $\mu\text{g}/\text{min}$.

The usual pediatric dose is 0.1–0.5 $\mu\text{g/kg/min}$. If needed, an initial bolus of 200–500 μg (5–20 $\mu\text{g/kg}$) can be given before the infusion.

If it is necessary to use the subcutaneous or intramuscular route, the usual adult dose is 2–10 mg repeated every 10–15 min. The pediatric dose is typically 0.05–1 mg/10 kg or 0.1 mg/kg (3 mg/ m^2) as a single dose. Because of the long duration of action of phenylephrine given by these routes, it should be administered only every 1–2 h.

Phenylephrine solutions for infusion generally are prepared by mixing 10 mg with 500 mL of any standard intravenous solution. For a more concentrated solution, 20 mg/500 mL may be used. When mixed with phenytoin, the solution may form precipitates.

Precautions and Contraindications

An enhanced pressor effect may be expected in patients taking guanethidine because of guanethidine's inhibition of phenylephrine uptake from the neuromuscular junction or possibly by adrenergic receptor hypersensitivity. Patients taking MAO inhibitors may be anticipated to have an exaggerated response to phenylephrine secondary to its indirect effects. In patients taking these agents, it is best to start with the lowest possible dose and titrate the dose as clinically indicated. Patients taking tricyclic antidepressants also may have an exaggerated response to phenylephrine, and they too should be treated with the lowest possible doses followed by a titration to clinical effect.

Grading System for Levels of Evidence Supporting Recommendations in *Critical Care Toxicology, 2nd Edition*

- I. Evidence obtained from at least one properly randomized controlled trial.
- II-1. Evidence obtained from well-designed controlled trials without randomization.
- II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III. Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

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